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Impact of Deceased Donor Cardiac Arrest Time on Postpancreas Transplant Graft Function and Survival

Joel R. Schroering, BS,¹ Richard S. Mangus, MD,¹ John A. Powelson, MD,¹ and Jonathan A. Fridell, MD¹

Introduction. Transplantation of pancreas allografts from donors that have experienced preprocurement cardiopulmonary arrest (PPCA) is not common, though use of PPCA grafts is routine in liver and kidney transplantation. This article reviews a large number of PPCA pancreas grafts at a single center and reports posttransplant outcomes including early graft dysfunction, length of hospital stay, rejection, and early and late graft survival. **Methods.** Preprocurement cardiopulmonary arrest, arrest time, and donor and recipient pancreatic enzyme levels were collected from electronic and written medical records. The PPCA donors were stratified into 4 groups: none, less than 20 minutes, 20-39 minutes, and 40 minutes or greater. Graft survival was assessed at 7 and 90 days and at 1 year. Long-term graft survival was assessed by Cox regression analysis. **Results.** The records of 606 pancreas transplants were reviewed, including 328 (54%) simultaneous pancreas and kidney transplants. Preprocurement cardiopulmonary arrest occurred in 176 donors (29%; median time, 20 minutes). Median peak donor lipase was higher in PPCA donors (40 μL vs 29 μL , $P = 0.02$). Posttransplant, peak recipient amylase, and lipase levels were similar ($P = 0.63$). Prolonged arrest time (>40 minutes) was associated with higher donor peak lipase and lower recipient peak amylase ($P = 0.05$ for both). Stratified by donor arrest time, there was no difference in 7-day, 90-day, or 1-year graft survival. Cox regression comparing the 4 groups demonstrated no statistical difference in 10-year survival. **Conclusions.** These results support transplantation of pancreas allografts from PPCA donors. Prolonged asystole was associated with higher peak donor serum lipase but lower peak recipient serum amylase. There were no differences in allograft survival.

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Donor selection for pancreas transplantation is more conservative as compared with other forms of solid organ transplantation.¹ Preprocurement cardiac arrest (PPCA)

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¹ Transplant Division, Department of Surgery, Indiana University School of Medicine, Indianapolis, IN.

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Correspondence: Jonathan A. Fridell, MD, Transplant Division, Department of Surgery, Indiana University School of Medicine, 550 N University Blvd, #4258, Indianapolis, IN 46202. (jfridell@iupui.edu).

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time has previously been considered a high-risk donor characteristic and potentially detrimental to overall donor quality in pancreas transplantation.² With decreasing numbers of pancreas transplants performed, reassessment of reasonable acceptance criteria is a suitable way to expand the donor pool.^{3,4} Donor PPCA time is one of several extended donor criteria that warrants specific evaluation when appraising the quality of a potential pancreas allograft donor. This is particularly relevant because recent reports on liver and intestine transplantation support the use of organs from donors with PPCA when carefully selected for other factors.⁵⁻⁸ In fact, for liver transplantation, a preprocurement arrest event has actually been hypothesized to potentially provide protection to the organ from later ischemia and reperfusion injury.⁶ This mechanism has been referred to as “ischemic preconditioning” and is not yet fully understood.⁹

There have been conflicting reports as to whether PPCA is a predictor of poor outcome after pancreas transplantation. It is one of the components that make up the preprocurement pancreas allocation suitability score which consists exclusively of donor factors (age, body mass index [BMI], intensive care unit stay, asystole, sodium, amylase, lipase, and inotropic therapy) and is primarily intended to identify suitable pancreas donors. In this context, PPCA was identified as a donor characteristic that was associated with a decreased likelihood of acceptance of the pancreas for transplantation.²

Alternatively, the Pancreas Donor Risk Index was designed to help predict graft survival after pancreas transplantation using data from the Organ Procurement and Transplantation Network. This model consists of 8 donor factors (age, sex, race, height, BMI, serum creatinine, cause of death, and deceased after circulatory death donors) and 2 transplant factors (cold ischemia time and type of transplant).¹⁰ This index notably does not include PPCA. There have not been any focused investigations of the individual impact of PPCA on clinical outcomes and long-term graft survival after pancreas transplantation. Additionally, prior studies that have addressed it as a variable among others have not assessed specific outcomes associated with varying lengths of arrest times. This single-center retrospective study was undertaken to determine if PPCA has an impact on outcome after pancreas transplantation.

MATERIALS AND METHODS

This was a retrospective study of all pancreas transplants performed at a single center from 2003 to 2016. Donor characteristics were obtained from records maintained by the local organ procurement organization, Indiana Donor Network. Recipient outcomes, laboratory values, and survival data were collected from the comprehensive transplant recipient registry maintained at our center, as well as individual written and electronic medical records. Recipient inclusion criteria included all pancreas transplant recipients, including simultaneous pancreas and kidney (SPK), pancreas after kidney (PAK), or pancreas transplant alone. Recipients receiving a pancreas allograft as part of a multivisceral or modified multivisceral transplant were excluded.

All transplant recipients were listed for transplantation in accordance with standard procedure and protocol as established by our center and the United Network for Organ Sharing. In patients that were retransplanted within 30 days of their initial transplant, data from only the first transplant were included in this study. Clinical outcomes included length of stay (LOS) at the hospital and incidence of acute cellular rejection within the first year. Early posttransplant pancreas graft function was determined by peak serum amylase and lipase levels. Early graft survival rates were measured both by 7-day and 90-day graft loss. Long-term allograft survival was assessed using Cox regression analysis.

Pancreas allografts were typically procured using an en bloc technique after aortic flush with preservation solution and topical cooling with saline slush as previously described.^{11,12} Note that the pancreas had to be accepted for transplant and appear transplantable by both the procuring surgeon and the transplanting surgeon to qualify for this study. Although graft quality is subjective, it is widely accepted that a normal pancreas would be one with no swelling, no edema, no firmness, no excessive fat, and no injury. The parenchyma appears normal. The back-table preparation of the pancreas allograft and transplantation techniques for each transplant type have also been previously described.¹³⁻¹⁶ Briefly, the recipient operation was performed through a midline incision. The pancreas was routinely positioned with the tail toward the pelvis and the head and duodenum oriented superiorly to facilitate the enteric anastomosis. Systemic venous drainage was performed to the vena cava or to the right common iliac vein. Arterial perfusion of the allograft was routinely established from the

right common iliac artery, although on rare occasions where this vessel was found to be diseased or had been the site for arterial anastomosis for a prior transplant, the inflow would be established either from the aorta or the left common iliac artery. All pancreas allografts were drained enterically using a stapled technique as described elsewhere.¹⁷ The immunosuppression protocol included rabbit antithymocyte globulin induction with early steroid withdrawal, and maintenance therapy with tacrolimus and sirolimus or mycophenolate mofetil.^{18,19} All recipients received routine perioperative antibiotics, prophylaxis against cytomegalovirus with oral valgancyclovir and prophylaxis against *Pneumocystis jiroveci* pneumonia with trimethoprim and sulfamethoxazole, unless contraindicated. Systemic anticoagulation was not routinely used unless the patient had a specific history of a coagulation disorder.

The key variable in this study, donor PPCA, was extracted from the documentation of emergency medical service providers, as well as emergency department or inpatient hospital records. The reported donor PPCA times in this study consist of all reported arrest time before organ procurement. These events could have occurred outside of the hospital before arrival to the emergency department, or subsequent to inpatient admission. Preprocurement cardiopulmonary arrest occurring before or after declaration of death was included. All eventual donors suffering a preprocurement arrest event were successfully resuscitated and stabilized prior to organ procurement. In the case that exact donor arrest time was unknown, the time from which cardiopulmonary resuscitation was initiated until return of spontaneous circulation was used as the best estimate of donor PPCA time. The expertise of those providing resuscitation efforts and quality of cardiopulmonary resuscitation performed were not available for consideration in this study. The peak donor serum amylase and lipase levels were obtained from the donor records as well. Donors were assigned to subgroups stratified by donor PPCA time (none, less than 20 minutes, 20 to 39 minutes, and 40 minutes or greater).

Standard statistical testing was utilized for continuous and categorical variables, as indicated. The Cox proportional hazards model was constructed using a direct entry method. Covariates were included in the final model for *P* value less than 0.10. Statistical testing was performed on SPSS software (IBM SPSS Statistics Version 24, IBM Corporation, Armonk, NY). Retrospective analysis of data for pancreas transplant patients at our centers was reviewed and approved by the institutional review board of the Indiana University School of Medicine (1011003619).

RESULTS

A total of 606 pancreas transplants (SPK, 54%; PAK, 19%; pancreas transplant alone, 27%) were included in this study (Table 1). Of these, 176 (29%) donors were recorded to have had a PPCA event. The median length of arrest time for these donors was 20 minutes (mean, 23; range, 1 to 90; standard deviation, 16 minutes). Of the 176 donors that had experienced an arrest event, 79 (45%) experienced PPCA time of less than 20 minutes, 75 (43%) between 20 and 39 minutes, and 22 (12%) had an arrest time of 40 minutes or more in duration. Demographics for the entire group are presented in Table 1. Donor cause of death was the most significant difference between the donor subgroups, in

TABLE 1.

Demographic data for 606 pancreas transplant patients with comparison of patients in which the deceased donor did or did not experience cardiopulmonary arrest in the period before organ donation

	Overall	No donor		Any donor		Donor cardiopulmonary arrest time			P*
		Cardiopulmonary arrest	Cardiopulmonary arrest	P	< 20 min	20 to 40 min	> 40 min		
Overall	606	430 (71%)	176 (29%)		79 (13%)	75 (12%)	22 (4%)		
Recipient									
Sex: male	56%	57%	55%	0.75	49%	64%	46%	0.22	
Race: white	91%	91%	94%	0.36	92%	95%	96%	0.37	
Age (median), y	43	43	44	0.45	42	46	44	0.10	
BMI (median)	24.9	24.7	25.5	0.13	25.5	24.6	27.5	0.01	
Donor									
Sex: male	63%	65%	57%	0.06	59%	55%	55%	0.27	
Race: white	79%	78%	80%	0.84	80%	80%	82%	0.81	
Age (median), y	24	25	22	0.01	21	22	26	0.05	
BMI (median)	23.9	23.7	24.8	0.20	24.5	24.9	25.1	0.43	
Donor cause of death									
Stroke	18%	20%	10%	<0.001	9%	9%	14%	<0.001	
Trauma	60%	72%	31%		43%	22%	19%		
Anoxia/other	22%	8%	59%		47%	69%	67%		
Donation after cardiac death	2%	1%	3%	0.03	4%	3%	5%	0.16	
Regional origin of graft									
Local	65%	67%	58%	0.59	60%	61%	50%	0.47	
Transplant data									
Transplant type								0.87	
Pancreas and kidney (n = 328)	54%	55%	53%	0.72	54%	55%	41%		
PAK (n = 116)	19%	20%	18%		17%	17%	27%		
Pancreas alone (n = 162)	27%	26%	29%		29%	28%	32%		
Total ischemia (median), h	8.0	8.4	7.5	0.08	7.3	7.4	8.4	0.29	

* Calculated *P* value for donor cardiopulmonary arrest groups compared with the "no donor cardiopulmonary arrest" group.

which donors exceeding 20 minutes of PPCA time were much more likely to have died from anoxic brain injury, as opposed to trauma or stroke ($P = 0.001$). A lower-median age was noted for PPCA donors when compared with the non-PPCA donor subgroup ($P = 0.01$). However, the donor subgroup exceeding 40 minutes of PPCA time had the highest median age ($P = 0.05$). Recipients were statistically different only in terms of BMI, in which those receiving an organ from a donor with PPCA time of greater than 40 minutes had the highest median BMI ($P = 0.01$). There were no significant differences in regional origin of the graft, or in total ischemia times. The type of transplant was not significantly different among any of the donor subgroups.

The median peak preprocurement amylase and lipase levels for all 176 donors with PPCA were 84 and 40 μL respectively, compared with 77 and 29 μL for the 430 donors with no PPCA ($P = 0.42$ and $P = 0.02$) (Table 2). Specifically looking at the smaller subgroups of donors with PPCA, the donor group exceeding 40 minutes of PPCA time had the highest median peak amylase levels compared with all donor groups ($P = 0.78$). Median peak lipase levels in the donor subgroups rose in a corresponding relationship with increasing length of PPCA time ($P = 0.05$). Posttransplant, the peak amylase and lipase levels for grafts with donor PPCA time was 180 and 142 μL , respectively, compared with 206 and 157 μL for grafts without donor PPCA time ($P = 0.63$, $P = 0.14$). Again, specifically reviewing the subgroups of PPCA donors, the recipient median peak amylase level was

the lowest among the donor subgroup exceeding 40 minutes of PPCA time ($P = 0.05$).

There was no significant difference in hospital LOS among any of the PPCA or non-PPCA groups. Acute cellular rejection within the first year was higher for non-PPCA donors (5% vs 2%, $P = 0.06$). A trend of increasing rejection was seen increasing PPCA time, but this did not reach statistical significance (0%, 3%, 5%; $P = 0.18$). Assessing graft survival by length of donor arrest time, there was no difference in graft loss at 7 or 90 days posttransplant for any PPCA time or for increasing PPCA time. Additionally, there was no difference in 1-year pancreas (or kidney for SPK recipients) allograft or patient survival, with all groups maintaining survival rates greater than 90% at 1 year.

Cox regression analysis was used to compare 10-year graft survival between non-PPCA and PPCA subgroups (Figure 1A), and no difference was noted ($P = 0.50$). The same analysis was performed for PPCA grafts only, and there was a clear disadvantage for the grafts with 40 minutes or more of PPCA time, but this did not reach significance (Figure 1B). Finally, assessing kidney grafts in SPK transplants, there was no difference in graft survival at 10 years. (Figure 1C).

DISCUSSION

This single-center study provides the first focused analysis of the impact of donor PPCA time on pancreas transplantation outcomes. Similar to other research of this type

TABLE 2.**Comparison of graft laboratory values and posttransplant outcomes by donor arrest time**

	Overall	No donor		Any donor		Donor cardiopulmonary arrest time			<i>P</i> ^a
		Cardiopulmonary arrest	Cardiopulmonary arrest	<i>P</i>	< 20 min	20 to 40 min	> 40 min		
Overall	606	430 (71%)	176 (29%)		79 (13%)	75 (12%)	22 (4%)		
Donor laboratory value (median)									
Peak amylase	78	77	84	0.42	77	79	163	0.78	
Peak lipase	31	29	40	0.02	37	41	76	0.05	
Recipient laboratory values (median)									
Peak amylase	202	206	180	0.63	276	164	105	0.05	
Peak lipase	154	157	142	0.14	159	86	187	0.53	
Hospital LOS (days, median)	7	7	7	0.38	8	7	6	0.26	
Acute cellular rejection first year	25 (4.1%)	22 (5.1%)	3 (1.7%)	0.06	0 (0%)	2 (2.7%)	1 (4.5%)	0.18	
Survival									
7-d Pancreas graft loss	20 (3.3%)	12 (2.8%)	8 (4.5%)	0.27	4 (5.1%)	3 (4.0%)	1 (4.5%)	0.72	
90-d Pancreas graft loss	33 (5.4%)	24 (5.6%)	9 (5.1%)	0.82	4 (5.1%)	4 (4.0%)	2 (9.1%)	0.82	
1-y Pancreas graft survival	93%	92%	94%	0.30	95%	95%	91%	0.68	
1-y Patient survival	97%	97%	98%	0.24	99%	99%	96%	0.56	
Simultaneous pancreas-kidney (n = 328)									
1-y Pancreas graft survival	93%	93%	94%	0.91	93%	95%	89%	0.92	
1-y Kidney graft survival	95%	95%	97%	0.38	95%	98%	100%	0.75	
1-y Patient survival	97%	97%	98%	0.55	98%	98%	100%		

^a Calculated *P* value for donor cardiopulmonary arrest groups compared with the "no donor cardiopulmonary arrest" group.

completed in the fields of liver and intestine transplantation, our results support the utilization of pancreas grafts from donors with a history of PPCA when appropriately selected with respect to other factors. Prolonged periods of asystole were associated with higher peak elevations in serum lipase in the donor, but lower peak amylase elevations in the recipient. These findings may support the hypothesis of a potential ischemic preconditioning event which has been discussed previously in the context of liver transplantation.

Clinical outcomes and survival rates were comparable among grafts from all donor groups, including donors with and without PPCA and among all donors with PPCA. In all outcomes measured in this study, donor PPCA was not statistically associated with detrimental effects. Additionally, among donors experiencing PPCA, an increased length of arrest time was also not associated with worse outcomes, though there was a trend toward worse long-term graft

survival for PPCA or 40 minutes or more that did not reach statistical significance.

In the current setting of too few pancreas allografts available for transplant, PPCA donors represent an important resource to pursue in expanding the donor pool. Note that this study is a retrospective analysis from a single center, so this only reflects pancreas allografts that appeared normal and were therefore transplanted despite the donor down time. It is certainly possible, as suggested by the preprocurement pancreas allocation suitability score, which includes PPCA as a variable, that there were additional allografts from donors with PPCA that were edematous, firm, inflamed, or had other features of pancreatitis and were therefore not transplanted. Preprocurement cardiopulmonary arrest time may help predict the appearance of the pancreas at the time of graft procurement, but if it appears normal, the data in this study support proceeding with transplantation.

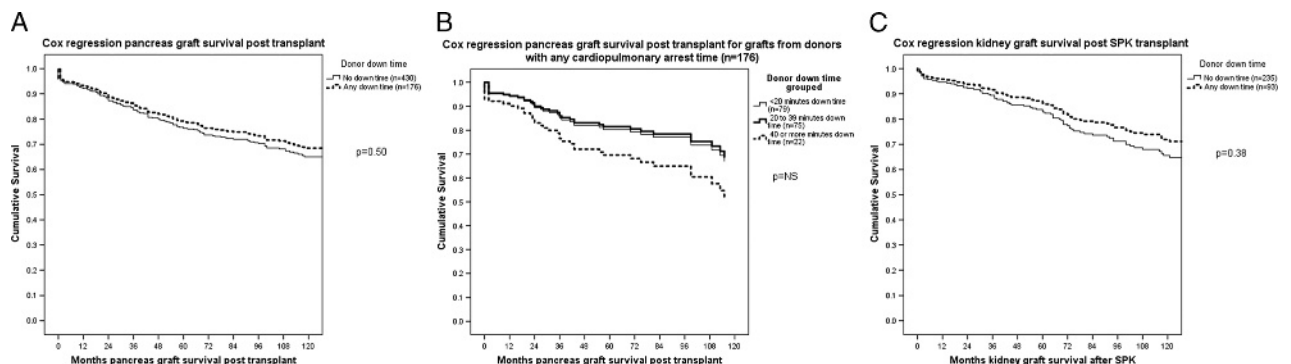


FIGURE 1. A, Ten-year Cox regression for pancreas graft survival comparing donor grafts with (n = 176) and without (n = 430) any preprocurement cardiac arrest. B, Ten-year Cox regression for pancreas graft survival for all donor grafts with preprocurement cardiac arrest (n = 176), comparing groups by total arrest time (in minutes). C, Ten-year Cox regression for kidney graft survival among SPK transplant patients (n = 328), grouped by preprocurement cardiac arrest.

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