Simultaneous Pancreas-Kidney Transplant From Donors After Brain Death vs Donors After Circulatory Death: A Single-Center Follow-up Study Over 3 Decades

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ABSTRACT

Background. Despite an increase in the number of pancreas transplants in the Scandiatransplant region in the last decade, there continues to be a gap between demand and supply of transplantable organs. This imbalance has encouraged the transplant community to consider new sources of grafts, such as the reintroduction of donors after circulatory death (DCD) who were the standard donors in our center before 1988.

Material and Methods. In this long-term follow-up study, we compare 44 consecutive, simultaneous pancreas kidney transplants performed at Karolinska University Hospital between 1986 and 1991: 21 patients received DCD grafts and 23 received grafts from donors after brain death.

Results. Both groups had similar donor and recipient characteristics, but cold ischemia times were significantly shorter in the DCD group. Warm ischemia times were very short compared with other studies on DCDs. Patient and graft survival rates were similar in both groups.

Conclusion. This study suggests that controlled DCD pancreas and kidney grafts transplanted simultaneously can be a feasible option for reducing organ shortage without any negative impact on the long-term results.

SIMULTANEOUS pancreas-kidney (SPK) transplant is the best therapeutic option for most patients with end-stage renal failure secondary to diabetes. The long-term results of SPK show a clear survival benefit [1].

Despite a decrease in pancreas transplant activity in the United States and a plateau reached in Europe [2], the Scandiatransplant community (Denmark, Finland, Iceland, Norway, and Sweden) has increased the annual number of pancreas transplants performed over the last decade. However, despite this increase, the supply of transplantable organs is still not meeting the demand. The gap between available grafts and potential recipients has encouraged the worldwide transplant community to consider new sources of transplantable organs. Alternatives include living donors [3], pediatric donors [4], and acceptance of so-called marginal donors (ie, elderly or obese donors) [5]. Another approach to expanding the donor pool includes the use of organs from donors after circulatory death (DCD) [6].

The idea of using DCD organs is not new in Sweden or internationally. Brain death criteria were not legally accepted as death until 1988 in Sweden. Therefore, all Swedish grafts had to be obtained from DCDs until the Swedish law was amended on January 1, 1988, to legally accept brain death as a criterion for human death. Because of a persistent worldwide donor organ shortage and a lengthening of waiting lists, the interest in using grafts from DCDs has gained renewed attention. While this is already a standard procedure in many countries, in Sweden there is ongoing debate about reintroducing DCDs.

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In this study, we present a retrospective analysis of SPK transplants performed at Karolinska University Hospital between 1986 and 1991 using grafts from DCDs and donors after brain death (DBD).

PATIENTS AND METHODS

Study Design

All patients who received a first-time SPK at the Department of Transplantation Surgery at Karolinska University Hospital between January 1986 and December 1991 were considered for inclusion in the study. This time span was chosen because the Swedish Human Death Act determining the criteria of brain death was adopted in January 1988. All donors before 1988 were DCDs and all donors thereafter were DBDs. Between 1986 and 1991, a total of 48 SPK transplants were performed, including 1 patient who received an SPK twice. Three patients lost to follow-up were excluded from the study (1 of these was the patient who received a transplant twice). Of the 44 remaining patients, 21 received transplants with a DCD graft and 23 received transplants with a DBD graft. Data were collected retrospectively from the transplant database with a follow-up period from the date of SPK to March 1, 2017, or the patient's death. The study protocol was approved by the Regional Ethical Review Board in Stockholm. The clinical and research activities reported in this study are consistent with the principles of the Helsinki Declaration.

Donor after cardiac death grafts. All the DCDs included in the study met the criteria for brain death but were not legally dead before cardiac arrest. Therefore, our DCDs can be considered as controlled Maastricht category IV organ donors [7]. Death was pronounced by an anesthesiologist in the operating room when no pulse could be palpated on the donor. According to the Swedish guidelines, heparin was given and the aorta was cannulated using a double-balloon catheter inserted via the femoral artery before withdrawal of the respiratory support. Thereafter the ventilator was disconnected and cold perfusion was started immediately after the occurrence of cardiac arrest. Organ procurement was carried out using an en bloc technique [8]. Warm ischemia time (WIT) was defined as the interval from withdrawal of respiratory support to cold perfusion. Cold ischemia time (CIT) was defined as the interval from cold perfusion to reperfusion in the recipient and Δ CIT as kidney CIT − Pancreas CIT.

Pancreas transplant and immunosuppression. All SPKs included in the study were performed through a midline incision. The pancreas graft was placed intraperitoneally in the middle of the abdomen, while the kidney graft was placed extraperitoneally. All pancreas transplants between 1986 and 1987 were performed using segmental (body and tail) pancreatic grafts (23 cases), but from 1988 onward all pancreatic grafts except 2 were whole organs [9]. The portal vein of the pancreatic graft was anastomosed end-to-side to the recipient's inferior vena cava or common iliac vein. An interposition vein graft to extend the portal vein stump was used in 2 cases of DBD grafts. In all cases of segmental pancreas transplant, the celiac artery (CA) or splenic artery (in those cases where the CA was kept with the liver graft) was anastomosed end-to-side to the recipient iliac artery. In recipients undergoing whole pancreas transplant, the superior mesenteric artery and CA were kept in the same aortic patch that was anastomosed end-to-side to the recipient iliac artery. In 7 cases, an arterial Y-graft was used to connect the superior mesenteric artery and graft's splenic artery. In all cases, pancreatic exocrine drainage was provided by anastomosis to the bowel. Temporary pancreatic duct catheters for draining the exocrine pancreatic fluid during healing of the bowel anastomosis were used in 41 out of 44 cases [10]. Cold perfusion was accomplished either using Perfadex (XVIVO Perfusion; Göteborg, Sweden) (32 cases) or University of Wisconsin (UW) solution (11 cases). At the back table, organs were flushed and preserved at hypothermia using Perfadex, Euro-Collins, or UW perfusates. All recipients except 1 received either triple or quadruple immunosuppressive therapy [11]. The triple regimen consisted of cyclosporine, azathioprine, and prednisolone. Patients on quadruple treatment were, in addition to the triple regimen, given induction therapy consisting of antithymocyte globulin (25 cases) or Muromonab-CD3 (2 cases). In 1 case, a dual regimen of only cyclosporine and prednisolone was used.

Endpoints and statistical analysis. Primary endpoints of this study were patient survival and graft survival. Secondary endpoints were delayed graft function (DGF) and retransplant. We compared recipient and donor characteristics, immunosuppression protocols, surgical procedures, and long-term graft outcomes. Perioperative mortality was defined as patient death within 30 days after transplant, and perioperative graft loss was defined as graft loss within 30 days after transplant. Delayed graft function of the pancreas was defined as the need for exogenous insulin within the first post-transplant week. Renal DGF was defined as the need for dialysis within the first post-transplant week. Pancreas graft failure was defined as the need for continuous exogenous insulin therapy post transplant, removal of the graft, or death with a functioning graft. Kidney graft failure was defined as the need for continuous dialysis therapy, removal of the graft, or death with a functioning graft. All statistical analysis was performed using Statistica software, version 13.0 (TIBCO Software Inc., Palo Alto, CA, USA). Continuous data are presented as mean and standard deviations, and the difference between the 2 groups was tested using the Mann-Whitney test. Categorical data are presented as total numbers and percentages. The significance of an association between 2 categorical variables was analyzed using the Fisher exact test. Kaplan-Meier analysis was used for graft and patient survival, with comparison of groups by means of the log-rank test. Statistical significance was set at $P \leq .05$.

RESULTS

Donor and Recipient Characteristics

Donor and recipient characteristics were similar in the DBD and DCD groups, with no significant difference (Tables 1 and 2).

Surgery-Related Factors

Differences regarding surgery-related factors are shown in Table 3. All pancreatic grafts in the DCD group were segmental grafts, in contrast to the DBD group where all pancreatic grafts except 2 were whole pancreas ($P < .001$). An arterial Y-graft was used in 7 SPK recipients receiving grafts from a DBD but never when the graft came from a DCD ($P = .006$). Organs from DBDs had significantly longer CIT than those from DCDs (pancreas CIT mean 375 [standard deviation [SD], 166] and 263 [SD, 56] minutes, respectively; $P = .007$; kidney CIT mean 715 [SD, 183] and 566 [SD, 117] minutes, respectively; $P = .002$). Perfadex

Table 1. Donor Characteristics

Characteristic	DBD N = 23	DCD N = 21	*P* Value
Sex, No. (%), female/male	10/13 (43.5/56.5)	6/15 (28.6/71.4)	.24
Age, mean (SD), y	35 (11)	37 (16)	.50
BMI, mean (SD)	24.2 (4) (m = 2)	22.7 (3) (m = 10)	.51
Blood group, No. (%)			
O	12 (52.2)	6 (28.6)	
A	10 (43.5)	12 (57.1)	
B	1 (4.3)	2 (9.5)	
AB	0	1 (4.8)	
Cause of death, No. (%)			
Asphyxiation	1 (4.3)	3 (14.3)	
Cardiovascular	1 (4.3)	1 (4.8)	
Intracranial hemorrhage/stroke	14 (60.9)	13 (61.9)	
Brain trauma	6 (26.2)	4 (19.0)	
Other	1 (4.3)	0	
Laboratory parameters			
Serum creatinine, mean (SD), μmol/L	92 (41.06) (m = 1)	104 (32.61) (m = 1)	.29
Serum glucose, mean (SD), mmol/L	9 (3.75) (m = 1)	12 (6.2) (m = 3)	.20
Serum amylase, mean (SD), μkat/L	6 (6.04)	4 (3.12) (m = 5)	.47
CMV status, No. (%), +/−	17/5 (77.3/22.7) (m = 1)	9/5 (64.3/35.7) (m = 7)	.43

m = No. of patients where data are missing.
Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CMV, cytomegalovirus; DBD, donor after brain death; DCD, donor after circulatory death.

solution was used for preservation in all cases of DCD, while UW solution (or a combination of UW and Perfadex) was used in 17 DBD cases.

Patient and Graft Survivals

The 1-, 3-, 5-, 10-, and 20-year patient survival rate was numerically higher in the DCD group but did not reach statistical significance (Fig 1). No patients from either group died in the perioperative period. At the last follow-up in March 2017, a total of 4 patients are still alive (3 DCD recipients and 1 DBD recipient).

There was no difference in pancreas graft survival between the 2 groups (Fig 2). Four pancreas grafts in each group were lost in the perioperative period. Loss of the pancreatic graft because of rejection was similar in both groups. No pancreas graft was lost because of thrombosis in

Table 2. Recipient Characteristics

Characteristic	DBD N = 23	DCD N = 21	*P* Value
Sex, No. (%), female/male	10/13 (43.5/56.5)	10/11 (47.6/52.4)	.51
Age, mean (SD), y	36 (7)	37 (6)	.48
BMI, mean (SD)	22.4 (2.61)	21.5 (1.61) (m = 2)	.29
Blood group, No. (%)			
O	11 (48)	6 (30)	
A	11 (48)	11 (52)	
B	1 (4)	2 (9)	
AB	0	2 (9)	
CMV status, No. (%), +/−	13/10 (56.5/43.5)	10/6 (62.5/37.5) (m = 5)	.29
CMV mismatch, No. (%)	9 (39)	2 (13) (m = 6)	.09
HLA mismatch, No. (%)			
0–1	0	0	
2–4	3 (13)	8 (38)	
5–6	20 (87)	13 (62)	
Duration of disease, mean (SD), y	24 (7)	26 (6)	.47
Pretransplant dialysis, No. (%)	12 (52)	9 (43)	.38
HD/PD, No. (%)	6/6 (26/26)	4/5 (19/24)	.57

m = number of patients where data are missing.
Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CMV, cytomegalovirus; DBD, donor after brain death; DCD, donor after circulatory death; HD, hemodialysis; PD, peritoneal dialysis.

Table 3. Surgery-Related Factors

Characteristic	DBD N = 23	DCD N = 21	*P* Value
Pancreas graft, No., segmental/whole	2/21	21/0	<.001
Arterial Y-graft, No. (%)	7 (30)	0	.006
Interposition vein graft, No. (%)	2 (9)	0	.27
Temporary pancreas catheter, No. (%)	20 (87)	21 (100)	.13
WIT, mean (SD), min		4 (4)	
CIT pancreas, mean (SD), min	375 (165)	263 (56)	.007
CIT kidney, mean (SD), min	715 (183)	566 (117)	.002
Δ CIT, mean (SD), min	340 (59)	302 (82)	.14
Type of perfusion solution, No. (%)			
Perfadex/Perfadex*	1 (4.5)	21 (100)	
Perfadex/Euro-Collins*	4 (18.2)	0	
Perfadex/UW*	6 (27.3)	0	
UW/UW*	11 (50.0)	0	
Immunosuppression, No. (%), with/without induction	10/13 (43.5/56.5)	7/14 (33.3/66.7)	.35

Abbreviations: CIT, cold ischemia time; DBD, donor after brain death; DCD, donor after circulatory death; UW, University of Wisconsin solution; WIT, warm ischemia time.
*Solution used for cold perfusion in the donor/solution used at the back table and preservation.

the DBD group in contrast to 3 grafts lost in the DCD group ($P = .10$). Pancreatic DGF occurred more often among DBD patients but did not reach statistical significance. Annual pancreas survival rates were similar in both groups (Table 4).

Kidney graft survival was similar in both groups ($P = .25$) (Fig 3). Two patients in the DCD group still have functioning kidney grafts 31 years and 30 years post transplant, respectively. Kidney graft loss because of rejection and thrombosis were similar in both groups. Kidney DGF was seen more often in the DCD group than in the DBD group but did not reach statistical significance. There was no significant difference regarding the number of kidney retransplants in the 2 groups (19% vs 24%; $P = .47$). Perioperative graft losses and kidney graft survival were similar in both groups (Table 5).

DISCUSSION

Our single-center study demonstrates comparable long-term results for SPKs with grafts from DCDs and DBDs. This finding suggests that controlled DCD pancreas and kidney grafts with short WIT and CIT should be considered in order to expand the organ pool and thereby reduce the organ shortage.

A high number of pancreatic grafts were lost as early as during the first postoperative year. However, this was not related to differences between DCDs and DBDs since the survival curves were overlapping. Segmental pancreatic grafts were used in all DCD recipients in contrast to the DBD group, where 87% of the recipients were given the whole pancreatic graft. A segmental pancreas graft does not need an arterial Y-graft for transplant, while a whole pancreas graft may need it, especially if the CA is retained

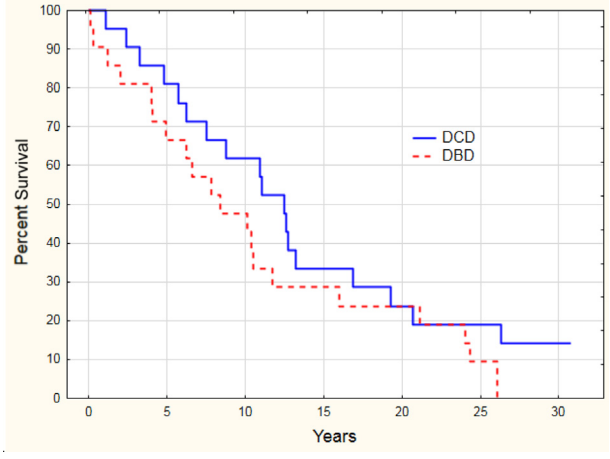

Fig 1. Patient survival in SPK transplant. DCD vs DBD. Abbreviations: DBD, donor after brain death; DCD, donor after circulatory death; DGF, delayed graft function; SPK, simultaneous pancreas-kidney.

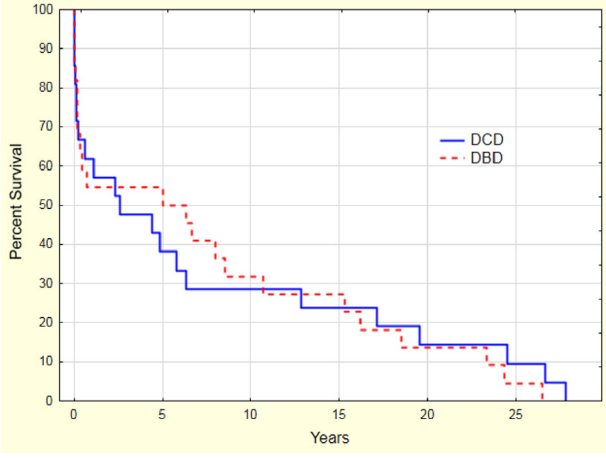

Fig 2. Pancreas graft survival in SPK transplant. DCD vs DBD. Abbreviations: DBD, donor after brain death; DCD, donor after circulatory death; DGF, delayed graft function; SPK, simultaneous pancreas-kidney.

Table 4. Pancreas Outcomes

Characteristic, No. (%)	DBD N = 23	DCD N = 21	*P* Value
DGF pancreas	10 (43)	6 (29)	.24
Cause of pancreas failure			
Rejection	6 (27.3)	5 (23.8)	.57
Abscess/fistula/pancreatitis	1 (4.5)	4 (19)	.15
Thrombosis	0	3 (14.3)	.10
Death with functioning graft	9 (40.9)	6 (28.6)	.34
Other	2 (9.1)	0	.27
Unknown	4 (18.2)	3 (14.3)	.55
Pancreas retransplant	1 (4.8) (m = 2)	1 (4.8)	.74
Perioperative pancreas loss	4 (17.4)	4 (19)	.62

m = number of patients where data are missing.
Abbreviations: DBD, donor after brain death; DCD, donor after circulatory death; DGF, delayed graft function.

Table 5. Kidney Outcomes

Characteristic, No. (%)	DBD N = 23	DCD N = 21	*P* Value
DGF kidney	1 (4.3)	4 (19)	.15
Cause of kidney failure			
Rejection	8 (36.4)	8 (42.1)	.53
Thrombosis	1 (4.5)	3 (15.8)	.27
Death with a functioning graft	10 (45.5)	7 (36.8)	.35
Other	3 (13.6)	0	.13
Unknown	0	1 (5.3)	.48
Kidney retransplant	4 (19) (m = 2)	5 (23.8)	.49
Perioperative kidney loss	1 (4.3)	4 (19)	.16

m = number of patients where data are missing.
Abbreviations: DBD, donor after brain death; DCD, donor after circulatory death; DGF, delayed graft function.

with the liver graft from the same donor. Therefore, the use of arterial Y-grafts is a variable dependent on the type of pancreas graft used for transplant. These technical differences derive from developments in pancreas transplantation during the 1980s, when no standard surgical procedure existed. Use of the whole pancreas for transplant became increasingly common because of some inherent advantages (larger islet mass, larger vessels for the vascular anastomosis, and easier graft anastomosis to the bowel) even though there were no comparative studies showing superiority of whole graft vs segmental graft [12–14].

The mean WIT in the current study was 4 minutes (range, 0–12 minutes), which seems short compared with other studies [15–18]. There are at least 2 possible explanations for the difference. First, in accordance with the Swedish regulations in the 1980s, there was no requirement of a "no touch" period, and heparinization and cannulation of the aorta in the donor was performed before respiratory support was discontinued. Second, all the DCDs had an extremely short agonal phase because they were controlled Maastricht category IV donors (ie, already DBDs) and this led to short WIT. Such short WIT is hardly reproducible with the DCD regulations currently in use. However, studies performed in more recent clinical settings suggest that a WIT of up to 30 minutes is acceptable for DCD pancreas grafts [16,19]. Moreover, a novel approach in the organ procurement of DCD organs with the use of abdominal normothermic regional perfusion may potentially minimize ischemic damage, thus making longer WIT acceptable [20,21].

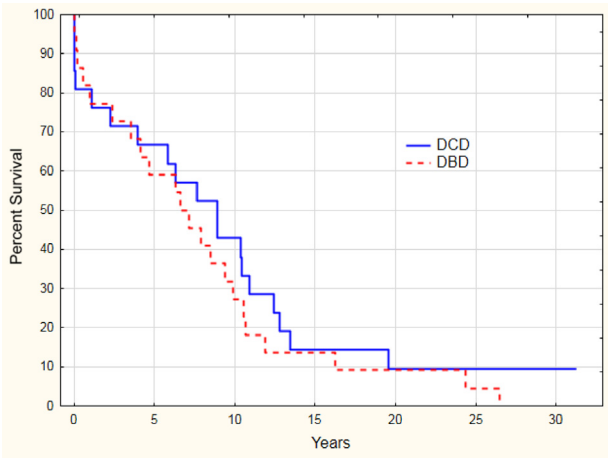

Fig 3. Kidney graft survival in SPK transplant. DCD vs DBD. Abbreviations: DBD, donor after brain death; DCD, donor after circulatory death; DGF, delayed graft function; SPK, simultaneous pancreas-kidney.

In our study the mean CIT was significantly longer in the DBD group than in the DCD group. It is possible that fear of the negative effects of WIT led to greater efforts to minimize CIT in the DCD cohort during the procurement, though there was no difference in terms of the operative time as shown by Δ CIT ($P = .14$). The short CIT in the DCD group is in line with recent recommendations made by Berney et al who suggest that the use of DCD pancreases is applicable on condition that CIT is kept to a minimum [22].

The recipients of DCD grafts in this study may have suffered the detrimental effects of brain death on the pancreas and kidney graft. Contreras et al demonstrate significantly reduced islet yields and functionality in β islet cells from pancreas obtained from brain dead test animals [23]. Brain death causes relevant changes in pancreatic microcirculation, which might have an impact on the pancreatic graft function as shown in another animal model [24]. The negative effect of brain death on renal function [25] as well as on the renal transplant outcome is also well known [26]. Because only DCDs were used in Sweden before 1988 while only DBDs were used from that year onward, the recipients of this study were not matched with either a DCD or DBD graft based on their characteristics. There was no difference between the 2 groups in terms of selection criteria of a suitable transplantable graft for a certain recipient. On the contrary, other studies instead compare the simultaneous use of DCDs and DBDs, thus implying the possibility of selecting a graft

from a DCD or a DBD based on the recipient's characteristics. Muthusamy et al analyzed 1009 pancreas transplants performed between 2006 and 2010 in the United Kingdom and demonstrated comparable short-term results in the DCD and DBD cohorts. However, this was achieved using DCDs that were significantly younger, had lower body mass index, and whose cause of death was less frequently cerebrovascular than was the case with the DBDs. Furthermore, sensitized recipients were selected to receive DBD grafts rather than DCD grafts [16]. Qureshi et al found no difference in outcome in SPKs when comparing the 2 donor groups, even though the DCDs were younger than the DBDs with a median age of 31.5 vs 45.5 years, respectively [17]. Likewise, Fernandez et al reported indistinguishable long-term outcomes between DCD and DBD SPKs, though in this study no efforts were made to match certain recipients with DCD organs [15].

In line with previous studies, in our study kidney DGF was more frequently seen in the DCD cohort, although this did not affect graft survival. Moreover, the rates of kidney DGF in both groups is most likely underestimated because half of the patients were not on dialysis prior to transplant. In our study, the number of pancreatic DGFs was higher in the DBD group than among DCD recipients, and although the difference was not statistically significant, we found it noteworthy. The higher number of pancreatic DGFs in the DBD group did not affect graft survival.

In conclusion, our 30-year follow-up analysis shows that the results in terms of short- and long-term graft and patient survival are similar with grafts from DCDs and DBDs. Hence, although much has changed in surgical techniques, immunosuppression protocols and postoperative care over the last 3 decades, we believe that controlled DCD pancreas and kidney grafts can be a feasible option for expanding the pool of organ donors.

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