ORIGINAL ARTICLE

Impact of donor cardiopulmonary resuscitation on the outcome of simultaneous pancreas–kidney transplantation—a retrospective study

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SUMMARY

Previous cardiac arrest in brain-dead donors has been discussed as a potential risk factor in pancreas transplantation (PT), leading to a higher rate of organ refusal. This study aimed to assess the impact of cardiopulmonary resuscitation (CPR) in brain-dead donors on pancreas transplant outcome. A total of 518 type 1 diabetics underwent primary simultaneous pancreas–kidney (SPK) transplantation at our center between 1994 and 2018. Patients were divided into groups, depending on whether their donor had been resuscitated or not. A total of 91 (17.6%) post-CPR donors had been accepted for transplantation (mean duration of cardiac arrest, 19.4 ± 15.6 min). Those donors were younger ($P < 0.001$), had lower pancreas donor risk index (PDRI, $P = 0.003$), and had higher serum creatinine levels ($P = 0.021$). With a median follow-up of 167 months (IQR 82–229), both groups demonstrated comparable short- and long-term patient and graft survival. The resuscitation time (<20 min vs. ≥20 min) also showed no impact, with similar survival rates for both groups. A multivariable Cox regression analysis suggested no statistically significant association between donor CPR and patient or graft survival. Our results indicate that post-CPR brain-dead donors are suitable for PT without increasing the risk of complications.

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Key words

cardiopulmonary resuscitation, donor selection, ischemia, patient and graft survival, reperfusion injury, simultaneous pancreas–kidney transplantation

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Introduction

Simultaneous pancreas–kidney transplantation (SPK) is currently considered the gold standard therapy for type 1 diabetics with terminal renal insufficiency [1]. Advances in surgical techniques and perioperative care, such as innovations in immunosuppression, have led to better patient survival and graft function. Although SPK is preferable to kidney transplantation alone, especially for long-term prognosis of diabetic patients [2–5], the number of SPK transplants has recently been declining, especially in Germany. A restrictive acceptance policy adopted by transplant centers and the lack of suitable donor organs have led to a significant increase in patient numbers and their waiting time [6]. However, it must be mentioned that this trend in Germany differs

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from that in the USA. In the past decade, not only has there been a significant decrease in the number of patients on the waiting list and in the number of pancreas transplants performed, but also shorter waiting times have been achieved [7,8].

Furthermore, there is an increasing shortage of German surgeons experienced in pancreas removal and pancreas transplantation. The few German centers that still have an active pancreas transplantation program must achieve the same good results of recent years by using more marginal donor organs [9]. The marginality is mainly due to the higher age of the organ donors and their comorbidity. Some studies have shown that the outcomes using such organs are comparable to those from standard-criteria donors (SCD) [9,10]. A previous history of donor cardiopulmonary resuscitation (CPR) is a criterion in many centers for refusal of the organ [11–13] as it is assumed that a higher rate of postoperative complications leads to frequent early pancreatic graft loss. Earlier studies on other solid organ transplantations have readily shown that a previous history of asystole followed by CPR in brain-dead organ donors has no significant influence on patient survival or allograft function [14–16]. However, a few studies have considered the use of such organs in SPK [17,18].

The goal of the present study was to compare the outcome of SPK using organs from brain-dead donors who had previously undergone CPR, with SPK using organs from donors without a history of CPR.

Patients and Methods

This study included all patients who underwent primary SPK at the University Hospital Knappschaftskrankenhaus Bochum from June 1994 to September 2018. The exclusion criteria were as follows: retransplantation, pancreas-after-kidney transplantation (PAK), and transplantation of the pancreas alone (PTA). All the patients were type 1 diabetic patients. This was a retrospective, single-center study. The patients were divided into two groups: recipients of organs from donors who had not undergone CPR (non-CPR group) and recipients of organs from donors who had suffered ≥1 brain death-associated asystole with CPR (CPR group). The evaluation of the donor data regarding resuscitation status and duration took basic and advanced life support measures into account.

A subgroup analysis further divided the CPR group according to duration of resuscitation (CPR <20 min vs. CPR ≥20 min). Twenty minutes was chosen on the basis of the average CPR duration (19.4 ± 15.6 min) of the resuscitated donors in our study.

Both donor and recipient data were analyzed. Data on the donors were obtained through the EUROTRANSPLANT donor reports and the transplant patients' medical records. The following donor data were collected: age, sex, height, weight, BMI, and cause of death; ABO blood type; cytomegalovirus (CMV) status; laboratory values for serum sodium, creatinine, amylase, and lipase; number and length of CPR events; duration of stay in the intensive care unit (ICU); preexisting conditions, nicotine and alcohol consumption; and perfusion solution used during organ removal. Two additional scores were determined for each donor: the preprocurement pancreas suitability score (P-PASS) and the pancreas donor risk index (PDRI).

The following data were included for the graft recipients: age, sex, height, weight, and BMI; ABO blood type; CMV status; length of hospital stay; type and duration of dialysis; duration of diabetes mellitus (DM); patient and graft survival and early postoperative complications; initial immunosuppression; cold ischemia time (CIT); early post-transplant peak serum amylase, lipase and c-reactive protein (CRP) levels, and human leukocyte antigen (HLA) mismatch.

A renal graft failure was defined as patient death with a functioning graft, allograft nephrectomy, or the need for permanent dialysis or retransplantation. A pancreas graft failure was defined as the need for a return to exogenous insulin therapy, removal of the organ, or patient death. Early graft failure (EGF) was defined as graft failure within 3 months after transplantation.

Statistical analysis

All the statistical analyses were conducted using the IBM SPSS Statistics 25 package (IBM, Armonk, NY, USA). The quantitative variables were expressed as mean ± standard deviation. The differences in quantitative variables between the groups were performed using Student's *t*-test for normally distributed data and the Mann–Whitney *U*-test for non-normally distributed data. The categorical variables were expressed as frequencies and percentages. The differences between the groups were calculated through Fisher's exact test. A survival time analysis was carried out using the Kaplan–Meier method and applied to a comparison of the results between the groups as determined by the log-rank test. A multivariable analysis, with time until organ loss or death of the patient as dependent variables, was

carried out using the Cox regression model. All *P*-values <0.05 were considered statistically significant.

This study was approved by the local ethics board of the Faculty of Medicine at the Ruhr-University of Bochum, Germany (registry number: 18-6546 – BR). It was performed in accordance with the ethical standards of the Declaration of Helsinki.

Results

A total of 518 primary SPK transplantations were carried out from June 1994 to September 2018, at our center. Because of missing data regarding donor resuscitation status, two patients were excluded from the analysis. Out of the remaining 516 patients, 91 (17.6%) had received organs from donors who had undergone cardiac arrest followed by CPR. In 79 (86.8%) of these patients, information on the duration of donor CPR was available. The average resuscitation time was 19.4 ± 15.6 min (median, 15; range, 1–80). The mean time from resuscitation to transplantation was 5.1 ± 3.7 days. Figure 1 presents the distribution of all transplantations for each year within the study period, classified into the CPR and the non-CPR group.

Table 1 shows the donor data for both groups. There were no significant differences between the groups for donor sex, height, weight, BMI, or cause of death. However, the accepted donors who had undergone resuscitation were significantly younger than those in the comparison group ($P < 0.001$) and had significantly lower PDRI ($P = 0.003$). The average P-PASS in the CPR group was also lower than in the non-CPR group but without any statistical significance. The length of stay in the ICU was also comparable in both donor groups. The serum levels of amylase, lipase, sodium, and the highest sodium values were comparable between the two groups, but the CPR group had a significantly higher level of serum creatinine ($P = 0.021$). The University of Wisconsin solution was used significantly more frequently for the perfusion solution in the non-CPR group ($P < 0.001$). The 2007–2018 period included significantly more resuscitated donors compared to the 1994–2006 period ($P < 0.001$).

Table 2 shows the characteristics of the organ recipients of both groups. No significant differences were seen between the groups in terms of recipient sex, age, BMI, dialysis type and duration, and duration of DM. HLA mismatch and immunosuppression were comparable. Post-transplant peak serum amylase and CRP values were comparable, but peak serum lipase was significantly higher in the CPR group ($P = 0.003$).

Table 3 shows donor and recipient data for the two subgroups divided on the basis of CPR duration. There were no significant differences between the donors or recipients for age, BMI, or sex ratio, even though donors in the ≥20-min CPR group were on average 2 years younger. The donors with ≥20 min CPR also spent a significantly longer time in the ICU ($P = 0.006$) and showed higher levels of serum lipase (51.4 ± 48.6 vs. 93.2 ± 94.7, $P = 0.038$). Additionally, the time from

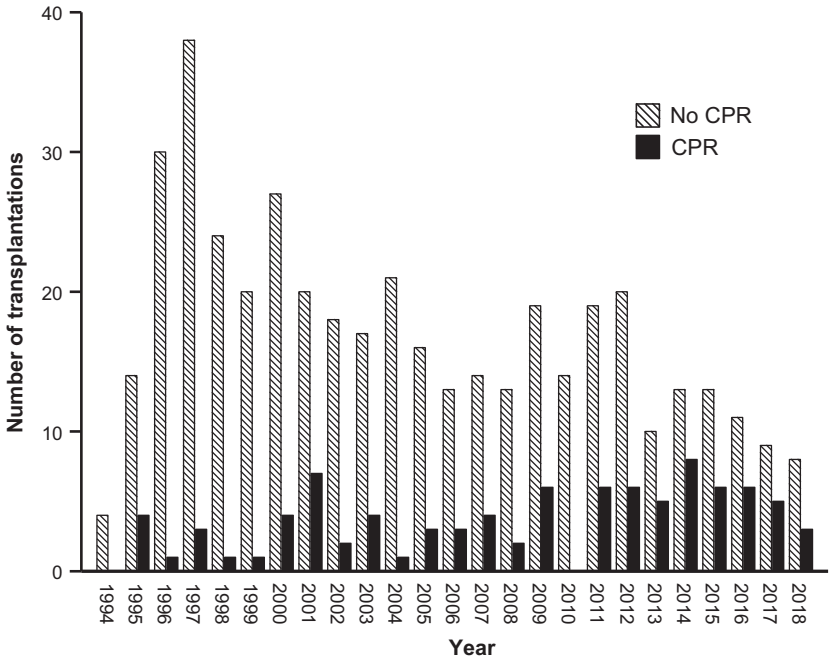

Figure 1 Distribution of all transplantations for each year within the study period, classified into the CPR and the non-CPR group. Note: 1994 and 2018 do not represent observations of a whole year. CPR, cardiopulmonary resuscitation.

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Table 1. Donor characteristics.

Donor characteristics	CPR (n = 91)	No CPR (n = 425)	P-value
Gender male/female	43/48 (47.3/52.7)	197/228 (46.4/53.6)	0.908
Age (years)	29.8 ± 13.2	35.4 ± 12.5	<0.001
Weight (kg)	67.12 ± 15.40	69.46 ± 13.01	0.233
Height (cm)	169.6 ± 12.2	172.5 ± 10.9	0.061
BMI (kg/m^2)	22.98 ± 3.34	23.14 ± 2.82	0.666
Length of ICU stay (days)	4.0 ± 3.6	4.3 ± 7.1	0.590
Cause of death			
Traumatic	29 (31.9)	162 (38.2)	0.283
Nontraumatic	62 (68.1)	263 (61.8)	
Laboratory findings			
Hypernatremia yes/no	28/63 (30.8/69.2)	91/329 (21.7/78.3)	0.075
Highest value sodium (mmol/l)	162 ± 8	162 ± 5	0.746
Serum creatinine (μmol/l)	92.5 ± 70.2	79.1 ± 49.2	0.021
Peak amylase (U/l)	146 ± 177	128 ± 172	0.540
Peak lipase (U/l)	73 ± 80	76 ± 134	0.134
History of smoking	26 (35.6)	111 (34.9)	0.893
Alcohol consumption	16 (34.8)	55 (36.7)	0.862
P-PASS	16.9 ± 2.2 (n = 70)	17.4 ± 2.5 (n = 232)	0.076
≤17	40 (57.1)	115 (49.6)	0.278
>17	30 (42.9)	117 (50.4)	
PDRI	1.179 ± 0.383	1.326 ± 0.418	0.003
Perfusion solution			
UW	32 (35.2)	249 (58.6)	<0.001
HTK	58 (63.7)	169 (39.8)	
Other	1 (1.1)	7 (1.6)	
Year of transplantation	2008 ± 7 years	2004 ± 7 years	<0.001

BMI, body mass index; CPR, cardiopulmonary resuscitation; HTK, histidine–tryptophan–ketoglutarate; ICU, intensive care unit; PDRI, pancreas donor risk index; P-PASS, preprocurement pancreas allocation suitability score; UW, University of Wisconsin solution.

Values are given as mean ± SD or n (% of group).

CPR to transplantation was significantly longer in this group (4.1 ± 3.0 vs. 6.4 ± 4.3 days, P = 0.007). The peak post-transplant serum lipase and CRP values were comparable between the groups, whereas peak serum amylase was significantly lower in the ≥20-min CPR group (P = 0.017). No significant differences were seen between groups for HLA mismatch, cold ischemic time, duration of recipient's dialysis, and DM.

Patient and graft survival

Median follow-up time, estimated by the reverse Kaplan–Meier method, was 167 months (IQR 82–229). It was significantly longer in the non-CPR group (175 months, IQR 93–240) than in the CPR group (111 months, IQR 49–189, P < 0.001).

The overall survival rate for the patients was 96.3%, 89.9%, and 80.8% after 1, 5, and 10 years, respectively. For the same follow-up time-points, the kidney and pancreas grafts had survival rates of 90.4%, 80.3%, and 66.1% and 79.6%, 69.6%, and 59.8%, respectively. The patient survival rates after 1, 5, and 10 years were 96.7%, 89.2%, and 80.5% in the non-CPR group and 93.3%, 91.6%, and 79.4% in the CPR group, respectively (P = 0.769; Fig. 2). For the pancreas graft, the survival rates after 1, 5, and 10 years were 78.7%, 68.0%, and 58.6% in the non-CPR group and 82.1%, 76.7%, and 63.6% in the CPR group, respectively (P = 0.559) (Fig. 3). Similarly, the survival rates for the kidney graft after 1, 5, and 10 years showed no significant difference (P = 0.888; Fig. 4). A subgroup analysis considered the survival probability of patients who had received organs from resuscitated donors with known duration of CPR (n = 79). This analysis showed no statistical difference between recipients of organs from donors who had undergone <20 min of CPR (CPR <20-min group, n = 42) and those who had received organs from donors who had undergone CPR for ≥20 min (CPR ≥20-min group, n = 37, P = 0.955; Fig. 5). For the pancreas allograft, a trend toward

Table 2. Recipient characteristics.

Recipient characteristics	CPR (n = 91)	No CPR (n = 425)	P-value
Gender male/female	56/35 (61.5/38.5)	251/174 (59.1/40.9)	0.725
Age (years)	42.1 ± 9.5	41.7 ± 8.5	0.635
Weight (kg)	71.44 ± 13.12	70.76 ± 13.29	0.491
Height (cm)	172.5 ± 8.9	172.0 ± 8.8	0.582
BMI (kg/m^2)	23.88 ± 3.24	23.83 ± 3.46	0.685
AB0-identity, yes/no	85/6 (93.4/6.6)	408/17 (96.0/4.0)	0.268
Length of hospital stay (days)	39.3 ± 19.8	37.8 ± 21.3	0.276
Laboratory findings			
Peak amylase (U/l)	366 ± 380	287 ± 288	0.950
Peak lipase (U/l)	611 ± 632	374 ± 369	0.003
Peak CRP (mg/dl)	13 ± 7.9	14.5 ± 9	0.209
Type of dialysis			
None	13 (14.3)	48 (11.3)	0.446
Hemodialysis	53 (58.2)	283 (66.6)	
CAPD	19 (20.9)	71 (16.7)	
Both	6 (6.6)	23 (5.4)	
Duration of dialysis (months)	32.3 ± 21.2	31.4 ± 23.7	0.381
Duration of diabetes mellitus (years)	29.4 ± 8.6	29.5 ± 8.9	0.985
CMV			
R−/D+	18 (19.8)	113 (26.6)	0.652
R+/D+	23 (25.3)	104 (24.5)	
R−/D−	26 (28.5)	106 (24.9)	
R+/D−	24 (26.4)	102 (24.0)	
Cold ischemic time (min)			
Pancreas	698.9 ± 176.7	717.3 ± 183.8	0.276
Kidney	802.4 ± 197.6	786.1 ± 184.4	0.449
HLA mismatch			
A	1.2 ± 0.6	1.3 ± 0.7	0.120
B	1.7 ± 0.5	1.6 ± 0.5	0.111
DR	1.6 ± 0.6	1.5 ± 0.6	0.279
Total	4.5 ± 1.1	4.4 ± 1.2	0.531
Immunosuppression (initial)			
ATG/IL2-RA/both	89/0/2 (97.8/0.0/2.2)	397/3/25 (93.4/0.7/5.9)	0.293
Tac/CsA	82/9 (90.1/9.9)	349/69 (83.5/16.5)	0.147
MMF/Aza	87/4 (95.6/4.4)	380/31 (92.5/7.5)	0.367
Corticosteroids	91 (100)	425 (100)	1.000
1-year rejection rate	30 (33.0)	134 (31.5)	0.805

ATG, antithymocyte globulin; Aza, azathioprine; BMI, body mass index; CAPD, continuous ambulatory peritoneal dialysis; CMV, cytomegalovirus; CPR, cardiopulmonary resuscitation; CRP, c-reactive protein; CsA, cyclosporin A; D, donor; HLA, human leukocyte antigens; IL2-RA, interleukin 2-receptor antibody; MMF, mycophenolate mofetil; R, recipient; Tac, tacrolimus.

Values are given as mean ± SD or n (% of group).

higher graft survival rates was seen in the CPR ≥20-min group (88.5%, 82.9%, and 59.7% vs. 76.1%, 67.9%, and 53.9%), but was not statistically significant (P = 0.185; Fig. 6). The survival rates for the kidney graft after 1, 5, and 10 years were 85.6%, 66.1%, and 61.4% in the CPR < 20-min group and 91.1%, 85.7%, and 57.3% in the CPR ≥ 20 group (P = 0.532), respectively (Fig. 7).

There was no significant difference between any group for the 1-year rejection rate (Tables 2 and 3). Furthermore, early complications such as pancreatic graft thrombosis or relaparotomy rate within 3 months postoperatively were not increased in the CPR group (Table 4). Mean hospital stay was 39.3 ± 19.8 days in the CPR group (median 32 days) and 37.8 ± 21.3 days in the non-CPR group (median 31 days, P = 0.276; Table 2).

During the observation period, pancreas graft loss occurred in 249 (48.3%) of the cases. Out of these, 76 (14.8%) were early graft failures (EGF). The rate of EGF

Table 3. Donor and recipient characteristics related to duration of CPR.

Characteristics	CPR <20 min (*n* = 42)	CPR ≥20 min (*n* = 37)	*P*-value
Donor			
Gender male/female	21/21 (50.0/50.0)	15/22 (40.5/59.5)	0.498
Age (years)	30.9 ± 12.6	28.8 ± 13.9	0.495
BMI (kg/m^2)	23.00 ± 3.45	23.10 ± 3.52	0.886
Length of ICU stay (days)	2.9 ± 2.9	5.2 ± 4.3	0.006
Laboratory findings			
Hypernatremia, yes/no	11/31 (26.2/73.8)	14/23 (37.8/62.2)	0.335
Highest value sodium (mmol/l)	162 ± 5	163 ± 10	0.637
Serum creatinine (μmol/l)	93.7 ± 87.0	94.1 ± 57.0	0.984
Peak amylase (U/l)	139.8 ± 198.2	138.2 ± 134.6	0.969
Peak lipase (U/l)	51.4 ± 48.6	93.2 ± 94.7	0.038
P-PASS	17.0 ± 2.2	16.7 ± 2.3	0.600
PDRI	1.238 ± 0.417	1.132 ± 0.360	0.230
COD traumatic/nontraumatic	12/30 (28.6/71.4)	10/27 (27.0/73.0)	1.000
Duration of CPR (min)	8.1 ± 4.4	32.2 ± 13.6	<0.001
Time from CPR to TX (day)	4.1 ± 3.0	6.4 ± 4.3	0.007
Recipient			
Age (years)	42.4 ± 10.0	41.4 ± 9.2	0.638
Sex	25/17 (59.5/40.5)	22/15 (59.5/40.5)	1.000
BMI (kg/m^2)	23.38 ± 3.09	24.29 ± 3.18	0.202
Laboratory findings			
Peak amylase (U/l)	480.5 ± 471	268.2 ± 220.7	0.017
Peak lipase (U/l)	701.4 ± 692	518.2 ± 499.2	0.221
Peak CRP (mg/dl)	14.1 ± 8.8	12.7 ± 6.9	0.458
Duration of dialysis (months)	31.5 ± 26.8	34.9 ± 15.8	0.056
Duration of diabetes (years)	29.9 ± 9.7	29.7 ± 6.7	0.894
Cold ischemic time (min)			
Pancreas	697.0 ± 203.6	696.2 ± 152.0	0.983
Kidney	786.4 ± 228.3	816.0 ± 166.5	0.517
Total HLA mismatch	4.4 ± 1.2	4.5 ± 1.2	0.827
1-year rejection rate	15 (35.7)	11 (29.7)	0.636

BMI, body mass index; CPR, cardiopulmonary resuscitation; COD, cause of death; CRP, c-reactive protein; HLA, human leukocyte antigens; ICU, intensive care unit; PDRI, pancreas donor risk index; P-PASS, preprocurement pancreas allocation suitability score; Tx, transplantation.

Values are given as mean ± SD or *n* (% of group).

in the CPR group (12.1%) and the non-CPR group (15.3%) was comparable ($P = 0.516$). The CPR <20-min and CPR ≥20-min subgroups also showed no significant difference in EGF incidence (16.7% vs. 5.4%, $P = 0.162$). The causes for EGF were similar between all groups except bleeding, which was significantly more frequent in the CPR group ($P = 0.019$; Table 4).

A multivariable Cox regression analysis model for patient survival (independent variables: donor CPR, donor age, donor BMI, recipient age, recipient BMI, kidney CIT, pancreas CIT, recipient dialysis duration, PDRI, length of ICU stay, and year of transplantation) did not identify donor CPR status as a statistically significant risk factor for patient death (HR 1.327, 95% CI, 0.771–2.282, $P = 0.307$). Same models for kidney graft and pancreas graft survival did not show a significant association between donor CPR status and an increased risk for graft loss (HR 1.453, 95% CI, 0.922–2.292, $P = 0.108$ and HR 1.141, 95% CI, 0.760–1.714, $P = 0.525$; Table 5).

Discussion

This study aimed to analyze the effect of organ donor CPR on short-term and long-term outcomes after simultaneous pancreas–kidney transplantation. After analysis of the outcomes from 516 SPK transplantations using organs from CPR and non-CPR donors,

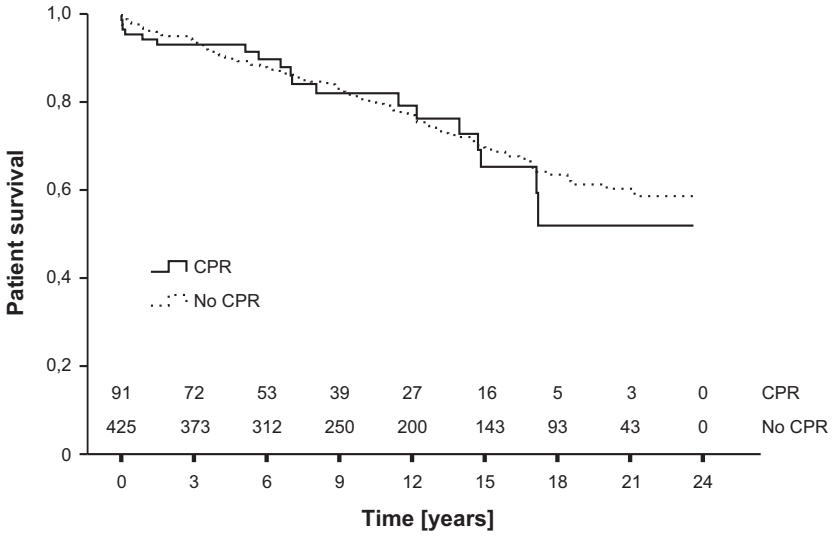

Figure 2 Kaplan–Meier curves representing patient survival for CPR and non-CPR group. No statistically significant difference was seen between the two groups (log-rank test, $P = 0.769$). CPR, cardiopulmonary resuscitation.

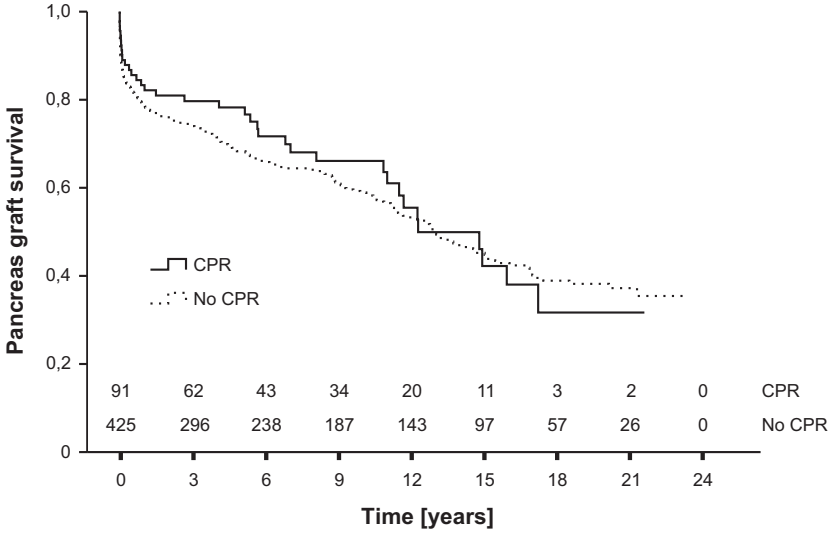

Figure 3 Kaplan–Meier curves representing pancreas graft survival for CPR and non-CPR group. No statistically significant difference was seen between the two groups (log-rank test, $P = 0.559$). CPR, cardiopulmonary resuscitation.

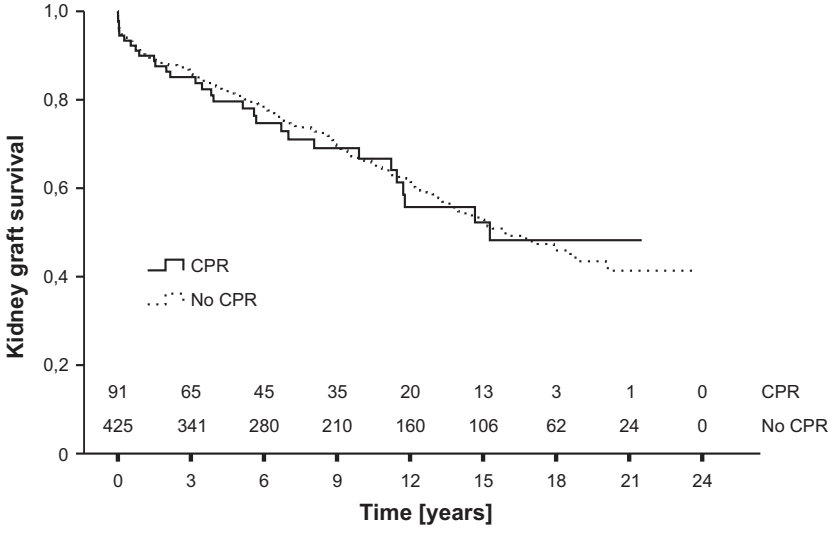

Figure 4 Kaplan–Meier curves representing kidney graft survival for CPR and non-CPR group. No statistically significant difference was seen between the two groups (log-rank test, $P = 0.885$). CPR, cardiopulmonary resuscitation.

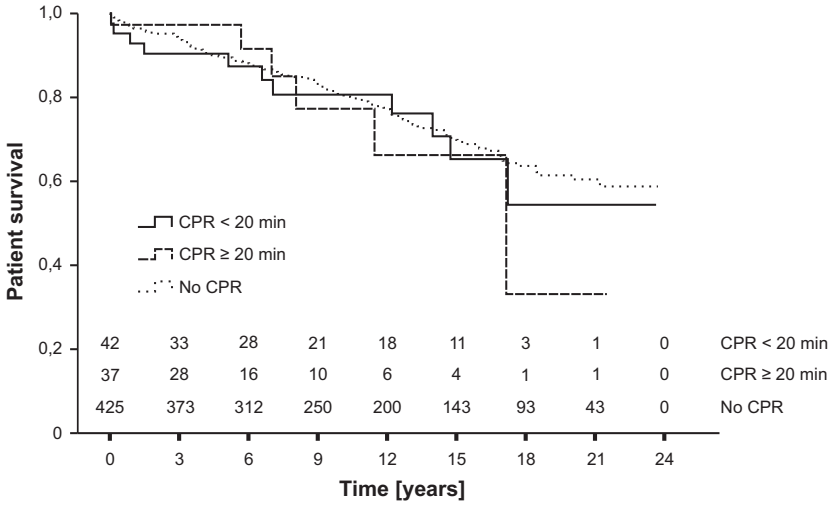

Figure 5 Kaplan–Meier curves representing patient survival for CPR <20-min and CPR ≥20-min group. There was no significant difference in patient survival (log-rank test, $P = 0.955$) between the two groups. CPR, cardiopulmonary resuscitation.

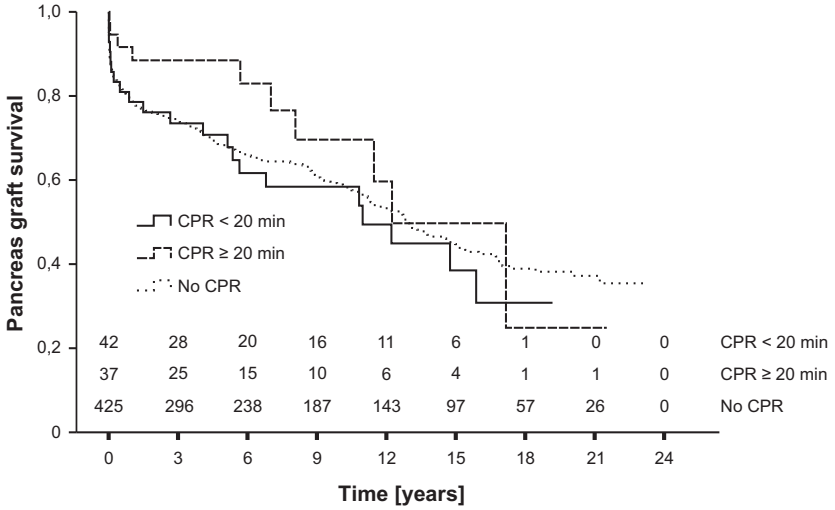

Figure 6 Kaplan–Meier curves representing pancreas graft survival for CPR <20-min and CPR ≥20-min group. There was no significant difference in pancreas graft survival (log-rank test, $P = 0.185$) between the two groups. CPR, cardiopulmonary resuscitation.

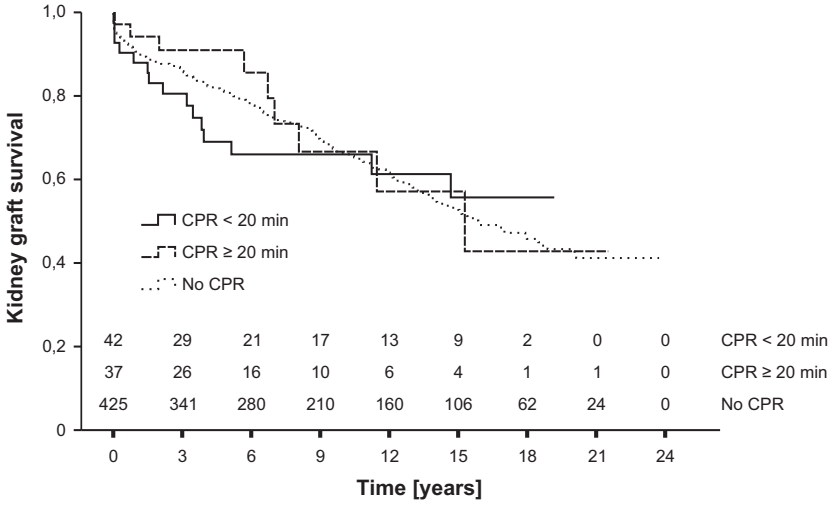

Figure 7 Kaplan–Meier curves representing kidney graft survival for CPR <20-min and CPR ≥20-min group. There was no significant difference in kidney graft survival (log-rank test, $P = 0.532$) between the two groups. CPR, cardiopulmonary resuscitation.

of which 91 were performed with organs from resuscitated donors, we found no differences in patient survival or graft survival between the two groups. Additionally, our study found that the duration of the resuscitation did not influence outcome. We were able to show that the use of organs after donor CPR did not lead to an increased rate of surgical complications after SPK transplantation, which is also

reflected in a comparable length of recipient´s hospital stay in both groups. With a median inpatient stay of 32 days in the CPR group and 31 days in the non-CPR group, our patients' hospital stay is relatively long compared with international standards, especially those of the USA. At our institution, we can still implement part of the rehabilitation during patients' initial admission, which may extend the hospitalization period. This length of inpatient hospitalization following pancreas transplantation has been established in most German transplantation centers.

Compared to other solid organ transplantations, acceptance of a donor for pancreas transplantation is especially restrictive. Until now, the risk factors under consideration included donor age >45–50 years, donor BMI >30 kg/m^2, donation after cardiac death (DCD), and cerebrovascular or nontraumatic cause of death [19]. Along with these risk factors, the influence of CPR on the donor following cardiac arrest is an often-discussed controversy. Loss *et al.* [11] investigated the reasons for refusal of donor pancreas in Germany between 2004 and 2009. They found that donor CPR was one of the most common criteria for donor refusal by transplant centers. Similarly, in our center during the 1990s, the acceptance of resuscitated donors was low. The proportion of donors with CPR has increased steadily since then, while the proportion of donors without CPR has fallen continuously over the same period. This reflects the efforts made to compensate the decreasing number of standard-criteria donors by increasing acceptance of marginal donors, thereby resulting in a significantly shorter follow-up time in the CPR group and a likely time-period bias. If such an organ was available, we usually only accepted it if there were no other risk factors. Thus, the donors we accepted with resuscitation were mostly younger and normal-weight patients, which is also reflected in a lower PDRI. This fact represents a selection bias in this study. On the other hand, the proportion of HTK-perfused donor organs in the CPR group was significantly higher [since 2007, in Germany, histidine–tryptophan–ketoglutarate (HTK) has increasingly used in the place of University of Wisconsin solution (UW)] and we also found a higher rate of acute kidney injury among these donors. Both factors are associated with negative effects on post-SPK transplantation results.

Previous studies have associated cardiac arrest with substantially reduced recovery of organs because of reduced hemodynamic stability [20,21]. Adrie *et al.* [22] explain the concerns regarding successful resuscitation in terms of whole-body ischemia/reperfusion injury. The clinical presentation of this so-called postresuscitation syndrome has several aspects that resemble sepsis. This is due to high levels of cytokines and adhesion molecules in blood, as well as dysregulated cytokine production arising from endotoxins in plasma and disrupted coagulation [22]. This cellular stress could lead to release of numerous damage-associated molecular patterns (DAMPs), which in turn activate the innate and adaptive immune system and cause rejection reactions [23].

Conversely, numerous studies on transplantations of other organs confirm the comparable success of CPR and non-CPR donors [14–16,24,25]. In 2018, Schroering *et al.* [18] investigated the influence of cardiac arrest (CA) in organ donors on clinical outcomes and long-term graft survival after pancreas transplantation. They subdivided their collective patients into four groups: no CA, CA <20 min, CA 20–39 min, and CA ≥40 min. They were able to show that the 1-year survival rates for patients, pancreas grafts, and kidney grafts were comparable in all groups. At 10-year follow-up, the pancreas graft survival showed a trend toward poorer outcomes in the CA ≥40-min group, but this did not reach statistical significance. Similar to our study, the donors from the group with CA were significantly younger. Aside from this, these donors died significantly less often from traumatic events. A similar trend was also seen in our sample, although it did not reach statistical significance. The group of donors with longer duration of cardiac arrest had higher peak serum lipase values, whereas the peak serum amylase values in the recipients of resuscitated organs, interestingly, were significantly lower. The authors interpreted this observation as a possible ischemic preconditioning effect, as has previously been described in the context of liver transplantation [26,27]. Another study by Ventura-Aguiar *et al.* [17] investigated the effect of a CA in brain-dead donors on the outcome after pancreas transplantation. This study included 342 pancreas transplant patients, and 49 (14.3%) donors who had undergone CPR were accepted. There were no significant differences regarding either pancreas or kidney graft survival after 1, 5, and 10 years, whereas overall patient survival in the group with resuscitated donors was significantly worse after 1 and 5 years. Their observed outcomes were dependent on resuscitation duration, with a fivefold higher risk of early graft failure of the pancreas grafts when the CPR duration was >15 min, compared with the group with a CPR duration of <15 min. Moreover, the pancreas graft survival rate in this group (CPR >15 min) was significantly lower than that in the others [17]. There were some differences between the results by Schroering *et al.* and Ventura-

Table 4. Post-transplant outcomes and reasons of early pancreas graft failure.

	CPR (n = 91)	No CPR (n = 425)	P-value	CPR <20 min (n = 42)	CPR ≥20 min (n = 37)	P-value
Patient						
1-year survival	93.3%	96.7%	0.769	90.4%	91.6%	0.955
5-year survival	91.6%	89.2%		87.4%	91.6%	
10-year survival	79.4%	80.5%		76.4%	66.3%	
Kidney						
1-year graft survival	88.7%	90.5%	0.888	85.6%	91.1%	0.532
5-year graft survival	78.0%	80.6%		66.1%	85.7%	
10-year graft survival	64.1%	66.2%		61.4%	57.3%	
Pancreas						
1-year graft survival	82.1%	78.7%	0.559	76.1%	88.5%	0.185
5-year graft survival	76.7%	68.0%		67.9%	82.9%	
10-year graft survival	63.6%	58.6%		53.9%	59.7%	
Relaparotomy rate	30 (34.5%)	160 (40.3%)	0.334	18 (45%)	10 (27.8%)	0.155
Pancreas graft thrombosis	4 (4.4%)	41 (9.6%)	0.150	2 (4.8%)	1 (2.7%)	1.000
Early pancreas graft failure	11 (12.1)	65 (15.3)	0.516	7 (16.7)	2 (5.4)	0.162
Thrombosis	2 (2.2)	32 (7.5)	0.065	2 (4.8)	0 (0)	0.496
Pancreatitis	2 (2.2)	12 (2.8)	1.000	1 (2.4)	1 (2.7)	1.000
Bleeding	3 (3.3)	1 (0.2)	0.019	2 (4.8)	1 (2.7)	1.000
Acute rejection	1 (1.1)	5 (1.2)	1.000	1 (2.4)	0 (0)	1.000
Other	3 (3.3)	15 (3.6)	1.000	1 (2.4)	0 (0)	1.000

CPR, cardiopulmonary resuscitation.

Values are given as n (% of group).

Aguiar *et al.* and the present study. First, in our patient population, there were no differences in either patient survival or graft survival between the two groups at 1, 5, and 10 years of follow-up. Second, in our subgroup analysis based on CPR duration, resuscitation time showed no negative influence on survival rates or early graft loss. Among our pancreas transplantations, there was even a trend toward higher graft survival probability in the CPR ≥20-min group. Additionally, the EGF rate of kidney and pancreas graft was lower in this group, although not statistically significant. It should be noted that the mean resuscitation time of our long-duration donors (32.2 ± 13.6 min) was shorter than that of the long-duration group in the analysis by von Schroering *et al.* (CA >40 min), but was longer than that of the long-duration group in the study by Ventura-Aguiar *et al.* (CA >15 min; mean, 25.4 ± 10.6 min). Moreover, our multivariable Cox regression analysis of CPR as a possible influencing factor indicated no statistically significant increased risk for patient death or graft loss. However, transplantation of a pancreas graft from a resuscitated organ donor has a similar effect on the results as transplantation of a pancreas graft using a ten-year older donor but without resuscitation. A possible root cause for the equally good outcomes seen in our study after SPK using organs from donors with CPR could be the effect of ischemic preconditioning (IP). This was first described for myocardial ischemia in dogs by Murry *et al.* [28] and refers to a tissue adaptation in stressful situations, brought about by preapplied short ischemic periods with subsequent reperfusions, which protects the organ from subsequent ischemic reperfusion injury (RI). This effect has been seen in a number of organs and has been detected up to 72 h poststimulation [29–31]. Several animal models have already indicated that such preconditioning is also possible in interventions involving the pancreas, and has a protective effect against postoperative complications [32,33]. Even if CPR is adequately administered or is uninterrupted, the macro- and microcirculation produced does not reach physiological baseline levels and the patient will undergo a relative ischemia or insufficient blood supply [34,35]. We therefore propose that CPR itself could be a potential trigger for ischemic tissue preconditioning, which could confer subsequent protection from RI and from further ischemia.

Therefore, IP could be a possible explanation for the absence of a statistically significant effect of donor CPR status on survival probability of the patients or the grafts. Interestingly, amylase and lipase values were not significantly different between the CPR and non-CPR

Table 5. Multivariable Cox regression analysis of risk factors for patient and graft survival.

Risk factors	Patient survival	*P*-value	Kidney graft survival	*P*-value	Pancreas graft survival	*P*-value
Donor CPR	1.327 (0.771–2.282)	0.307	1.453 (0.922–2.292)	0.108	1.141 (0.760–1.714)	0.525
Donor age (per year increase)	1.027 (0.996–1.059)	0.089	1.043 (1.016–1.070)	0.001	1.020 (0.998–1.043)	0.074
Donor BMI (per 1 kg/m^2 increase)	1.041 (0.970–1.116)	0.264	1.019 (0.963–1.077)	0.518	0.998 (0.950–1.048)	0.941
Recipient age (per year increase)	1.052 (1.025–1.079)	<0.001	1.007 (0.987–1.028)	0.468	1.005 (0.987–1.023)	0.589
Recipient BMI (per 1 kg/m^2 increase)	1.007 (0.947–1.070)	0.833	1.013 (0.965–1.062)	0.605	1.029 (0.987–1.073)	0.180
Kidney CIT (per hour increase)	1.017 (0.915–1.131)	0.749	1.036 (0.946–1.133)	0.448	0.977 (0.906–1.053)	0.541
Pancreas CIT (per hour increase)	0.994 (0.891–1.109)	0.916	1.016 (0.926–1.115)	0.737	1.036 (0.958–1.120)	0.380
Duration of dialysis (per month increase)	1.010 (1.003–1.018)	0.005	1.006 (1.000–1.013)	0.036	1.001 (0.995–1.007)	0.666
PDRI (per 0.1 point increase)	0.445 (0.181–1.089)	0.076	0.502 (0.244–1.034)	0.062	0.992 (0.527–1.868)	0.980
Length of ICU stay (per day increase)	1.017 (0.977–1.058)	0.405	1.013 (0.980–1.047)	0.431	1.008 (0.976–1.041)	0.622
Year of transplantation (per year increase)	0.981 (0.937–1.028)	0.424	0.979 (0.945–1.014)	0.232	1.007 (0.979–1.036)	0.613

BMI, body mass index; CPR, cardiopulmonary resuscitation; CIT, cold ischemic time; ICU, intensive care unit; PDRI, pancreas donor risk index.

Values are given as hazard ratio (95% CI).

donor groups. In the CPR ≥20-min subgroup, the lipase values were significantly increased. This could be explained by the fact that the times from resuscitation to transplantation and time spent by the donor in the ICU were significantly longer in this group than in the CPR <20-min group. Accordingly, long-term outcomes in the CPR ≥20-min group were not worse and showed a better trend regarding pancreas graft survival. Although it is possible that the longer time until transplantation allowed better detection of the full extent of the organ damage, it perhaps allowed for more effective organ regeneration. Thus, the donor lipase values of the CPR <20-min group were significantly lower than in the non-CPR group, with a shorter ICU stay. Conversely, the donor creatinine values were significantly elevated in the CPR group but were same between the resuscitation subgroups. Furthermore, unlike the results of Schroering *et al.*, we found significantly increased peak serum lipase values within the first postoperative week in the CPR group ($P = 0.003$). The peak serum amylase was also higher in this group, without statistical significance. These results appear to contradict the hypothesis of an IP effect. However, there was a trend to lower peak serum lipase values in the CPR ≥20-min group, compared to the CPR <20-min group. For peak serum amylase, this decrease was significant ($P = 0.017$). Serum peak CRP levels did not differ between any of the four groups.

Another reason against a potential IP effect is the resuscitation-to-transplantation time interval in our donor population. Our resuscitation-to-transplantation time (average 5.1 ± 3.7 days) falls clearly above the time ranges (maximum of 72 h after IP stimulus) previously demonstrated to be protective of tissue through an IP effect.

Our study has some limitations. First, it was a retrospective study design with a monocentric patient population. The donors were only included if their organs were ultimately used for a transplantation. This could have hindered the detection of resuscitation-related organ damage, because of their exclusion from transplantation, and may support the influence of a so-called survivor benefit in the CPR donors. Second, as mentioned before, the donors in the resuscitation group have been transplanted mainly in the second half of our study period. They were statistically significantly younger and had significantly lower PDRI scores. This could have influenced the long-term results, since both these factors have been demonstrably associated with long-term survival after SPK [19,36].

In this study, we were able to show that SPK transplantation using organs from selected donors who had

undergone CPR resulted in comparable outcomes to those without donor CPR. In all results measured in this study, donor CPR was not statistically associated with deleterious effects. This indicates that donor CPR, in otherwise acceptable pancreas donors, poses no contraindication for pancreas transplantation. In light of the current organ shortages in Germany, the use of these organs could lead to a significant expansion of the donor pool.

Authorship

JH: collected and analyzed data, performed research, performed statistical analysis and wrote the manuscript. SG, TL, NP, MH and HMV: collected and analyzed data, performed research and critically revised the manuscript. THW and RV: critically revised the manuscript. PS: conceived and designed the study, collected and analyzed data, performed statistical analysis and wrote the manuscript.

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Conflict of interest

The authors have no conflicts of interest to declare.

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