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Original Article

The impact of donor pancreas extraction time on graft survival and postoperative complications in pancreas transplant recipients

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A B S T R A C T

Background: Simultaneous pancreas kidney transplantation (SPK) is the best therapeutic option for patients with diabetes mellitus type 1 and end-stage renal disease. Recently, donor organ extraction time has been shown to affect kidney and liver graft survival. This study aimed to assess the effect of pancreas donor extraction time on graft survival and postoperative complications.

Methods: We retrospectively analyzed all pancreas transplants performed in two Eurotransplant centers. The association of pancreas extraction time with pancreas graft survival was analyzed by a Cox proportional hazards regression analysis after 3 months, 1 and 5 year. Besides, the effect of pancreas extraction time on the incidence of severe postoperative complications was analyzed.

Results: A total of 317 pancreas transplants were included in this study. Death-censored pancreas graft survival was 85.7% after one year and 76.7% after five years. Median pancreas donor extraction time was 64 min [IQR: 52–79 min]. After adjustment for potential confounders, death censored graft survival after 30 days (HR 1.01, 95% CI 0.9–1.03 (p = 0.23), 1 year (HR 1.01, 95% CI 0.99–1.03 (p = 0.22) and 5 years (HR 1.00, 95% CI 0.99–1.02 (p = 0.57) was not associated with pancreas donor extraction time. However, extraction time was significantly associated with a higher incidence of Clavien-Dindo ≥3 complications compared to Clavien-Dindo 1 + 2 complications: OR 1.012, 95% CI 1.00–1.02 (p = 0.039).

Conclusions: Our findings suggest that although no effect on graft survival was found, limiting pancreas extraction time can have a significant impact on lowering postoperative complications.

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Introduction

Simultaneous pancreas and kidney transplantation (SPK) is the best therapeutic option for diabetes mellitus type 1 (DM type 1) patients with end-stage renal failure. Improvement of surgical techniques and immunosuppressive strategies have led to better graft survival after pancreas transplantation in the last decades [1,2]. However, since pancreas transplantation is still associated with serious complications and considerable morbidity, further optimization of the donation and transplantation process is desirable. The gold standard for pancreas preservation after procurement is static cold storage at ≤4 °C, as lower temperatures lead to decreased mitochondrial oxygen consumption, accompanied by a reduction in the production of reactive oxygen species [3,4]. Despite reduced metabolic processes in the cold, organs are still negatively affected by ischemic injury due to lack of oxygen supply. This injury aggravates with time and prolonged preservation time of the pancreas (>20 h) is associated with an increased likelihood for surgical complications after transplantation [5]. Recently, donor organ extraction time, the period between the aortic cold flush and the procurement of the organ from the donor body, has emerged as a potential ischemic period negatively affecting post-transplant outcome. In this period, despite efforts to cool down the organs by cold flush via the vasculature and the abdominal cavity, temperatures never reach the desired threshold of 4 °C, with potentially harmful consequences [6–8]. The scarce data on organ temperature during procurement shows an average kidney temperature during extraction of 11.6 °C, and a pancreas temperature of 9.0–16.5 °C 30 min after the cold flush [9,10]. Recent studies show...
that prolonged donor organ extraction time is an independent risk factor for kidney and liver graft survival, in particular for the more marginal donation after circulatory death (DCD) organs [7,11,12]. The effect of donor pancreas extraction time on outcome after pancreas transplantation has not yet been investigated. Here, we present the results of a dual-center study with the aim to assess the association between pancreas extraction time, graft survival and postoperative complications.

Materials and methods

Study population

In this dual-center retrospective database study, all consecutive pancreas transplants performed at the University Medical Center Groningen (UMCG) and the Medical University of Innsbruck (MUI) between January 1996 and December 2018 are included. The indication for pancreas transplantation in all patients was DM type 1 (according to the listing criteria of the Eurotransplant Manual) [13]. The only exclusion criteria were the unavailability of donor pancreas extraction time or recipient outcome. Pancreata were procured from both donors after brain death (DBD) as well as from donors after circulatory death (DCD). Patient data were processed and digitally stored according to the declaration of Helsinki ethical principles for medical research involving human subjects. This study was approved by the institutional review board of the UMCG (METc2019/144). Data transfer agreements were prepared for both centers and reviewed by the legal departments and research coordinators. The clinical and research activities were in line with the principles of the Declaration of Istanbul as outlined in the ‘Declaration of Istanbul on Organ Trafficking and Transplant Tourism’.

Surgical procedure

Pancreases were performed either as simultaneous pancreas kidney (SPK), pancreas after kidney (PAK) or pancreas transplant alone (PTA). In DBD donors, predissection of the abdominal organs is carried out before start cold perfusion to prevent prolonged cold ischemia time. Five minutes after the administration of heparin (300 IE/kg body weight), the distal aorta is ligated. Cold perfusion is performed through the proximal aorta with ice cold University of Wisconsin (UW) or histidine-tryptophan-ketoglutarate (HTK) solution with decompression through the inferior vena cava above the diaphragm. The abdominal cavity is filled with saline ice slush for additional topical cooling. The pancreas is procured en-bloc with the spleen according to the no-touch technique [14,15] and transported together with a vascular toolkit (common, internal and external iliac arteries and veins procured from the donor) by static cold storage (SCS) to the recipient hospital. In DCD procedures, a rapid splanchnoparaportalization is performed after which the aorta is cannulated for quick start of cold perfusion with UW/HTK (enriched with 50,000 IE/4L of perfusion solution), followed by dissection and procurement of the organs in the cold.

Before pancreas transplantation, a thorough back table inspection of the pancreas is performed at the recipient hospital, evaluating any injury of the pancreatic parenchyma or vessels. The spleen is removed after ligation of the arteries and veins. The donor external iliac artery is anastomosed to the graft superior mesenteric artery and the donor internal iliac artery to the graft splenic artery (thereby creating a Y-graft). The surgical transplantation techniques were carried out according to techniques described before [16,17]. In short, the pancreas grafts were transplanted intraperitoneally in the right iliac fossa. The common iliac artery of the Y-graft was anastomosed to the common iliac artery of the recipient and the graft portal vein was anastomosed to the recipients inferior vena cava. In about 90% of the patients a duodenojejunostomy was performed for exocrine drainage, in 10% a bladder drainage was performed.

Immunosuppression

Standard induction therapy at the UMCG consisted of OKT3 (1996), ATG or basiliximab (1997–2009), basiliximab (2009–2017) or alemtuzumab (2017–2018) while at the MUI all patients received induction therapy with antithymocyte globulin (4 mg/kg; standard agent) or alemtuzumab (30 mg). In both centers recipients received methylprednisolone (500 mg) intra-operatively. Standard maintenance immunosuppressive therapy contained tacrolimus (trough level: initial 10–15 ng/mL, 8 ng/mL at 9 months, and 4–6 ng/mL after 12 months), or cyclosporine A (only MUI; trough level: initial 180–200 ng/mL, 100–130 ng/mL at 9 months, 80–100 ng/mL at 12 months) prednisone (post-operatively tapered to 5 mg/d), and mycophenolic acid (2000 mg/d).

Data collection and definitions

Donor characteristics and procurement data were obtained from the Eurotransplant donor report and recipient characteristics were extracted from the centers’ prospective databases and supplemented, if necessary, with data from the electronic hospital registries. Pancreas extraction time was defined as the time from aortic cross-clamp until the start of the cold ischemic time by static cold storage on the back table, according to the Eurotransplant manual on donor management [14]. Pancreas Donor Risk Index (PDRI) was calculated for every pancreas according to Axelrod et al. [18] The Charlson Comorbidity Index, a scoring system based on the presence or absence of comorbidity which has been validated in patients with end stage renal disease, was calculated for all recipients [19].

Outcome

The primary outcome parameter of this study was death censored pancreas graft survival (excluding graft loss as a result of patient death). Pancreas graft failure was defined as the resumption of exogenous insulin therapy. The effect of pancreas donor extraction time on death censored graft survival was analyzed using Cox proportional hazards regression analysis after 3 months, 1 and 5 year. The secondary outcome parameter was the effect of pancreas donor extraction time on the incidence of postoperative complications during the initial hospital stay. The following postoperative complications were registered: acute rejection (Y/N, defined as clinically suspected or histologically proven and treated), graft thrombosis (Y/N, demonstrated by Duplex or Computer Tomography), graft pancreatitis (Y/N), postoperative bleeding (Y/N), relaparotomy (Y/N), pancreas delayed graft function (PDGF) (Y/N, as defined by the transient need for exogenous insulin therapy in the immediate post-transplant period [20]), urinary tract infection and wound infection (Y/N). Complications were scored using the Clavien-Dindo classification and the Comprehensive Complication Index, which adds up every single complication scored according to the Clavien Dindo system and calculates a score in between 0 and 100 [21]. The effect of pancreas donor extraction time on death censored graft survival and complications was also analyzed when stratified in three groups based on extraction time: group 1 = 0–45 min, group 2 = 46–90 min and group 3 > 90 min. The group classification was partly based on a previous publication on liver donor extraction time [11].

In a subgroup analysis, only SPK transplants performed
between 2000 and 2018 were included. The effect of pancreas donor extraction time on death censored graft survival was analyzed in this sub group using Cox proportional hazards regression analysis after 3 months, 1 and 5 year.

**Statistical analysis**

Baseline characteristics were presented as mean ± standard deviation (SD) or median with interquartile range (IQR) depending on distribution. Skewness of data was tested using a histogram or Q-Q plots. The effect of each baseline variable on death censored graft survival was analyzed by univariable Cox regression analysis and presented as Hazard Ratios (HRs) (95% confidence interval [CI]). Multivariable Cox regression models were built, analyzing outcome after 30 days, 1 year and 5 year, including variables that were significant in univariable analysis or were shown to be associated with graft survival according to literature (PDRI, recipient BMI, transplant type [SPK/PTA/PAK], initial exocrine drainage, Charlson Comorbidity index, year of transplantation and preservation solution [UW/HTK]). The reported HRs for pancreas donor extraction time refer to an increase of 10 min in extraction time. The effect of pancreas donor extraction time on the comprehensive complication index was analyzed by linear regression analysis, adjusted for year of transplantation, PDRI and charlson comorbidity index. The effect on individual complications was analyzed by binary logistic regression analysis, adjusted for the same variables.

In the second analysis, recipients were divided in three groups of extraction time. Graft survival was estimated using Kaplan–Meier methods and log rank tests were used to determine significant differences between groups. The incidence of complications per group were analyzed by Pearson chi-square tests.

SPSS for windows version 23 was used and a two-sided P value less than 0.05 was considered significant. Figures were made using R: A Language and Environment for Statistical Computing, version 3.6.153 for Mac (R Foundation for Statistical Computing, Vienna, Austria), with the software R-Package “survival”, “ggplot2” and “survminer”.

**Results**

**Donor, transplant and recipient characteristics**

A total of 317 pancreas transplants were included in this study. Eighteen pancreas transplants were performed before the year 2000. Median follow up time was 73 months (IQR: 30–125 months). In total 273 patients (86.4%) received a SPK transplantation, 17 patients (5.4%) PTA and 26 (8.2%) PAK transplantation. Median pancreas extraction time was 64 min [IQR: 52–79 min]. Donor, transplant and recipient characteristics are shown in Table 1. Supplemental Table 1a–b give an overview of the distribution of donor, transplant and recipient characteristics between the three groups of pancreas extraction time.

**Patient and graft survival**

Death-censored pancreas graft survival in this cohort was 85.7% after one year and 76.7% after five years. One- and five-year patient survival was 96% and 88%. In SPK patients, death censored pancreas graft survival was 87% and 80%, in PTA patients 59% and 32%, and in PAK patients 92% and 69% at one and five year, respectively.

**Pancreas extraction time**

Pancreas donor extraction time was associated with the number of procured organs per donor but neither with donor type (DBD or DCD) nor donor BMI. Pancreas graft survival was unaffected by extraction time in univariable analysis (HR 0.997 [95% CI: 0.988–1.007]; p = 0.614). After adjustment for potential confounders, death censored graft survival after 30 days (HR 1.11, 95% CI 0.95–1.3, p = 0.198), year (HR 1.12, 95% CI 0.95–1.31, p = 0.186) and 5 years (HR 1.04, 95% CI 0.91–1.19, p = 0.53) was not significantly associated by pancreas donor extraction time (Table 2). The effect of pancreas donor extraction time on graft and patient survival was also analyzed when stratified by extraction time in three groups. One and five-year death censored pancreas graft survival was 93%, 84% and 87% after one year (log rank p = 0.32) and 84%, 75% and 80% after five years (log rank p = 0.39) in group 1, 2 and 3, respectively (Fig. 1+2). One and five-year patient survival was also not different between the three groups of extraction time after one and five year (log rank p = 0.472 after one and log rank p = 0.379 after five years respectively (Supplementary Fig. 1+2)). In a sub analysis 256 ‘only SPK patients’, were analyzed using Cox regression analysis after 30 days, 1 year and 5 years (Table 3). The increase of 10 min extraction time was not correlated with death censored graft survival after 30 days (HR 1.07, 95% CI 0.884–1.290, p = 0.497), 1 year (HR 1.071, 95% CI 0.887–1.294, p = 0.476) and 5 years (HR 0.997, 95% CI 0.849–1.172, p = 0.975).

**Complications**

In Table 4 the associated of extraction time and the incidence of postoperative complications is shown. No correlation was observed between pancreas donor extraction time and rejection, thrombosis, pancreatitis, relaparotomy, PDGF, urinary tract infection, wound infection and postoperative bleeding. The number of severe complications (scored as Clavien Dino >3a) was significantly associated with extraction time (OR 1.012, 95% CI 1.00–1.02, p = 0.039). No significant association between pancreas donor extraction time and the comprehensive complication index was observed (p = 0.88). In Table 5 the complications are shown when stratified in three groups of extraction time. The incidence of Clavien Dino >3 complications is significantly higher in the group 3 (58.5%), versus group 2 (48.1%) and group 1 (27.9%) [p = 0.014]. Comprehensive complication index was non-significantly lower in group 1 (21, IQR 9–41) versus group 2 (30, IQR 21–45) and group 3 (34, IQR 21–45) [p = 0.364].

**Discussion**

This is, to our knowledge, the first study addressing the effect of pancreas donor extraction time on outcome after transplantation. No significant association between pancreas extraction time and short- and long-term graft survival was demonstrated. However, prolonged pancreas extraction time was associated with a significantly higher incidence of severe complications. The one and five year death-censored graft survival in this cohort is comparable with other series in the literature with reported numbers of respectively 78.6–88% and 76.4–81.5% [2,22].

Donor organ extraction time is influenced by multiple factors such as the number of organs procured per donor, donor BMI, level of experience of the surgical team and anatomical variations [23]. In contrast to donor BMI and donor type (DBD versus DCD), pancreas extraction time was significantly associated with the number of organs procured per donor. Strikingly, the longest extraction time was observed in the period 2008–2016, compared to the shortest extraction time in 2003–2010, indicating that pancreas donor extraction time has increased over the last decade. Possible explanations are the increase in multi-organ pancreas donors nowadays, and that the complexity of the organ donation procedures has
Table 1
Donor, transplant and recipient variables and their influence on death censored pancreas graft survival in univariate analysis.

<table>
<thead>
<tr>
<th>Donor Variables</th>
<th>Hazard ratio</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (male/female)</td>
<td>189 (59.6%)</td>
<td>1.467</td>
<td>0.968–2.224</td>
</tr>
<tr>
<td>Age (years)</td>
<td>31 ± 10.8</td>
<td>1.031</td>
<td>1.010–1.052</td>
</tr>
<tr>
<td>Donor type (DBD/DCD)</td>
<td>23.3 ± 2.7</td>
<td>1.004</td>
<td>0.927–1.087</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>305* (96.2%)</td>
<td>1.799</td>
<td>0.560–5.783</td>
</tr>
</tbody>
</table>

Cause of death

| Trauma capsitis | 136 (42.9%) | 0.859 | 0.489–1.508 | 0.596 |
| SAB | 70 (22.1%) | 0.859 | 0.489–1.508 | 0.596 |
| iCVA | 33 (10.4%) | 1.050 | 0.550–2.003 | 0.882 |
| ICB | 40 (12.6%) | 1.037 | 0.557–1.931 | 0.909 |
| Suicide | 14 (4.4%) | 0.169 | 0.023–1.233 | 0.080 |
| Other | 24 (7.6%) | 0.390 | 0.121–1.258 | 0.115 |
| Serum amylase (U/L) | 66 (35–125) | 0.999 | 0.997–1.001 | 0.500 |

Number of organs procured

| Number of organs procured | 5 (5–6) | 0.776 | 0.577–1.043 | 0.092 |

Thoracic organs procured

| Thoracic organs procured | None | 38 (12%) | 0.659 | 0.347–1.251 | 0.202 |
| Heart | 102 (32.2%) | 0.682 | 0.302–1.542 | 0.358 |
| Lungs | 41 (12.9%) | 0.643 | 0.346–1.197 | 0.164 |
| Heart + Lungs | 136 (42.9%) | 0.643 | 0.346–1.197 | 0.164 |

Transplant Variables

| Transplant type | SPK | 273 (86.1%) | 4.211 | 2.264–7.832 | 0.000 |
| PTA | 17 (5.4%) | 2.093 | 1.127–3.888 | 0.000 |
| PAK | 26 (8.2%) | 2.093 | 1.127–3.888 | 0.000 |

Preservation solution (UW/HTK)

| Preservation solution | UW | 189 (60%) | 0.828 | 0.524–1.326 | 0.442 |
| HTK | 714 ± 192 | 1.001 | 1.000–1.002 | 0.200 |

Cold ischemia time (min)

| Cold ischemia time | 64 (52–79) | 0.997 | 0.988–1.007 | 0.614 |

Pancreas extraction time (min)

| Pancreas extraction time | 1.11 (0.86–1.41) | 2.134 | 1.170–3.893 | 0.013 |

PDRI

| PDRI | 0.997 | 0.577–1.043 | 0.092 |

Transplant year

| Transplant year | 2009 | 0.969 | 0.929–1.010 | 0.138 |

Recipient Variables

| Recipient Variables | Donor type (DBD/DCD) | 195* (61.5%) | 0.869 | 0.562–1.445 | 0.529 |
| Gender (male/female) | 44.8 ± 8.8 | 1.014 | 0.990–1.039 | 0.251 |
| BMI (kg/m²) | 23.3 ± 3.2 | 1.137 | 1.071–1.207 | 0.000 |
| Cold ischemia time (min) | 714 ± 192 | 1.001 | 1.000–1.002 | 0.200 |
| Cause of death | Suicide | 14 (4.4%) | 0.169 | 0.023–1.233 | 0.080 |
| Other | 24 (7.6%) | 0.390 | 0.121–1.258 | 0.115 |
| SAB | 70 (22.1%) | 0.859 | 0.489–1.508 | 0.596 |
| iCVA | 33 (10.4%) | 1.050 | 0.550–2.003 | 0.882 |
| ICB | 40 (12.6%) | 1.037 | 0.557–1.931 | 0.909 |
| Trauma capitis | 136 (42.9%) | 0.643 | 0.346–1.197 | 0.164 |

Data given as Hazard ratio [CI and p-value by Cox regression analysis. Hazard ratio, 95% confidence interval (95% CI), and p-value. BMI — body mass index, DBD — donation after brain death, DCD — donation after circulatory death, SAB — subarachnoidal bleeding, iCVA — ischemic cerebral vascular accident, ICB — intracranial bleeding, SPK — simultaneous pancreas kidney, PTA — pancreas transplant alone, PAK — pancreas after kidney, UW — University of Wisconsin, HTK — histidine-tryptophan-ketoglutarate, PDRI — pancreas donor risk index. Normally distributed variables presented as mean ± standard deviation, skewed variables presented as median (interquartile range), categorical variables as numbers (percentage).

Table 2
Multivariable analysis of factors associated with death-censored pancreas graft survival.

<table>
<thead>
<tr>
<th>Death censored graft survival</th>
<th>30 days</th>
<th>1 year</th>
<th>5 year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pancreas extraction time (per 10 min increase)</td>
<td>1.11 [0.95–1.3]</td>
<td>1.12 [0.95–1.31]</td>
<td>1.04 [0.91–1.19]</td>
</tr>
<tr>
<td>PDRI (per 1 point increase)</td>
<td>3.03 [1.06–8.62]</td>
<td>2.99 [1.06–8.47]</td>
<td>1.91 [0.80–4.54]</td>
</tr>
<tr>
<td>Recipient BMI (per increase of 1 kg/m²)</td>
<td>1.18 [1.08–1.30]</td>
<td>1.18 [1.08–1.30]</td>
<td>1.15 [1.06–1.24]</td>
</tr>
<tr>
<td>Transplant type (PAK versus SPK)</td>
<td>0.88 [0.21–3.8]</td>
<td>0.89 [0.20–3.81]</td>
<td>1.26 [0.44–3.58]</td>
</tr>
<tr>
<td>Initial exocrine drainage (vesical compared to enteric)</td>
<td>1.06 [0.46–2.44]</td>
<td>1.08 [0.47–2.50]</td>
<td>1.31 [0.65–2.63]</td>
</tr>
</tbody>
</table>

Data given as Hazard ratio [CI and p-value. PDRI — pancreas donor risk index, BMI — body mass index, SPK — simultaneous pancreas kidney transplantation, PTA — pancreas transplant alone, PAK — pancreas after kidney transplantation.
study on liver extraction time in DCD donors, median donor liver extraction time in the Netherlands was shown to be substantially longer compared to other studies (63 min in the Netherlands compared to 50 and 35 min in a Belgian and British study). The implementation of several strategies to lower the liver extraction time has led to a substantial decrease to 42 ± 12 min without affecting the occurrence of liver injuries during procurement [11]. The authors highlight the importance of training and regular evaluations in donor organ procurement, which we also consider to be of major importance in pancreas procurement, to enable a shorter pancreas extraction time without comprising pancreas graft quality.

Recently there have been a few studies published on the effect of donor organ extraction time on liver and kidney transplantation outcomes. In a study from the Eurotransplant Registry, assessing outcome in 12,974 liver transplant recipients, donor liver extraction time was independently associated with liver graft loss. Every 10 min increase in extraction time led to an increase in graft loss with a comparable magnitude to the effect of 1 hour of additional cold ischemia time. Especially marginal donor livers (from DCD donors and livers derived from donors with a higher donor risk index) were proven to be more susceptible to a prolonged extraction time [7]. Two other studies investigating the influence of extraction time on DCD liver transplantation showed an independent association of prolonged extraction time and graft survival and the development of non-anastomotic biliary strictures [11,23]. The effect of kidney extraction time has been evaluated in two studies by Osband et al. [6,24] In the first study, a direct correlation between extraction time and early graft failure (EGF) was reported and a shorter extraction time was strongly associated with recovery from delayed graft function (DGF) within three months post-transplantation [6]. The effect was more pronounced in extended criteria donor (ECD) kidneys with 36.4% early graft failure vs. 14.5% in the standard criteria donors. In the second larger study (n = 576), a significant association between longer extraction time and DGF was demonstrated. The incidence of DGF was 27.8% after 60 min and doubled to nearly 60% after 120 min extraction time. A more recent study reported that kidney extraction time was significantly longer in DCD donors compared to DBD donors: median 57 (43–78) versus 50 (39–64) minutes respectively (p < 0.001). Prolonged kidney extraction time was associated with graft loss in DCD but not in DBD kidneys [25]. In contrast to the studies in kidneys and livers, we did not find a significant association between pancreas donor extraction time and graft survival. This can partly be explained by the observation that marginal donor organs are more susceptible to ischemic injury [7,12]. In pancreas transplantation only higher quality donors are selected, which most likely contributes to the differences in outcome compared to the kidney and liver studies.

Ischemia has not only been correlated with harmful effects, since various studies have found beneficial effects of periods of (controlled) ischemia before major surgery. In experimental and clinical settings, remote ischemic preconditioning (RIC) is shown to have a protective effect on ischemia reperfusion injury of the heart after major cardiac surgery [26], although the effect could not be repeated in other studies [27]. A study on RIC in kidney transplant recipients reported no effect of preconditioning on graft recovery after transplantation [28]. In a study examining the effect of donor cardiac arrest prior to organ donation, no significant difference in pancreas graft survival after transplantation was reported [29]. Higher peak elevations in serum lipase in the donor were seen after prolonged periods of asystole, accompanied by lower peak amylase elevations in the recipient. In a more recent study analyzing 371 SPK transplantations, short- and long-term outcomes of recipients from donors with and without cardiac arrest, as proxy for ischemic

increased with organ donors with extensive medical history such as prior surgery or severe arteriosclerosis, leading to a prolonged procurement procedure and thereby extraction time. In a recent

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**Fig. 1.** One-year death-censored graft survival stratified by extraction time (group 1: 0-45 min, group 2: 46-90 min, group 3: >90 min). No differences were seen between groups (log rank p = 0.323).

**Fig. 2.** Five-year death-censored graft survival stratified by extraction time (group 1: 0-45 min, group 2: 46-90 min, group 3: >90 min). No differences were seen between groups (log rank p = 0.392).
The effect of pancreas donor extraction time (per 10 min increase) on the incidence of postoperative complications was observed for both groups. The trend toward superior transplant outcomes after prior donor cardiac arrest might be explained by the concept of ischemic preconditioning, in which an episode of ischemia followed by reperfusion seems to have a protective effect on ischemia-reperfusion injury [20]. The exact underlying mechanisms have not been identified yet and will be subject of many future studies. In light of the current study we think that donor organ extraction time is more an extension of cold ischemia or “lukewarm” ischemia time, and therefore does not seem to have the same protective effect.

Despite the improvement in surgical techniques and immunological strategies, pancreas transplantation is still associated with considerable perioperative morbidity. Severe complications leading to relaparotomy rates of 43% are reported, subsequently resulting in a reduction in patient and graft survival [30–32]. Therefore, donor and recipient criteria are strict and the number of pancreas transplants is still low, and declining, despite an increase in DM type 1 patients [20,33]. Two recent studies show superior outcomes of SPK transplantation compared to deceased or living donor kidney transplantation as renal replacement therapy in DM type 1 patients, with a significant improvement in 10- and 20-year survival in favor of SPK transplantation [34,35]. Also, SPK recipients with a functioning pancreas graft at 1 year have a significantly higher 10-year patient survival compared to recipients with graft failure.
within the first year (respectively 80% vs. 50%) [34]. Given this benefit in patient survival we should keep improving our patient and donor management to maintain or even improve our outcomes and make pancreas transplantation available for all suitable DM type 1 patients. Our secondary outcome parameter was the association between pancreas donor extraction time and postoperative complications, given that pancreas transplant recipients are very susceptible to the development of complications requiring surgical or other invasive treatment. An increased pancreas donor extraction time was associated with a higher incidence of severe complications, indicating that even in these relatively good quality organs the prolonged ischemic insult results in graft injury. The comprehensive complication index, a generally more reliable approach of measuring the total complication burden, was not significantly associated with extraction time. It appears that a prolonged pancreas extraction time, and ischemic injury in particular, leads to more severe surgical complications (for instance postoperative bleeding, anastomotic leakage), with the need for re-intervention.

This study has a few limitations that need to be addressed. This retrospective database study includes all pancreas transplants that have been performed in the past 22 years in two transplant centers in the Eurotransplant region. Despite combining the data of two high volume centers, the relatively small number of patients can lead to either type 1 or type 2 bias. One of the major risks of performing research with large historical cohorts is the possible heterogeneity in patient characteristics and medical treatments over time, which might have an effect on the outcome parameters. In addition, outcome of pancreas transplantation has significantly improved over the last decades. In order to correct for these factors, we performed a multivariable analysis including all potential confounding factors, including year of transplantation, showing pancreas extraction time not to be a significant factor for graft survival. Besides, in a subgroup analysis, including only SPK transplants performed between 2000 and 2018, again no differences in outcomes were observed compared to the main analysis.

In conclusion, in this study pancreas extraction time was not associated with pancreas graft survival. However, given the positive association between Clavien Dindo ≥3a complications and extraction time, efforts in minimizing this period may lead to lower morbidity and consequently better outcomes.

Contributions
ML and FM performed data collection, conceptualized and wrote the manuscript.
SB performed statistical analysis and wrote the manuscript.
FKJ performed data analysis and wrote the manuscript.
RP, HGD and CM conceptualized and revised the manuscript.

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Declaration of competing interest
The authors declare no conflicts of interest.

Appendix A. Supplementary data
Supplementary data to this article can be found online at https://doi.org/10.1016/j.pan.2021.05.001.

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