Transplant International

ORIGINAL ARTICLE

Donor cardiac arrest and cardiopulmonary resuscitation: impact on outcomes after simultaneous pancreas–kidney transplantation – a retrospective study

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Local ethics committee: No. 1069/2019.

SUMMARY

Donor cardiac arrest and cardiopulmonary resuscitation (CACPR) has been considered critically because of concerns over hypoperfusion and mechanical trauma to the donor organs. We retrospectively analyzed 371 first simultaneous pancreas–kidney transplants performed at the Medical University of Innsbruck between 1997 and 2017. We evaluated short- and long-term outcomes from recipients of organs from donors with and without a history of CACPR. A total of 63 recipients received a pancreas and kidney graft from a CACPR donor. At 1, and 5-years, patient survival was similar with 98.3%, and 96.5% in the CACPR and 97.0%, and 90.2% in the non-CACPR group (log rank $P = 0.652$). Death-censored pancreas graft survival was superior in the CACPR group with 98.3%, and 91.4% compared to 86.3%, and 77.4% (log rank $P = 0.028$) in the non-CACPR group, which remained statistically significant even after adjustment [aHR 0.49 (95% CI 0.24–0.98), $P = 0.044$]. Similar relative risks for postoperative complications Clavien Dindo > 3a, pancreatitis, abscess, immunologic complications, delayed pancreas graft function, and relative length of stay were observed for both groups. Donors with a history of CACPR are, in the current practice, safe for transplantation. Stringent donor selection and short CPR durations may allow for outcomes surpassing those of donors without CACPR.

Transplant International 2020; 33: 657–666

Key words
cardiac arrest, cardiopulmonary resuscitation, kidney transplantation, pancreatitis, simultaneous pancreas

Received: 14 November 2019; Revision requested: 12 December 2019; Accepted: 3 February 2020; Published online: 27 February 2020

Introduction

Simultaneous pancreas-kidney transplantation (SPK) is the standard of care for patients with type 1 diabetes mellitus (T1DM) and end-stage renal disease. In this setting, SPK provides a significant survival benefit compared to deceased donor kidney transplantation alone, with estimated 5-year patient survivals of 81% and 71% and 8-year patient survivals of 72% and 55%, respectively [1]. Despite these encouraging outcomes, pancreas

doi:10.1111/tri.13591

transplantation is associated with the highest risk of postoperative complications of all abdominal organ transplants [2,3].

Acute graft pancreatitis (AGP) is one of these complications, occurring in 35–38% of cases within 3 months after pancreas transplantation. As AGP is associated with 1-year graft loss rates of 78–91%, prevention of its occurrence is crucial [4]. Several donor [2,5,6], procurement [2,5,7–14], and recipient [15–22] risk factors are associated with a higher frequency of post-transplant AGP.

Overall, numbers of pancreas transplantation are declining. In 2017, only 167 pancreas transplants were performed in the Eurotransplant (ET) region. Despite this trend, more patients are waiting for a pancreas graft than are being transplanted, with 468 patients actively listed at the end of 2017 in ET. Interestingly, in the same year, 857 pancreas grafts from organ donors were offered; however, only 19% were eventually transplanted, indicating an extremely low acceptance rate [23].

Because of the high associated morbidity and mortality in pancreas recipients of suboptimal donor organs, selection criteria in pancreas transplantation are more restrictive than in other abdominal organs, and macroscopic features of the pancreas graft are crucial in determining its transplantablility [24]. Donors with a history of cardiac arrest and cardiopulmonary resuscitation (CACPR), for instance, have historically been avoided because of concern for organ hypoperfusion and the risk of mechanical irritation with subsequent AGP [25,26].

In this manuscript, we evaluate the impact of donor CACPR on the outcome after pancreas transplantation in SPK recipients.

Patients and methods

Study population

The study was approved by the local ethics committee (No. 1069/2019). We retrospectively analyzed 375 consecutively performed first SPK performed at the Medical University of Innsbruck between January 1997 and December 2017. Donor characteristics (including donor cardiac arrest and cardiac arrest time) were obtained from the ET donor registration platform, and perioperative data, recipient characteristics, and follow-up data were retrospectively collected from medical records (electronic patient file, archived discharge, and follow-up letters). After exclusion of four patients with missing information on donor CACPR, 371 patients were included in the final analysis.

Surgical procedure

The SPK transplantations were carried out according to standard techniques as previously published [27–30]. Full-size pancreas grafts were procured in a no-touch technique after perfusion with University of Wisconsin or histidine–tryptophan–ketoglutarate solution. Briefly, the renal artery and vein were anastomosed to the left common iliac vessels, the pancreas graft was transplanted intraperitoneally into the right middle to lower quadrant. In routine cases, the portal vein was anastomosed to the inferior vena cava and the reconstructed Y-graft, using the donor iliac bifurcation, to the right common iliac artery. In most cases, a duodenojejunostomy was performed to the upper jejunum (40 cm distally to the ligament of Treitz) for exocrine drainage; however, in <3% of cases a bladder drainage or a duct occlusion using Ethibloc (Ethicon, Norderstedt, Germany) was performed. All patients received induction therapy with antithymocyte globulin (8 mg/kg; standard agent) or alemtuzumab (30 mg; as part of prospective study) [31] and methylprednisolone (500 mg) intraoperatively. Standard maintenance immunosuppression consisted of tacrolimus (trough level: initial 12–14 ng/ml, 8 ng/ml at 9 months, and 4–6 ng/ml after 12 months), or cyclosporine A (trough level: initial 180–200 ng/ml, 100–130 ng/ml at 9 months, and 80–100 ng/ml at 12 months) prednisone (postoperatively tapered to 5 mg/day), and mycophenolic acid (2000 mg/day). Perioperative antibiotics, antifungal, and antiviral treatment consisted of piperacillin/tazobactam, ciprofloxacin, fluconazole, trimethoprim–sulfamethoxazole, and ganciclovir or valganciclovir. Postoperatively, all patients received initially intravenous (PTT goal: 45–50 s) and later subcutaneous heparin (body-weight adapted). Long-term anticoagulation consisted of daily acetyl salicylic acid (50 or 100 mg/day) in most patients related to pre-existing conditions such as coronary artery and/or peripheral vascular disease.

Definitions

Donors with a history of cardiac arrest (CA) and cardiopulmonary resuscitation (CPR) are referred to as "CACPR" donors, in contrast to donors without a history of CA and CPR are referred to as non-CACPR. Follow-up time was calculated from date of transplanta-

tion until date of last known clinical status or death. Immunologic complications were clinically or histologically suspected/proven and treated rejection of the kidney or pancreas graft. Postoperative complications were classified according to the Clavien-Dindo criteria [32,33]. Delayed pancreatic graft function (DPGF) was defined as the transient need for exogenous insulin in the immediate post-transplant period, and delayed kidney graft function (DKGF) was defined as the need for more than two rounds of dialysis after SPK. The pancreas donor risk index (PDRI) was calculated according to the publication by Axelrod et al. [34].

Outcomes

Primary outcome parameters were patient survival as well as all- and death-censored pancreas and kidney graft survival. All- and death-censored graft survival was defined as functioning graft without the need for exogenous insulin for pancreas grafts (dcPGS) and without the need for dialysis for kidney grafts (dcKGS), including and excluding graft loss as a result of patient death, respectively.

Secondary outcome parameters included the occurrence of immunologic complications, infections, pancreatitis, postoperative hemorrhage, severe postoperative complications Clavien-Dindo > 3a, delayed pancreas and kidney function, and relative length of hospital stay.

Statistical analysis

We used chi-squared tests (categorical variables) and rank-sum tests (continuous variables) to compare donor and recipient demographics and clinical characteristics. Patient, all-, and death-censored pancreas and kidney graft survival were estimated by the Kaplan–Meier method and compared by log-rank test. Patient and graft survival between recipients of CACPR and non-CACPR donor organs were compared by Cox proportional hazard regression adjusted for PDRI, recipient age at transplant, donor creatinine level, donor cause of death, and year of transplantation. The relative risk (RR) of secondary outcomes between the two groups was estimated by log-binomial regression adjusted for PDRI, recipient age at transplant, donor creatinine level, donor cause of death, and year of transplantation. All tests were two-sided, and a p-value of 0.05 was considered statistically significant. Confidence intervals are reported as per the method of Louis and Zeger [35]. All analyses were performed using Stata 15 for Linux (College Station, TX, USA).

Results

Study population

Of the 371 SPK recipients, 63 (17%) of recipients received a pancreas and kidney graft from a CACPR and 308 (83%) from a non-CACPR donor (Table 1). CACPR donors displayed higher creatinine levels [0.92 (IQR: 0.7–1.14) vs. 0.8 (IQR: 0.64–1) mg/dl; $P = 0.014$] and significant differences in causes of death (CVA: 15.9% vs. 26.3%; trauma: 46% vs. 57.8%; and other: 38.1% vs. 15.9%; $P < 0.001$). Though not significant, CACPR donors showed trends toward younger age [median 26 (IQR: 20–37) vs. 31 (IQR: 22–41); $P = 0.095$] and lower PDRI [median 1.01 (IQR: 0.85–1.26) vs. 1.11 (IQR: 0.85–1.42); $P = 0.069$] compared to non-CACPR donors. CACPR and non-CACPR donors were equally likely to be male (71.4% vs. 63.6%; $P = 0.210$), displayed similar amylase levels before organ procurement [median 73 U/l (IQR: 38–128) vs. 79 U/l (IQR: 41–136); $P = 0.625$], and were equally likely to be CMV positive (57.2% vs. 48.4%; $P = 0.258$). Compared with recipients of non-CACPR donors, recipients of CACPR donors were transplanted significantly later [median year of transplantation 2009 (IQR: 2003–2015) vs. 2004 (IQR: 2000–2009); $P < 0.001$]. They had a similar age [median 43 (IQR: 38–51) vs. 43 (IQR: 35–50); $P = 0.278$], BMI [median 24 (IQR: 21–26) vs. 23 (IQR: 21–25); $P = 0.578$], management of endocrine (systemic 95.2% vs. 92.2%, portal 4.8% vs. 7.8%; $P = 0.290$) and exocrine drainage (enteric 100% vs. 97.4%, vesical 0% vs. 2.6%; $P = 0.361$), wait-list time [median 5 months (IQR: 2–11) vs. 5 months (IQR: 2–9); $P = 0.995$], and they were equally likely to be male (65.1% vs. 64.6%; $P = 0.892$) and CMV positive (47.6% vs. 50.7%; $P = 0.480$). No differences were seen in panel reactive antibodies (PRA) levels > 20% (4.8% vs. 4.2%; $P = 0.435$) and creatinine levels at discharge [1.2 (IQR: 1.0–1.5) vs. 1.1 (IQR: 0.9–1.4); $P = 0.431$]. (Table 1).

Patient survival

Ninety-day, and 1-, 5-, and 10-year patient survival was 100%, 98.3%, 96,5%, and 81.4% in the CACPR recipients compared to 99.0%, 97.1%, 90.3%, and 79.4% (log rank $P = 0.652$) in the non-CACPR group (Fig. 1, Table 2). After adjustment for donor and recipient factors, the patient survival was still similar comparing both groups [aHR 0.84 (95% CI 0.43–1.65); $P = 0.622$; Table 3].

Table 1. Donor and recipient demographics.

	CACPR	non-CACPR	*P*-value
Number	63 (17%)	308(83%)	
Donor CPR duration (minutes), median (IQR)	10 (5, 15)	–	
Donor age, median (IQR)	26 (20, 37)	31 (22, 41)	0.095
Donor male	71.4%	63.6%	0.210
Donor creatinine (mg/dl), median (IQR)	0.92 (0.70, 1.14)	0.80 (0.64, 1.00)	0.014
Donor BMI, median (IQR)	23 (22,25)	23 (22,25)	0.411
Donor amylase level (U/l), median (IQR)	73 (38, 128)	79 (41, 136)	0.625
PDRI, median (IQR)	1.01 (0.85, 1.26)	1.11 (0.85, 1.42)	0.069
Donor CMV+	57.2%	48.4%	0.258
Donor blood type			0.574
A	34.9%	41.2%	
AB	1.6%	3.3%	
B	12.7%	14.9%	
O	50.8%	40.6%	
Donor cause of death			<0.001
Other	38.1%	15.9%	
CVA	15.9%	26.3%	
Trauma	46%	57.8%	
Recipient age (years), median (IQR)	43 (38, 51)	43 (35, 50)	0.278
Recipient BMI	24 (21, 26)	23 (21, 25)	0.578
Recipient CMV+	47.6%	50.7%	0.480
Endocrine drainage			0.290
Systemic	95.2%	92.2%	
Portal	4.8%	7.8%	
Exocrine drainage			0.361
Enteric	100%	97.4%	
Vesical	0%	2.6%	
PRA			0.435
0%	57.1%	75.7%	
≤20%	0%	2.9%	
>20%	4.8%	4.2%	
Missing	38.1%	17.2%	
Recipient male	65.1%	64.6%	0.892
Recipient blood type			0.334
A	30.2%	40.3%	
AB	7.9%	5.5%	
B	18.5%	14.9%	
O	44.4%	39.3%	
Recipient wait time (months), median (IQR)	5(2,11)	5(2,9)	0.995
Recipient creatinine level at discharge	1.20 (1.00, 1.50)	1.10 (0.90, 1.40)	0.431
Transplant year, median (IQR)	2009 (2003, 2015)	2004 (2000, 2009)	<0.001
Cause of pancreas graft loss			0.108
Thrombosis	3.1%	5.1%	
Acute rejection	3.1%	4.2%	
Chronic rejection	7.8%	16.7%	
Infection	0.0%	4.5%	
Hemorrhage	0.0%	1.6%	
Death with functioning graft	10.9%	13.5%	
Other	1.6%	1.9%	

All-cause and death-censored pancreas and kidney graft survival

Patients who received transplants from a donor with a history of CACPR displayed a superior dcPGS at 90 days, and 1, 5, and 10 years with 100%, 98.3%, 91.4%, and 80.0% survival compared to 89.4%, 86.3%, 77.4%, and 67.0% in the non-CACPR group (log rank $P = 0.028$) (Fig. 2a, Table 2). All-censored pancreas graft survival (AcPGS), in contrast, was similar between

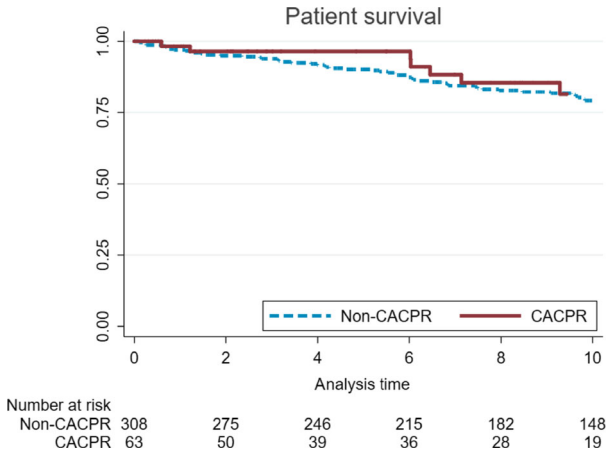

Figure 1 Patient survival comparing the CACPR and non-CACPR groups. Similar survival was seen in both groups (log rank $P = 0.652$). CACPR, cardiac arrest and cardiopulmonary resuscitation.

Table 3. Adjusted hazard ratio for patient, death-censored and all-censored pancreas and kidney graft survival comparing the CACPR and non-CACPR groups.

	aHR*	95% CI	*P*-value
Pancreas			
DCGF	0.49	0.24–0.98	0.044
ACGF	0.63	0.37–1.08	0.092
Kidney			
DCGF	0.50	0.21–1.16	0.107
ACGF	0.62	0.36–1.11	0.107
Patient			
Death	0.84	0.43–1.65	0.622

*Model adjusted for PDRI, recipients age at transplant, donor creatinine level, donor cause of death, transplant year

the groups, with 100%, 96.6%, 87.9%, and 65.2% survival at 90 days, and 1, 5, and 10 years in the CACPR group and 89.9%, 85.5%, 74.6%, and 58.7% survival in the non-CACPR group (log rank $P = 0.091$) (Fig. 2b, Table 2). Ninety-day, and 1-, 5-, and 10-year dcKGS survival was 100%, 100%, 97.6%, and 87.2% in the CACPR group and 98.1%, 96.4%, 87.2%, and 77.4% in the non-CACPR group (log rank $P = 0.087$) (Fig. 3a, Table 2). In the CACPR group, all-censored kidney graft survival (acKGS) was 100%, 98.2%, 94.1%, and 76.6%,

Table 2. Patient, death-censored and all-censored pancreas and kidney graft survival comparing recipients CACPR ($n = 63$) and non-CACPR donor organs ($n = 308$) transplanted between 1997 and 2017 at the Medical University of Innsbruck.

	CACPR	95% CI	Non-CACPR	95% CI
Pancreas death-censored graft survival				
90 day	100%	-	89.4%	85.4–92.3%
1 year	98.3%	88.9–99.8%	86.3%	82.1–89.8%
5 year	91.4%	78.2–96.8%	77.4%	72.4–82.0%
10 year	80.0%	59.1–88.6%	67.0%	61.3–72.7%
Pancreas all-cause graft survival				
90 day	100%	–	89.9%	85.9–92.8%
1 year	96.6%	87.4–99.2%	85.5%	81.2–89.1%
5 year	87.9%	75.7–94.7%	74.6%	69.5–79.5%
10 year	65.2%	47.9–79.6%	58.7%	52.9–64.8%
Kidney death-censored graft survival				
90 day	100%	-	98.1%	95.7–99.1%
1 year	100%	-	96.4%	93.6–98.0%
5 year	97.6%	84.3–99.7%	87.2%	82.7–90.7%
10 year	87.2%	69.7–95.3%	77.4%	71.8–82.5%
Kidney all-cause graft survival				
90 day	100%	–	97.1%	94.5–98.5%
1 year	98.2%	88.6–99.8%	94.1%	90.9–96.3%
5 year	94.1%	82.9–98.1%	81.6%	76.4–85.4%
10 year	76.6%	60.1–87.7%	65.2%	59.4–71.1%
Patient survival				
90 day	100%	–	99.0%	97.0–99.7%
1 year	98.3%	88.6–99.8%	97.1%	94.4–98.5%
5 year	96.5%	86.8–99.1%	90.3%	86.3–93.2%
10 year	81.4%	64.8–91.3%	79.4%	73.8–83.9%

and in the non-CACPR group 97.1%, 94.1%, 81.6%, and 65.2% (log rank $P = 0.124$) (Fig. 3b, Table 2). After adjustment for various donor and recipient factors (Table 3), death-censored pancreas survival was still superior between the CACPR and non-CACPR groups [dcPGS: aHR 0.49 (95% CI 0.24–0.98), $P = 0.044$]. All-cause pancreas as well as all-cause and death-censored kidney graft survival remained similar in both groups [acPGS: aHR 0.63 (95% CI 0.37–1.08), $P = 0.092$; dcKGS: aHR 0.50 (95% CI 0.21–1.16), $P = 0.107$; acKGS: aHR 0.62 (95% CI 0.36–1.11), $P = 0.107$].

Postoperative complications

For recipients of organs from a CACPR and non-CACPR donor, similar complications were recorded after transplantation (Table 4). Both groups had a similar rate of infections, 73% vs. 62%; aRR 1.1 (95% CI 0.92–1.33); $P = 0.302$], abscess, 10.9% vs. 9.8%; aRR 1.57 (95% CI 0.73–3.38); $P = 0.252$], graft pancreatitis [5% vs. 8%; aRR 0.74 (95% CI 0.23–2.38); $P = 0.619$], thrombosis [3.1% vs. 5.1%; aRR 0.78 (95% CI 0.19–3.25); $P = 0.729$], hemorrhage [17% vs. 19%; aRR 0.72 (95% CI 0.39–1.3); $P = 0.276$], PDGF [34% vs. 31%; aRR 0.93 (95% CI 0.69–1.26); $P = 0.658$], and KDGF [40% vs. 56%; aRR 0.85 (95% CI 0.55–1.33); $P = 0.478$]. Though not statistically significant, there was a trend toward fewer overall immunologic complications in the CACPR group [13% vs. 24%; aRR 0.52 (95% CI 0.26–1.03); $P = 0.059$]; however, similar rates of treated pancreas [9.8% vs. 15.1%; aRR 0.59 (95% CI 0.25–1.35); $P = 0.210$] and kidney graft rejections [4.7% vs. 8.9%; aRR 0.62 (95% CI 0.18–2.08); $P = 0.436$] were recorded in both groups. In addition, a similar length of hospital stay [mean, 23 (18, 30) vs. 26 (20, 34); aRR 0.95 (95% CI 0.9–1.0); $P = 0.074$] and comparable rates of Clavien-Dindo > 3a complications [30% vs. 38%; aRR 0.77 (95% CI 0.51–1.17); $P = 0.218$] were seen in the CACPR and non-CACPR groups.

CPR duration and impact on patient and graft survival

The grafts from donors who received CPR for <10 min ($n = 35$) had a 90-day, and 1-, 5-, and 10-year recipient survival of 100%, 100%, 96.8%, and 76.9%, and those with >10 min of CPR ($n = 20$) had a similar survival rate with 100%, 94.7%, 94.7%, and 94.7% (log rank $P = 0.617$). In terms of graft survival, similar results were observed regardless of CPR duration. For the pancreas grafts, 90-day, and 1-, 5-, and 10-year dcPGS was 100%, 97.0%, 85.3%, and 79.9% for the CACPR < 10 min group and 100%, 100%, 100%, and 76.2% for the CACPR group >10 min (log rank $P = 0.116$). DcKGS was 100%, 100%, 95.8%, and 89% and 100%, 100%,100%, and 78.8% in the <10 min and >10 min CACPR groups at 90 days, and 1, 5, and 10 years, respectively (log rank $P = 0.389$). After adjustment for donor and recipient factors, no differences could be detected in patient, all-cause and death-censored pancreas, or kidney graft survival for the CACPR < 10 or >10 min compared to the non-CACPR group (Table 5).

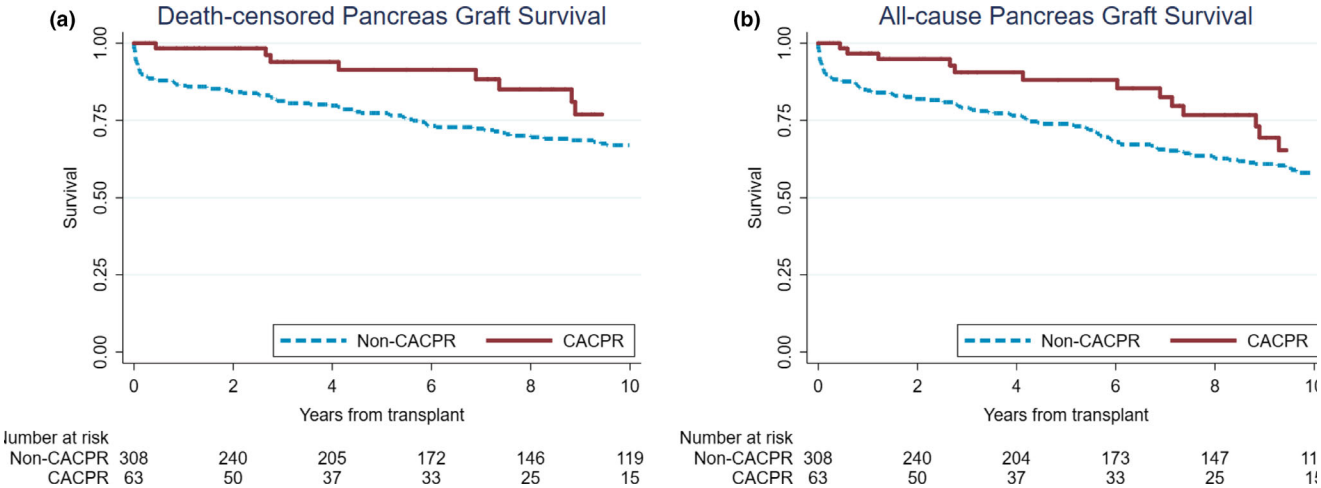

Figure 2 Death-censored and all-censored pancreas graft survival. Death-censored pancreas graft survival was superior in the CACPR compared with the non-CACRP group (log rank $P = 0.028$). All-cause pancreas graft survival, however, was similar between the two groups (log rank $P = 0.091$). CACPR, cardiac arrest and cardiopulmonary resuscitation.

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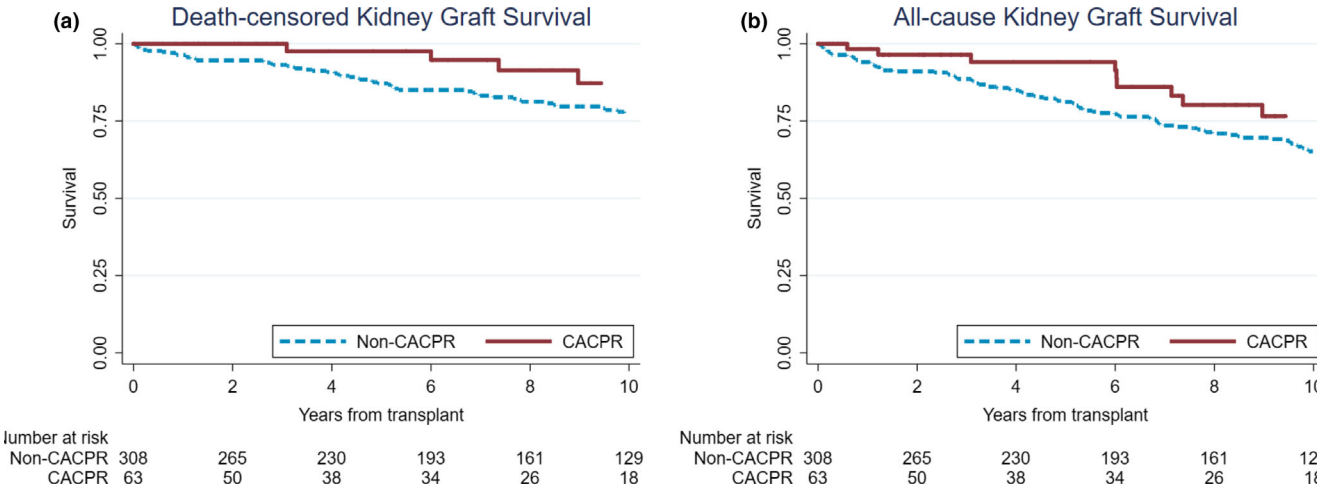

Figure 3 Death-censored and acKGS. Kidneys from CACPR donors had similar survival to those from non-CACPR donors (dcKGS log rank $P = 0.087$; acKGS log rank $P = 0.124$). CACPR, cardiac arrest and cardiopulmonary resuscitation; dcKGS, death-censored kidney graft survival; and acKGS, acKGS.

Table 4. Relative risk of postoperative complications, delayed graft function, and length of hospital stay.

	RR*	95% CI	*P*-value
Overall immunologic complications	0.52	0.26–1.03	0.059
Rejection pancreas	0.59	0.25–1.35	0.210
Rejection kidney	0.62	0.18–2.08	0.436
Infection	1.10	0.92–1.33	0.302
Abscess	1.57	0.73–3.38	0.252
Pancreatitis	0.74	0.23–2.38	0.619
Thrombosis	0.78	0.19–3.25	0.729
Hemorrhage	0.72	0.39–1.30	0.276
Clavien Dindo >3a	0.77	0.51–1.17	0.218
Pancreas delayed graft function	0.93	0.69–1.26	0.658
Kidney delayed graft function	0.85	0.55–1.33	0.478
Relative length of stay	0.95	0.90–1.00	0.074

*Model adjusted for PDRI, recipients age at transplant, donor creatinine level, donor cause of death, transplant year.

Discussion

Donor CA and CPR has been regarded critically in the past due to the concern for hypoperfusion of and subsequent damage to abdominal organs [25,26]. The mechanical impact of chest compressions has, especially in the setting of pancreas transplantation, the potential to induce graft damage and pancreatitis, both of which contribute to high morbidity and mortality after transplantation [2,4,5]. Despite these concerns, our data and other published reports indicate that grafts from donors with a history of CACPR lead to similarly good results after SPK.

In our cohort, excellent 1-, 5-, and 10-year patient survival rates of 98.3%, 96.5%, and 81.4% for the CACPR and 97.0%, 90.2%, and 79.2% for the non-CACPR group were seen (Fig. 1, Table 2), which are similar to previously reported 1- and 5-year patient survivals of 97% and 88.4% in pancreas transplantation [36]. Our data indicated that dcPGS was superior in the CACPR group compared with the non-CACPR group with 100%, 98.3%, 91.4%, and 80.0% dcPGS in CACPR recipients and 89.4%, 86.3%, 77.4%, and 67.0% dcPGS in non-CACPR at 90 days, and 1, 5, and 10 years (log rank $P = 0.028$, Table 2). DcPGS remained superior after adjustment for PDRI, recipients age at transplant, donor creatinine level, donor cause of death, and transplant year (Table 3). Yet, similar acPGS (Table 2, and 3) and comparable aHRs for dcPGS were seen after division into short (0–10 min) and long (>10 min) CPR durations (Table 5). Thus far, two single-center studies investigated donor CACPR in the setting of pancreas transplantation

Table 5. Adjusted hazard ratio for patient, all-cause and death-censored pancreas and kidney graft survival according to duration of cardiopulmonary resuscitation comparing the CACPR (0–10 min: $n = 35$; >10 min: $n = 20$) and non-CACPR groups.

	0–10 min			>10 min		
	aHR*	95% CI	*P*-value	aHR*	95% CI	*P*-value
Patient						
Death	1.05	0.96–1.15	0.251	0.94	0.81–1.08	0.385
Pancreas						
ACGS	1	0.93–1.08	0.956	0.95	0.87–1.05	0.329
DCGS	0.95	0.85–1.05	0.299	0.97	0.86–1.09	0.611
Kidney						
ACGS	0.99	0.91–1.08	0.836	0.98	0.89–1.07	0.648
DCGS	0.96	0.86–1.07	0.445	1	0.91–1.10	0.970

*Model adjusted for PDRI, recipients age at transplant, donor creatinine level, donor cause of death, transplant year

[25,26]. Both studies showed, similar to our findings, comparable pancreas graft survival rates between the CACPR and non-CACPR groups. A group from Indiana University School of Medicine [25] retrospectively analyzed their 606 pancreas transplants performed between 2003 and 2016 and compared 430 (71%) non-CACPR donors to 176 (29%) donors with preprocurement CA. As indicated, no differences were seen in 1-year pancreas graft survival with 97% in the CACPR compared to 92% in the non-CACPR group. Recently, a Spanish group retrospectively analyzed 342 pancreas transplants performed between 2000 and 2016. Of those, a total of 49 (14.3%) received organs from donors with a history of a previous CA. Estimated 1- and 5-year pancreas graft survival was 90% and 78% for the CACPR and 87% and 81% for the non-CACPR group ($P = 0.6$). For dcKGS, survival rates were not significantly different between the two groups with 100%, 97.6%, and 87.2% survival at 1, 5, and 10 years in the CACPR group compared to 96.4%, 87.2%, and 65.2% survivals in the non-CACPR group (Table 2, Fig. 3). This trend is still seen after adjustment for different donor and recipient factors (Table 3), and thus is comparable to published reports [25,26].

Similar to the survival data, no differences in postoperative adverse outcomes were seen in our analysis (Table 4). Both groups had a low rate of pancreatitis, with 5% in the CACPR and 8% in the non-CACPR group. In our cohort, hospital stay was a median of 23 and 26 days for the CACPR and non-CACPR groups, respectively, reflecting both that there was no difference in length of inpatient treatment as well as our rather conservative discharge policy for those patients especially when comparing to reports from the United States [25] and Spain [26] where hospital length of stay in CACPR and non-CACPR SPK recipients were 7 and 7 days, and 13 and 15 days, respectively. In addition, our analysis showed a comparable rate of postoperative complications Clavien Dindo >3a (30% vs. 38%, $P = 0.218$) between the two groups, which goes in line with the overall lower complication rate reported by the Spanish group with 17.4% and 24.3% of Clavien Dindo >3a complications ($P = 0.53$) [26]. Taken together, these data indicate that under current acceptance policies and assessment strategies, similar risks of postoperative complication are seen in both donor groups.

To further investigate the impact of CPR length, we stratified our CACPR cohort at the median CPR duration of 10 min. Both short and prolonged durations of CPR resulted in similar patient and graft survival despite adjusting for PDRI, recipients age at transplant, donor creatinine level, donor cause of death, and transplant year in our study population (Table 5). These results are in line with the findings of the Indiana Group [25]; however, cutoff times for CPR durations for their subgroup analysis were with 20 and 40 min, substantially longer than what we report in this manuscript [25]. The only group that did find differences after stratification was the Spanish group [26]. When splitting their cohort at 15 min of CPR duration, they saw a significantly inferior dcPGS as well as a more than fivefold increased risk of early graft failure [HR 5.8 (95% CI 1.82–18.56); $P = 0.003$] in the >15 min CPR group.

Our report is unique in that it suggests a trend toward better long-term outcomes compared to non-CACPR donor organs after adjustment for PDRI, recipients age at transplant, donor creatinine level, donor cause of death, and transplant year. This might be attributed to a stringent donor selection that is performed at our center,

especially in the setting of donor CACPR, that is reflected by a trend toward lower PDRI (1.01 vs. 1.11), lower donor age (median 26 vs. 31 years), and similarly low donor preprocurement amylase level (median 73 vs 79 U/l) in the CACPR compared with non-CACPR group. Also, median CPR time was 10 min (IQR 5–15), a duration lower than reported elsewhere [25,26].

Though no definite causality can be attributed, there are a few possible reasons that our analysis found equal outcomes in both groups with a trend toward superiority in the CACPR group. One reason might be the thorough investigation of the graft in the procurement. In the setting of pancreas transplantation, macroscopic inspection of the donor organ by an experienced transplant surgeon is crucial [24]. Any severe or obvious injury or trauma to the graft will be noted, and the graft can subsequently be discarded and not transplanted. This might also be the case for pancreata from CACPR donors, where grafts with obvious capsule or parenchymal damage and signs of contusion (e.g., subcapsular hematoma, edema, and frank saponification) can be detected during organ procurement or back table preparation.

Another possible reason for our findings is the theoretical physiologic effect of the CPR. Even though CA and CPR have been regarded as injurious to donor organs [37–40], reports exist that show that ischemia and subsequent reperfusion may actually have a protective influence. Ischemic preconditioning, effectively an outcome of donor CA, has been repeatedly reported to improve outcomes after transplantation in other solid organ transplant as well as pancreas [41–46]. With an ischemic episode and subsequent restoration of blood flow, the preconditioning effect has the potential to decrease the ischemia-reperfusion injury seen with all organs subject to ischemia time in transplantation, though exact mechanisms have not been identified in this context [45].

Limitations to this study include its retrospective, single-center nature. As well, like the other reports on this topic, we were only able to include transplanted donor organs. Thus, this study does not account for organs from CACPR donors that were eventually not transplanted. Also, our relatively low patient numbers might introduce either type 1 or type 2 bias. As our study includes transplants performed over a substantial amount of time, differences in patient care, immunosuppression, and operative technique may also skew final results, as more of the CACPR organs were used in the more recent era. Based on the split demographics, several confounding variables including donor creatinine levels, donor cause of death, and transplant year were identified that also may have biased reported long-term outcomes.

In summary, our data suggest that the use of organs from donors with a history of CA and CPR is safe, and, with stringent donor selection and short duration of CPR, outcomes may even surpass those of organs without CPR.

Authorship

FM: performed data collection, conceptualized and wrote and revised the manuscript. YY: performed statistical analysis and wrote and revised the manuscript. JWE: wrote and revised the manuscript. FJK, VB, and CB: performed data collection, wrote and revised the manuscript. GB, RO, SS, MM, DÖ, SS, and CM: conceptualized and revised the manuscript.

Funding

The authors have declared no funding.

Conflicts of interest

The authors have declared no conflicts of interest.

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