Donor risk factors, retrieval technique, preservation and ischemia/reperfusion injury in pancreas transplantation

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Purpose of review
Pancreas transplantation is still hampered by a high incidence of early graft loss, and organ quality concerns result in high nonrecovery/discard rates. Demographic donor characteristics, surgical retrieval strategy, preservation fluid and ischemia time are crucial factors in the process of organ selection and are discussed in this review.

Recent findings
The donor shortage is driving an increasing utilization of nonideal organs which would previously have been identified as unsuitable. Recent literature suggests that organs from extended criteria donors – older (>45 years), BMI >30 kg/m^2, and donation after cardiac death (DCD) – can achieve the same graft and patient survival as those from standard criteria donors, with the proviso that the accumulation of risk factors and long ischemic times should be avoided. Visual assessment of the pancreas is advisable before declining/accepting a pancreas. University of Wisconsin represents the gold standard solution; however, histidine–tryptophan–ketoglutarate and Celsior result in equal outcomes if cold ischemia time (CIT) is less than 12 h. Currently in pancreas transplantation, there is no proven effective ischemia/reperfusion injury prophylaxis than trying to keep CIT as short as possible.

Summary
Demographic risk factors, inspection of the pancreas by an experienced surgeon and predicted CIT are crucial factors in deciding whether to accept a pancreas for transplantation. However, there is a need for an improved evidence base to determine where to set the 'cut-off' for unsuitable pancreatic grafts.

Keywords
DCD, ischemia, nonstandard donor, pancreas transplantation, risk score

INTRODUCTION

Simultaneous pancreas kidney (SPK) transplantation represents the treatment of choice for most diabetic patients suffering from end-stage renal disease. Similarly, pancreas transplantation alone (PTA) may be indicated in patients with poor blood glucose control and recurrent life-threatening hypoglycaemic episodes [1]. Despite the published benefits of pancreas transplantation, clinicians are often reluctant to refer patients for this procedure (particularly PTA) due to its complexity and risks. Pancreas transplantation is still hampered by a high burden of early nonimmunological graft losses due to thrombosis, pancreatitis, leakage from the duodenal anastomosis and bleeding [International Pancreas Transplant Registry (IPTR), http://www.iptr.umn.edu]. Surgical complications are associated with reduced long-term graft survival [2,3] and pancreatic graft loss results in a three-fold increased risk ratio for recipient death [4▪]. As a result transplant units are reluctant to accept higher-risk organs resulting in much higher nonrecovery/discard rates compared to other abdominal donor organs [5,6▪▪,7]. In this review, we address the clinical dilemma that faces a transplant surgeon on call, focusing on aspects which influence the decision as to whether or not to accept a pancreas, such as

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KEY POINTS

- No reliable scoring system identifying a 'cut-off' for suitable vs. nonsuitable graft is currently available.

- Surgical assessment of the graft as crucial determinant in graft selection.

- Avoidance of accumulation of donor risk factors.

- Minimization of ischemic times is essential if nonstandard donor grafts are accepted.

demographic donor risk factors, retrieval technique and preservation, and on ischemia/reperfusion injury (IRI).

DEMOGRAPHIC DONOR RISK FACTORS

Accurate donor selection is crucial in pancreas transplantation [8]. Regarding demographic variables an ideal donor can be defined as a donation after brain death (DBD) donor, between 10 and 40 years of age, with a BMI less than 27.5 kg/m^2 and a cause of brain death other than cerebrovascular [9]. Recent IPTR data confirm the importance of donor demographics, with significantly better long-term graft function associated with donors that were young or had a cause of death other than cerebrovascular [10▪▪]. In response to the increasing incidence of nonstandard donors and a high nonrecovery rate, the Eurotransplant Pancreas Advisory Committee introduced the Pre-Procurement-Pancreas-Suitability-Score (P-PASS) that is based on donor parameters available at the time of reporting. Parameters included are age, BMI, ICU stay, cardiac arrest, sodium, amylase, lipase, and catecholamine dose. Total points range from 9 to 28. Retrospective analysis of pancreas donors reported in Eurotransplant demonstrated a three-fold more likelihood to discard the organ if the score was above 17 [7]. Even though this score has been developed to assess the chance of acceptance for transplantation, several centres tested whether it could also predict graft survival. Results are conflicting, with retrospective Eurotransplant registry data showing significantly higher 1-year graft survival in SPK recipients with a P-PASS less than 17 [11], and single-centre analyses reporting no differences in the incidence of IRI and for 1-year or long-term graft survival [12–14].

Review of the Scientific Registry of Transplant Recipients resulted in the development of the Pancreas-Donor-Risk-Index (P-DRI), a measure of organ quality aiming at predicting 1-year graft survival [15▪]. Factors such as sex, age, race, BMI, height, cause of death, serum creatinine and donation after circulatory death (DCD) are included, as well as preservation time. The median donor has a P-DRI of 1 and is defined as male, 28 years of age, nonblack, BMI of 24 kg/m^2, with a height of 173 cm, DBD with a cause of death other than cerebrovascular, serum creatinine less than 2.5 mg/dl and 12 h cold ischemia time (CIT). Age above 45 years, BMI higher than 30 kg/m^2 and DCD increase the P-DRI up to 1.56, 1.17 and 1.39, respectively, resulting in higher risk ratio for graft failure. Although the P-DRI represents a valuable tool for donor selection, different single-centre studies challenge these findings reporting equal outcomes with donors older than 45 years of age, and also successful transplantation of paediatric organs [16–19]. Similarly, recent reports show good outcomes using donors with a BMI higher than 30 kg/m^2 [20▪]. Pancreatic grafts from DCD donors – currently limited to controlled DCD – have also dramatically increased [21]. An analysis of more than 1000 pancreatic grafts transplanted in the UK showed no difference between DCD and DBD in the 1-year patient and graft survival. However, this mirrors a more conservative selection for DCD donors (younger donors, lower BMI, higher incidence of trauma as cause of death). Furthermore, aiming at short ischaemic times, DCD organs were significantly more likely to be locally transplanted [6▪▪]. Similarly, Cambridge showed comparable results between the DCD and DBD transplants; again, cerebrovascular causes of death were less frequent and CIT significantly shorter in the DCD group. Interestingly, the time from withdrawal of treatment to cold perfusion ranged from 16 to 110 min, exceeding by far the threshold of 60 min proposed in the UK and 45 min in the USA [22]. The recently published DCD experience from Madison, Wisconsin, confirms European findings with excellent 1, 3 and 10-year graft survival. The longer mean CIT, compared to European studies, was balanced by the very short mean time from withdrawal of treatment to cold perfusion, pointing at the importance of avoiding accumulation of risk factors in these donors [9,23▪].

RETRIEVAL TECHNIQUE

There are two retrieval strategies in DBD donation: rapid dissection of vasculature and organs in the cold after flush-out (mandatory if the donor is unstable) [24] or warm dissection before cold perfusion [25▪]. Whereas the first technique has the major advantage of shortening the procurement procedure, the second technique gives the possibility of a thorough inspection of possible anatomical variations. Although impaired hepatic microcirculation has been associated with liver hilum

preparation during the warm phase [26] there is no evidence to favour either one of these techniques. Key points of pancreas retrieval are to inspect the organ before perfusion to decide whether it is transplantable, to identify abnormalities in the hepatic arterial supply, to avoid traumatic injury to the pancreas during retrieval, and to procure an intact iliac bifurcation (without excessive traction that can cause intimal dissection) for back-table arterial reconstruction. Following general abdominal inspection opening of the lesser sac permits visual and tactile assessment of the pancreas. Pancreases with extensive fibrosis/calcification, intra-lobular fat and severe oedema should be discarded, whereas peri-pancreatic fat often surrounds a suitable pancreas. An aberrant/accessory right hepatic artery originating from the superior mesenteric artery (SMA) has to be recognized but is only a contraindication for simultaneous liver and pancreas procurement if it is of very narrow calibre and runs through the pancreatic parenchyma. For successful liver transplantation a vessel of typical calibre can be divided outside the pancreas and anastomosed to the stump of the gastroduodenal artery (GDA) [27]. The majority of accessory arteries run behind the pancreas and can be dissected and removed with a patch of proximal SMA patch leaving the distal SMA stump for back-table reconstruction of the pancreatic arterial inflow.

If small bowel is retrieved (for a different recipient to the pancreas) the SMA and the superior mesenteric vein (SMV) can be transected at the insertion point of the mid-colic vessels immediately distally to the uncinate process allowing enough vascular length for the intestinal graft without harming pancreatic arterial supply [28,29]. According to centre preferences abdominal organs can be retrieved either en bloc and separated on the back table [24,28], or in one after the other, with the liver first, followed by intestine, pancreas and kidneys [25"]. In both cases (no evidence favours one strategy) it is of prime importance that the pancreas is retrieved without parenchymal injuries or capsular breaches. Typically these occur by dissecting the GDA (upper margin of the pancreatic head), stapling the mesenteric axis (uncinate process protruding into the mesentery) and by dissecting the pancreas free from all peritoneal attachments and retroperitoneal connective tissue. This is best performed by using the spleen as a handle to minimize surgical trauma of the organ. The excised pancreas comprises the duodenal C, the pancreas itself and the spleen. The three arteries supplying the graft (SMA, splenic artery and GDA) should be intact and the two latter marked with a 6-0 prolene. The iliac bifurcation (Y-graft) should be packed in a separate bag with preservation solution. In addition to these caveats,

external cooling of the pancreas by ice slush placed into the lesser sac is recommended to further reduce the core temperature. Portal perfusion should be performed after completely transecting the portal vein or after venting the splenic or inferior mesenteric vein to avoid congestion of the pancreas [24].

The retrieval technique for DCD organs differs in the timing of the cross clamping, which is either done by 'super rapid recovery' through laparotomy and immediate cannulation of the aorta or by immediate cannulation of the femoral artery. This to keep the ischemia time following cessation of cardiorespiratory function and the recommended 5 min observation period prior to declaration of death as short as possible [30"].

PRESERVATION

Whilst in kidney [31] and liver transplantation [32], there is current debate regarding static cold storage and hypothermic machine perfusion, preservation of the pancreas is achieved by simple cold storage [33]. The three solutions used are in the order of frequency: University of Wisconsin; histidine–tryptophan–ketoglutarate (HTK); Celsior solution [34]. The current 'gold standard' for preservation of the pancreas graft is University of Wisconsin solution, which was, in fact, originally developed by Belzer and Southard as a preservation solution for pancreas transplantation [35]. Other solutions such as HTK and Celsior were originally developed as cardioplegic solutions [36,37] but have been increasingly utilized in the perfusion/preservation of abdominal organs. As the exact composition of the solution goes beyond the scope of this manuscript we refer to recent reviews dealing with this topic [34,38,39]. Comparison of University of Wisconsin with HTK shows conflicting data. In a retrospective single-centre study including 308 organs there were no differences in University of Wisconsin or HTK perfused/preserved grafts regarding patient and graft survival [40""]. These observations are supported by two retrospective studies [41,42] and by a small prospective randomized multicentre study showing no advantage in graft survival of University of Wisconsin compared to HTK [43]. Two retrospective studies contrast these reports. In a United Network for Organ Sharing database analysis Stewart *et al.* [44] reported HTK solution to be associated with a higher risk of graft loss already during the first month following transplantation, especially if CIT exceeded 12 h, and a single-centre analysis describes a four-fold higher thrombosis rate with HTK [45]. There is, however, consensus regarding equal results using University of Wisconsin or HTK if CIT is less than 12 h. Even

though high-volume flush of HTK is recommended by the manufacturer, results of these studies suggest a higher incidence of graft pancreatitis, if the HTK volume exceeds 5 l. Less common is the use of Celsior. In a prospective, randomized study Boggi *et al.* [46] reports similar safety profiles between University of Wisconsin and Celsior. In line with this study Manrique *et al.* [47] shows similar 2-year graft and patient survival for University of Wisconsin and Celsior perfused/preserved pancreases.

ISCHEMIA/REPERFUSION INJURY

The pancreas is highly susceptible to ischemic periods. This is reflected also in the increased incidence of pancreatitis following haemorrhagic shock and cardiac by-pass surgery [48,49]. So far there are no reliable early markers for pancreatic IRI. Serum amylase, lipase and C-reactive protein levels do not correlate well with the intensity of pancreatitis until after a few days after transplantation.

Postischemic microcirculatory failure is considered the hallmark of pancreatic IRI [50–52]. With venous thrombosis of the transplanted graft accounting for the highest number of early graft losses major efforts in experimental pancreas transplantation are focussed on agents aimed at increasing postreperfusion blood flow. These include nitric oxide [53], anticoagulation prophylaxis [54] and prevention of neutrophil adhesion [55]. However, none of these strategies has yet been tested in prospective randomized trials. Recently, a single-centre experience with prophylactic high-dose application (3000 IU) of antithrombin reported lower thrombosis rates and significantly reduced serum amylase and lipase in treated patients [56]. Antiadhesive prophylaxis with a recombinant P-selectin antagonist (YSPSL) has been recently tested in human kidney transplantation showing prevention of inflammatory gene transcription without, however, decreasing delayed graft function [57,58]. Further results are needed to estimate the value of these strategies. Remote ischaemic preconditioning is a promising new approach; originally applied in paediatric cardiac surgery [59], this has been shown to prevent IRI in experimental pancreas transplantation [60,61]. A current randomized controlled trial is now testing this approach evaluating the influence of a short period of blood flow occlusion of the lower extremity prior to organ recovery on kidney, liver and pancreas graft survival (clincaltrials.gov number NCT00975702).

CONCLUSION

Current donor scoring systems may help transplant surgeons to achieve uniform practice and improve utilization of higher-risk organs but these are not reliable in identifying a 'cut-off' for suitable vs. non-suitable organs. As surgical assessment of the graft (probably the most important determinant in organ selection process) is not included, nonstandard organs should always be visually inspected by an experienced pancreas transplantation surgeon before deciding the nonrecovery. Prolonged life expectancy associated with a functioning SPK compared to patients remaining on the waiting list [17,62,63], increased quality of life [64] and psychological issues of the potential recipient should also influence the decision-making. Available evidence suggests the need to avoid an accumulation of demographic donor risk factors. Higher-risk organs should probably be transplanted only if CIT can be kept below 12 h.

The quality of evidence for the best retrieval strategy and optimum perfusion solution is poor; however, there is a broad agreement about the necessity to minimize CIT, since the pancreas is probably the most susceptible abdominal organ to IRI. Currently there is no specific treatment for IRI and prevention is clearly more likely to be effective than treatment.

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Conflicts of interest

The authors have no conflict of interest to declare.

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