First Canadian experience with donation after cardiac death simultaneous pancreas and kidney transplants

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Background: Compared with neurologic determination of death (NDD) donor organs, donation after cardiac death (DCD) donor organs have traditionally been considered of inferior quality owing to warm ischemia experienced during procurement. We present, to our knowledge, the first analysis of simultaneous pancreas and kidney (SPK) transplants using DCD donor organs in Canada.

Methods: We carried out a retrospective cohort study of SPK transplants from 13 DCD and 68 NDD donors performed between October 2008 and July 2016. In all patients immunosuppression was induced with thymoglobulin and continued with tacrolimus, mycophenolate mofetil and prednisone maintenance therapy.

Results: Donor and recipient characteristics of DCD and NDD groups were similar with respect to age, sex, body mass index, kidney and pancreas cold ischemia times, and donor terminal creatinine. Mean DCD graft warm ischemia time was 0.5 (range 0.4–0.7) hours. Median follow-up was 2.2 (range 0.1–6.7) years and 2.7 (range 0.3–6.3) years for the DCD and NDD groups, respectively. The DCD and NDD groups were similar with regards to recipient percent panel reactive antibody and presence of human leukocyte antigen antibodies. The groups also received similar total doses of thymoglobulin. In total 38% of patients in the DCD group experienced renal delayed graft function (DGF) compared with 10% in the NDD group ($p = 0.027$). There were 7 cases of pancreas graft thrombosis requiring relaparotomy in the NDD group compared with none in the DCD group. No patients from either group required insulin at any time after transplant. Although the estimated glomerular filtration rate (eGFR) was lower in the DCD than the NDD group on postoperative days 7 and 14 ($p = 0.025$), no difference was noted on day 30 or through 4 years after transplant. No differences were seen between the groups with respect to amylase, lipase, or HbA1c up to 4 years after transplant, or in kidney, pancreas, or patient survival at any time after transplant.

Conclusion: Our results show that, apart from a higher renal DGF rate, SPK transplants with DCD donor organs have comparable outcomes to standard transplants with NDD donor organs.

Contexte : Comparativement aux organes prélevés après détermination de la mort cérébrale (ou détermination du décès neurologique [DDN]), les organes prélevés après détermination du décès cardiocirculatoire (DDC) sont en général considérés de moindre qualité en raison du phénomène d'ischémie chaude inhérent à ce type de prélèvement. Nous présentons, à notre connaissance, la première analyse sur la double greffe rein–pancréas effectuée avec des organes prélevés après DDC au Canada.

Méthodes : Nous avons procédé à une étude de cohorte rétrospective sur les doubles greffes rein–pancréas effectuées entre octobre 2008 et juillet 2016, soit 13 après DDC et 68 après DDN. Chez tous les patients, l'immunosuppression a été induite par la thymoglobuline et a été maintenue au moyen d'un traitement d'entretien par le tacrolimus, le mycophénolate mofétil et la prednisone.

Résultats : Les caractéristiques des donneurs et des receveurs des 2 groupes (DDC et DDN) étaient semblables sur les plans de l'âge, du sexe, de l'indice de masse corporelle, de la durée de l'ischémie froide du rein et du pancréas, et de la créatinine terminale (donneur). La durée moyenne de l'ischémie chaude des greffons prélevés après DDC a été de 0,5 (étendue : 0,4–0,7) heure. Le suivi médian a été d'une durée de 2,2 (étendue : 0,1–6,7) ans et de 2,7 (étendue : 0,3–6,3) ans, respectivement, pour les groupes DDC et DDN. Les 2 groupes étaient similaires pour ce qui est des pourcentages d'anticorps réactifs et de la présence d'anticorps anti-HLA (human leukocyte antigen) chez les receveurs. Les 2 groupes avaient aussi reçu des doses totales semblables

de thymoglobuline. En tout, 38 % des patients du groupe DDC ont manifesté un retard de fonctionnement du greffon rénal, contre 10 % dans le groupe DDN (p = 0,027). On a dénombré 7 cas de thrombose du greffon pancréatique ayant nécessité une réintervention dans le groupe DDN, contre aucun dans le groupe DDC. Aucun des patients n'a eu besoin d'insuline après la transplantation. Le débit de filtration glomérulaire estimé (DFGe) était moins élevé dans le groupe DDC que dans le groupe DDN aux jours 7 et 14 (p = 0,025), mais on n'a plus noté de différence à ce chapitre au jour 30 ni au cours des 4 années suivant la greffe. On n'a observé aucune différence entre les groupes pour ce qui est de l'amylase, de la lipase ou de l'HbA1c jusqu'à 4 ans suivant la greffe, ni pour ce qui est de la survie des greffons rénaux ou pancréatiques ou celle des patients, peu importe le temps écoulé depuis la greffe.

Conclusion : Selon nos résultats, si ce n'est un taux plus élevé de retard de fonctionnement du greffon rénal, les receveurs d'une double greffe rein–pancréas après DDC obtiennent des résultats semblables à ceux qui subissent une greffe standard d'organes prélevés après DDN.

Patients with diabetes mellitus and end-stage renal disease (ESRD) have high rates of morbidity and mortality.[1–3] The simultaneous pancreas and kidney transplant (SPK) has been shown to improve quality of life and significantly impact survival of patients with ESRD and diabetes.[4] However, the global demand for SPK transplant continues to outpace the availability of suitable donor grafts, which has led to long transplant wait lists.[5–8] To overcome this barrier, expansion of donor criteria is being studied to address the imbalance in organ supply and demand in North America.[9,10]

One such provision in the expansion of donor criteria has been the use of donation after cardiac death (DCD) donor grafts in patients requiring an SPK transplant. Compared with the standard neurologic determination of death (NDD) donor grafts, pancreas grafts from DCD donors have traditionally been believed to be of inferior quality owing to the damage to these grafts during the period of warm ischemia between cessation of donor cardiopulmonary circulation and administration of cold perfusion during organ procurement.[11,12] The theoretical risks about graft quality have limited the use of DCD grafts in SPK transplantation. Between 2006 and 2012, only 320 pancreas grafts from DCD donors were transplanted in the United States compared with 20 448 pancreas grafts from NDD donors.[13]

As a measure of quality assurance, we present a study of, to our knowledge, the first Canadian experience with DCD SPK transplants. Specifically, we compared the rates of postoperative complications, laboratory parameters of graft function, and long-term patient and graft survival between SPK transplants from DCD and NDD donors.

Methods

Patient selection

All patients who underwent SPK transplantation using DCD donor grafts between October 2008 and July 2016 at our single, large tertiary care institution were included in the study. Patient data were collected for analysis from the time of transplant until July 2016.

Study design

We performed a retrospective cohort study comparing all SPK transplants from DCD donors to those from all NDD donors. The demographic data, quantitative laboratory tests of short and long-term graft function, surgical complications, and patient and graft survivals were compared between the groups.

Organ procurement

After confirming the donors' histories were free of diabetes or pancreatitis, the decision to accept the grafts was mainly based on donor age, history of diabetes, body mass index (BMI) and quality of the organs during procurement surgery and after flushing. The pancreas was not used if there was evidence of significant trauma, severe fibrosis, or pancreatitis. Initial warm ischemia time was limited to 30 minutes, but with very minor impact on graft function and pancreas graft thrombosis, we extended this threshold to 60 minutes. Initially only younger patients were considered candidates for DCD grafts, but based on our experience of acceptable graft function with DCD grafts, all patients on our waiting list are considered for DCD transplant.

In all cases the pancreas and kidneys were flushed with Belzer University of Wisconsin solution. Kidneys were stored in either cold static solution using University of Wisconsin solution, or in a pulsatile cold preservation machine (LifePort, Organ Recovery Systems) using KPS solution (Organ Recovery Systems).

Transplant procedure

Standard kidney transplants were performed in the left iliac fossa. Pancreas transplants were completed in the right iliac fossa using systemic and enteric drainage.

Immune suppression

Immunosuppression was induced with 250 mg of methylprednisone, which was given on call to the operating room. Thymoglobulin (1.5 mg/kg) was started before skin incision and administered over 6–8 hours. Myfortic (720 mg orally twice daily) was started on postoperative day 0. Tacrolimus was initiated on day 3 (trough level 5–8). Methylprednisone was then started at 1 mg/kg with daily tapering by 10 mg/d until a minimum of 5 mg/d was reached. Steroids were withdrawn only if a protocol kidney biopsy at 3 months was free of rejection.

Delayed graft function (DGF) was defined as the need for dialysis within the first 7 days after SPK transplant.[14]

Statistical analysis

Statistical analysis was carried out using Graphpad Prism 6 (GraphPad Software, Inc.). We used the Mann–Whitney test to compare means between groups and the χ^2 test to compare categorical variables. Survival curves for patient and graft survival were generated using the Kaplan–Meier method and compared using the log-rank test. All statistical tests were 2-sided, and statistical significance was accepted at the 95% confidence interval with $p < 0.05$. Data are presented as means with standard deviations.

Results

Thirteeen DCD and 68 NDD SPK transplants were performed at our institution between October 2008 and July 2016 (Fig. 1). Median follow-up was 2.2 (range 0.1–6.7) years and 2.7 (range 0.3–6.3) years for DCD and NDD groups, respectively (Table 1).

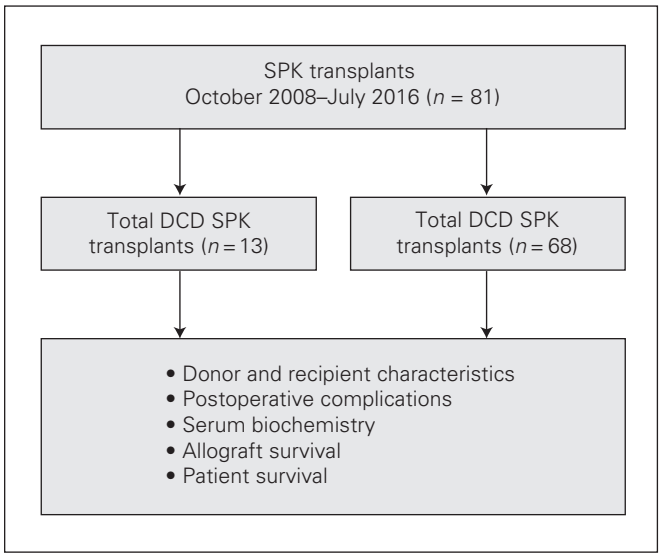

Fig. 1. Flow of patients through the study. DCD = donation after cardiac death donor; NDD = neurologic determination of death donor; SPK = simultaneous pancreas and kidney transplant.

Donor characteristics

Characteristics of the SPK donors and graft ischemia times are shown in Table 1. Donor characteristics were similar between the DCD and NDD groups with respect to age, sex, BMI, terminal creatinine and kidney cold ischemia time (CIT). The mean pancreas CIT was significantly different between the DCD and NDD groups (10.0 h v. 7.1 h, $p = 0.049$). The mean warm ischemia time of kidney and pancreas grafts procured from DCD donors was 0.5 (range 0.4–0.7) hours.

Recipient characteristics

Recipient characteristics were similar between the DCD and NDD groups with respect to age, BMI, sex, percent panel reactive antibodies (PRA%), and presence of donor-specific antibodies. There was no history of prior transplants in either of the groups (Table 1).

Postoperative complications

Complications are outlined in Table 2. We found no difference in the mean number of units of packed red blood cells transfused to patients between the DCD and NDD transplant groups. There was a significantly higher rate of renal delayed graft function (DGF) after transplant in the DCD group than in the NDD group. In total 38% of patients in the DCD group experienced DGF compared with 10% in the NDD group ($p = 0.027$). The mean

Table 1. Donor and recipient demographics of simultaneous pancreas-kidney transplants from DCD and NDD donors

Characteristic	Group; mean ± SD*		*p* value
	DCD (n = 13)	NDD (n = 68)	
Donors			
Age, yr	31.9 ± 2.5	31.8 ± 1.7	0.99
BMI	24.3 ± 2.0	25.6 ± 0.6	0.54
Sex, male:female	8:5	37:31	> 0.99
Terminal creatinine	83.9 ± 11.9	66.2 ± 4.4	0.12
Kidney CIT, hr	8.4 ± 2.6	5.9 ± 0.7	0.27
Pancreas CIT, hr	10.0 ± 2.7	7.1 ± 0.4	0.049
WIT, hr	0.5 ± 0.1	N/A	—
WIT range, hr	0.4 – 0.7	N/A	—
Recipients			
Age, yr	47.1 ± 2.0	42.0 ± 2.1	0.17
BMI	24.4 ± 0.7	26.6 ± 1.6	0.08
Sex, male:female	7 / 6	41 / 27	0.76
PRA%	15.7 ± 7.7	8.9 ± 2.5	0.31
Donor-specific antibodies, no. (%)	2 (15)	6 (12)	0.67
Follow-up, median (range), yr	2.2 (0.1–6.7)	2.7 (0.3–6.3)	—

BMI = body mass index; CIT = cold ischemia time; DCD = donation after cardiac death; NDD = neurologic determination of death; PRA = panel reactive antibodies; SD = standard deviation; WIT = warm ischemia time.

*Unless indicated otherwise.

Table 2. Postoperative complications of simultaneous pancreas and kidney transplants from DCD and NDD donors

	Group; mean ± SD*		
Complication	DCD (*n* = 13)	NDD (*n* = 68)	*p* value
Units of RBCs, mean ± SE	4.2 ± 1.2	3.4 ± 0.5	0.61
Kidney DGF, %	38	10	0.027
No. of HD sessions in DGF	2.6 ± 0.68	2.6 ± 0.93	> 0.99
No. of pancreas graft thrombosis and relaparotomy	0	7	0.50

DCD = donation after cardiac death; DGF = delayed graft function; HD = hemodialysis; NDD = neurologic determination of death; RBC = red blood cells; SD = standard deviation; SE = standard error.
*Unless indicated otherwise.

Table 3. Immunosuppression of simultaneous pancreas and kidney transplants

	Group; mean ± SD or no. (%)		
Immunosuppression	DCD (*n* = 13)	NDD (*n* = 68)	*p* value
Total thymoglobin dose, mg/kg	6.2 ± 0.6	5.9 ± 0.3	0.66
Tapered off methylprednisone	3 (23)	16 (33)	0.74

DCD = donation after cardiac death; NDD = neurologic determination of death; SD = standard deviation.

number of hemodialysis sessions required by patients in either group who experienced DGF was not found to be statistically different. There were also 7 cases of pancreas graft thrombosis requiring repeat laparotomy and graft removal in the NDD group. No cases of pancreas graft thrombosis were observed in the DCD group; however, this difference was not found to be significant ($p = 0.50$).

Immunosuppression

Table 3 lists the immunosuppression doses received by both the DCD and NDD groups. The mean total thymoglobulin doses and the number of patients who could be tapered off methylprednisone were not found to be statistically different between the groups.

Serum biochemistry

We compared the serum biochemistry of patients in the DCD and NDD groups up to 4 years after SPK transplant (Fig. 2). The mean estimated glomerular filtration rate (eGFR) was significantly higher on postoperative days 7 and 14 in the NDD group than in the DCD group. However, from postoperative day 30 to 4 years after transplant, there was no significant difference in mean eGFR

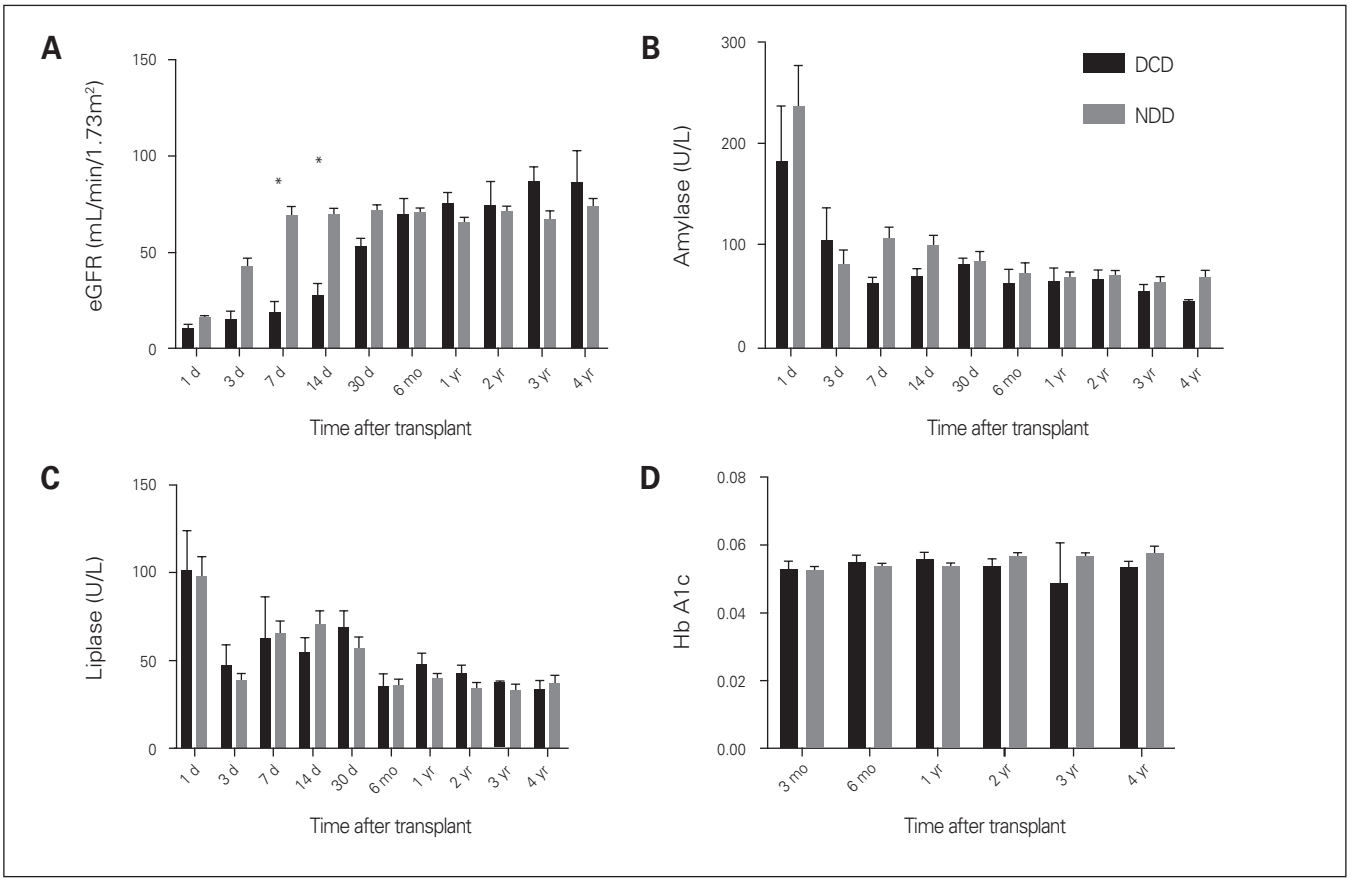

Fig. 2. Serum biochemistry after simultaneous pancreas and kidney transplant from donation after cardiac death (DCD) and neurologic determination of death (NDD) donors. *Statistically significant differences. eGFR = estimated glomerular filtration rate.

between the groups. There were no significant differences in mean serum amylase, lipase or HbA1c up to 4 years after transplant between the groups.

Patient and graft survivals

Patient and graft survival were followed up to 6 years after SPK transplant (Fig. 3). No significant differences in patient survival were found between the NDD and DCD groups. There was no significant difference in kidney graft survival between the NDD and DCD groups; however, 1 patient in the NDD group underwent severe acute rejection at 2 years after transplant, resulting in the loss of renal graft function. There were 7 events of acute pancreas graft thrombosis requiring relaparotomy and pancreatectomy in the NDD group. There were no pancreas thrombosis events in the DCD group, and no patient from the DCD group required insulin at any point after transplant. Overall, there was no significant difference in pancreas graft survival between the NDD and DCD groups.

Discussion

Our study represents, to our knowledge, the first account from a Canadian institution with regards to the use of grafts from DCD donors in SPK transplants. In select patients with type 1 diabetes and end-stage renal disease, SPK transplant has become an excellent treatment option. Traditionally, grafts are derived from NDD donors owing to concerns of increased graft damage during the low perfusion state experienced with DCD grafts. However, the increasing discrepancy between the demand for grafts and their relative scarcity has led to the increased use of DCD donor grafts in SPK transplants worldwide, and in October 2008 we performed the first DCD SPK transplant in Canada. With the novel use of DCD donor grafts, it was of vital importance to assess whether outcomes of DCD SPK transplants were comparable to those of transplants making use of NDD grafts as a measure of quality.

Following SPK transplant, there was a significantly higher rate of DGF in the DCD group than the NDD group (Table 1). This higher rate of DGF was associated

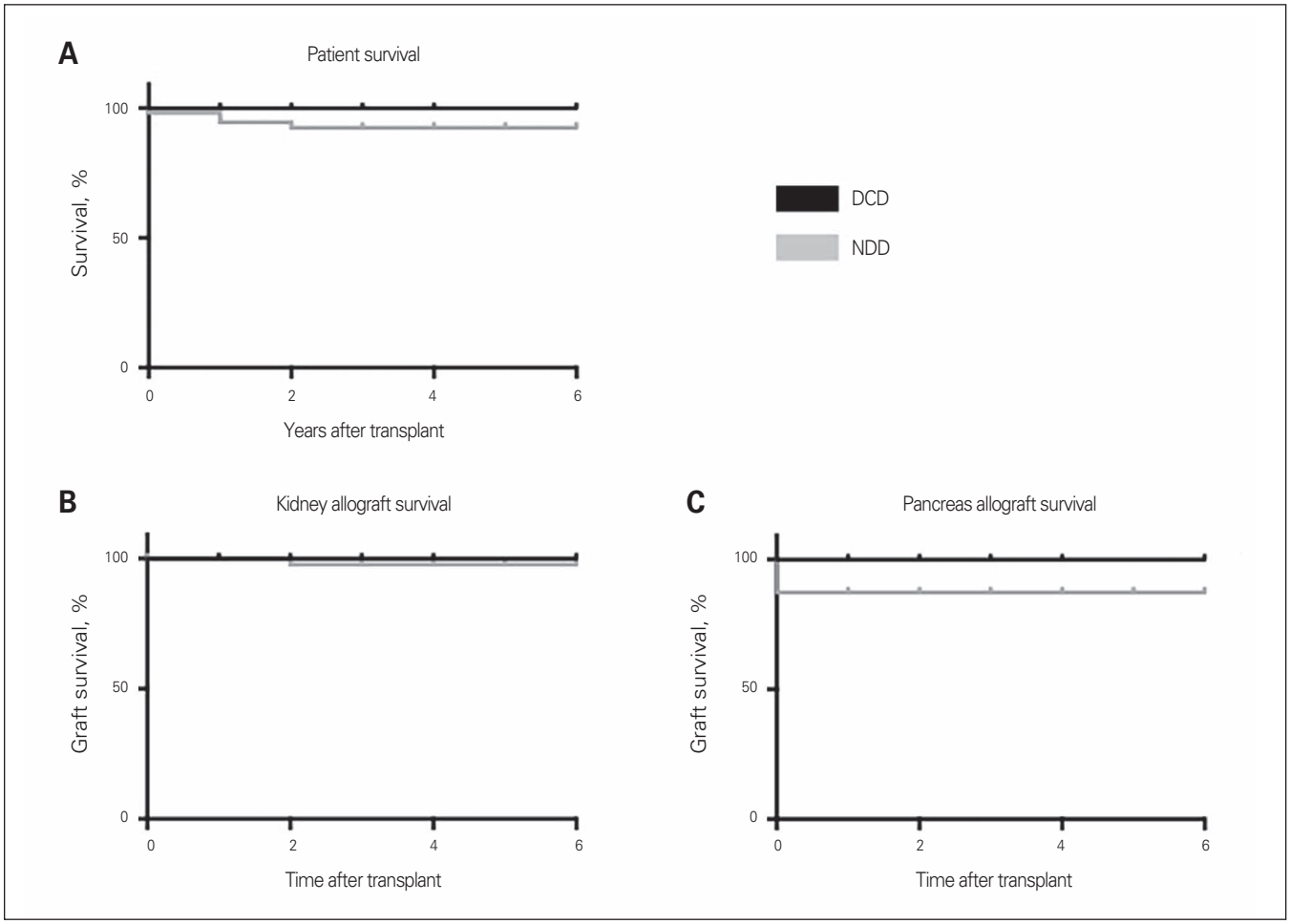

Fig. 3. Kaplan–Meier survival analysis of **(A)** patient survival, **(B)** kidney allograft survival and **(C)** pancreas allograft survival up to 6 years after simultaneous pancreas and kidney transplant from donation after cardiac death (DCD) and neurologic determination of death (NDD) donors. No significant differences were seen between groups for patient, kidney or pancreas graft survival.

with a lower eGFR in the DCD than the NDD group up to 14 days after transplant (Fig. 2A). However, by 30 days, the mean eGFR of the DCD group was comparable to that of the NDD group. Both renal function and survival were similar between the DCD and NDD groups up to 4 years after transplant (Fig. 3B). These results support earlier work by D'Alessandro and colleagues,[15] who found similar patterns when comparing DCD to NDD SPK transplants.

Although no differences were seen with regards to long-term pancreas survival, 7 patients in the NDD group had graft thrombosis and failure. These events primarily occurred within the first 48 hours after transplant. An explanation for the difference in graft thrombosis may be associated with institution changes to the postoperative management of patients receiving SPK transplants. Beginning in July 2009, all patients receiving SPK transplants were placed on a low-dose intravenous heparin infusion in the immediate postoperative period in order to prevent pancreas graft thrombosis. It is important to note that none of the 7 patients with a pancreas graft thrombosis received a heparin infusion as part of this protocol, and following this change, no events of pancreas graft thrombosis occurred, regardless of donor status.

Limitations

The main limitation of our study is the relatively small number of DCD SPK transplants available for our analysis. In addition, donors were relatively young in both groups, and warm ischemic time (WIT) was relatively low in the DCD group. When our institution initially began performing DCD SPK transplants, 30 minutes of WIT was considered the upper threshold owing to concerns of adverse outcomes on graft survival and function. However, our experience allowed us to increase our threshold to 60 minutes of WIT owing to relatively low rates of DGF and pancreas graft thrombosis. The upper limits of WIT for pancreas transplants is not known, but our findings of excellent immediate and long-term pancreatic graft function and absence of thrombosis and pancreatitis (amylase/lipase rise) supports assessment of a longer WIT in the future.

Fernandez and colleagues[16] were the first to report on the long-term outcomes of DCD grafts in SPK transplants. Their study included 37 DCD SPK transplants and supported their use, finding them to be equivalent to NDD grafts in the long term. Our study from a single Canadian tertiary care centre has been able to show similar long-term outcomes and strengthens the current evidence for use of DCD grafts in SPK transplants.

Conclusion

To our knowledge, our study is the first in Canada to support the use of DCD grafts in SPK transplants. We have shown that outcomes of SPK grafts from DCD and NDD donors are comparable in long-term follow-up. As the demand for organs continues to outpace their availability, we have initial evidence that supports the expansion of donor criteria to include DCD grafts in SPK transplantation.

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Competing interests: None declared.

Contributors: V. McAlister and P. Luke designed the study. P. Anderson, S. Aquil and K. McLean acquired the data, which P. Anderson, V. McAlister, A. Sener and P. Luke analyzed. P. Anderson and P. Luke wrote the article, which all authors reviewed and approved for publication.

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