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REVIEW

Utilization of organs from donors after circulatory death for vascularized pancreas and islet of Langerhans transplantation: recommendations from an expert group

Thierry Berney[1], Catherine Boffa[2], Titus Augustine[3], Lionel Badet[4], Eelco de Koning[5], Johann Pratschke[6], Carlo Socci[7] & Peter Friend[2]

1 Department of Surgery, University of Geneva Hospitals, Geneva, Switzerland
2 Nuffield Department of Surgery, Oxford Transplant Centre, University of Oxford, Oxford, UK
3 Department of Transplantation, Central Manchester University Hospitals, Manchester, UK
4 Division of Urology and Transplant Surgery, Hospices Civils de Lyon, Lyons, France
5 Department of Endocrinology, Leiden University Medical Center, Leiden, The Netherlands
6 Department of General, Visceral and Transplant Surgery, Charité-University Hospital, Berlin, Germany
7 Department of Surgery, Scientific Institute San Raffaele, Milan, Italy

Correspondence
Thierry Berney MD, MSc, Department of Surgery, HUG, 4, rue Gabrielle-Perret-Gentil, 1211 Geneva 14, Switzerland.
Tel.: +41 22 372 3404;
fax: +41 22 372 7689;
e-mail: thierry.berney@hcuge.ch

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SUMMARY

Donation after circulatory death (DCD) donors are increasingly being used as a source of pancreas allografts for vascularized organ and islet transplantation. We provide practice guidelines aiming to increase DCD pancreas utilization. We review risk assessment and donor selection criteria. We report suggested factors in donor and recipient clinical management and provide an overview of the activities and outcomes of vascularized pancreas and islet transplantation.

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Introduction – why use the pancreas from DCD donors?

Replacement of beta-cell function by transplantation of the whole pancreas or its constituent islets has become firmly established as the best therapeutic option for many patients with renal failure secondary to diabetes, for some diabetic patients with functioning kidney transplants and for a selected population of patients with life-threatening complications of blood glucose control, particularly hypoglycaemia-unawareness, in the absence of renal failure.

However, despite the prevalence of diabetes, the number of patients undergoing pancreas/islet transplantation is still much smaller than those undergoing kidney or liver transplantation. This reflects the risk–benefit balance that is required in every case: patients with uncomplicated diabetes are better served by insulin therapy than transplantation with its attendant risks from the procedure and immunosuppression. Although the long-term results of pancreas transplantation now demonstrate a clear survival benefit, at least in the context of simultaneous pancreas–kidney transplantation [1], it is not an immediately life-saving procedure. For this reason, the use of 'high-risk' organs has to be approached with caution.

However, there is an increasing demand for transplantable organs. In particular, islet transplantation makes high demands on donor numbers both because many recipients require the islets from two or more donors, but also because not all organs provide transplantable yields.

Since the turn of the century, there has been some evidence of a decrease in worldwide pancreas transplantation activity [2]. Activity reports from European organ sharing agencies seem to indicate stability in donation after brain death (DBD), but a significant increase in the mean age of DBD donors and in the percentages of DBD donors >50 years [3–6]. These donors are considered as marginal [7] and are frequently turned down by transplant centres or directly offered for islet transplantation [4,8]. In this context, the use of so-called expanded criteria donors, that is older, high-BMI, but mostly DCD donors, has been instrumental in maintaining a sustained pancreas transplant activity in some European countries, such as the United Kingdom (UK) or the Netherlands [3,5,6,9]. As islet transplantation activity remains marginal in terms of numbers of patients transplanted, pancreases procured from DCD donors have almost exclusively been used for vascularized organ transplantation.

The growing interest in utilizing DCD pancreases is mitigated by the low rate of conversion from organ offer to effective transplantation. A conversion rate of only 3% was reported in a 2000–2008 European survey, but it should be noted that this rate was already 7% in the UK in the study period [6]. The UK has been the European leader in terms of DCD utilization for pancreas transplantation and has a current conversion rate of 12% considering all donors, and even 25% considering only donors within nationally agreed limits for pancreas transplantation [3]. These figures compare well with pancreas conversion rates from DBD donors of 30% and 47% [3]. Lower conversion rates are related to the perception that DCD donor pancreases may be associated with a higher rate of delayed graft function or technical complications. Indeed, DCD status is a component of the pancreas donor risk index (PDRI) that is used in the United States (US) as a tool to decide whether to accept a pancreas for vascularized organ transplantation or not [10], which contributes to the low conversion rate of DCD pancreases in this country. Conversion rates to islet transplantation are unknown and probably marginal.

These considerations demonstrate that there is significant room for improvement in the utilization of DCD pancreases for vascularized organ and islet transplantation. There is a definite need to provide transplant surgeons and physicians with practice guidelines aiming at increasing DCD pancreas utilization, while maintaining a high level of safety for their patients and of functionality of the transplanted organs or tissues. Recommendations of this expert group, with their levels of evidence, are listed in Table 1.

Risk assessment

The pancreas is much more vulnerable to damage than other transplanted organs. A number of factors are known to increase the risk of postoperative complications or failure. These include pre-donation factors (older age, obesity, alcohol, cardiovascular disease) and surgical factors (primarily damage during retrieval).

Although DCD status is a risk factor in relation to the outcome of pancreas transplantation, the use of DCD organs is based upon the hypothesis that the careful selection and management of DCD pancreases (i.e. the mitigation of other risk factors) should allow results that are at least equivalent to those of DBD organs.

It is generally accepted that ischaemia–reperfusion injury is more severe in DCD organs than in DBD, all

other factors being equal; this is based on the depletion of ATP and accumulation of metabolites that occurs much more rapidly during warm than cold ischaemia. DCD organs are, thereby, more prone to reperfusion pancreatitis and this may underlie the greater incidence of venous thrombosis reported in some series. The precise interaction between DCD status and other risk factors (i.e. whether specific other risk factors should be avoided in DCD) is difficult to establish with the level of evidence available.

Conversely, there is evidence that the absence of the systemic manifestations of brain death in DCD donors may be beneficial to post-transplant β-cell function. Toyama *et al.* [11] reported augmentation of macrophages-associated inflammatory molecules (IL-1β, IL-6, TNF-α and MCP-1) in islets from experimental brain-dead donor animals. Contreras *et al.* demonstrated reduced islet recovery from brain-dead donor rats compared with non-brain-dead controls, associated with increased expression of TNF-α, IL-1β and IL-6 and islet cell apoptosis. More importantly, he demonstrated significantly reduced *in vitro* and *in vivo* function of islets from brain-dead donors [12]. In a clinical setting, Zhao *et al.* [13] showed that DCD donor organs yielded 12.5% more islets than DBD organs. It should be noted that a proportion of DCD donors probably fulfil the criteria for brain death (but are not tested), so this may be an underestimate of the true effect.

Axelrod *et al.* [10] analysed data from the Scientific Registry of Transplant Recipients relating to 9401 solid organ pancreas transplants in order to establish the PDRI. Ten donor-related variables were identified as being independently predictive of 1-year pancreas graft survival. These include the following: age (above 45); DCD status; race (Black, Asian); cause of death (CVA); body mass index (BMI; above 30); cold ischaemia time; renal function; and gender (male). Of note, the greatest relative risk was observed in age (RR 1.56) and DCD status (RR 1.39). The data were used to construct an algorithm to assign a score to a donor (PDRI) and this was shown to be predictive of outcome [10].

Theoretical and experimental evidence suggests, therefore, that the use of DCD pancreases is appropriate on condition that the accumulation of other risk factors, especially BMI and cold ischaemia time, is minimized. This may particularly be the case in islet transplantation [14,15]. Organ allocation algorithms should prioritize transport times over other variables in order to minimize cold ischaemia.

Donor management and organ recovery technique

The effect of the duration of warm ischaemia is not well documented in the pancreas, but is likely to be important, as it is in other organs. Warm ischaemia times (WITs) in the UK are short [16], but longer warm ischaemia periods are also tolerated. The defined starting point of warm ischaemia requires consistency: there is an increasing consensus that arterial pressure below 50 mm Hg or oxygen saturation below 70% is a more physiologically relevant end-point than asystole, and defines the increasingly accepted concept of 'functional warm ischaemia' [17]. Similarly, there is no good evidence that the duration of the period between life support withdrawal and asystole is relevant to outcome. It is the duration of the agonal phase of hypotension and hypoperfusion that is critical to the hypoxic effect [18].

The technique of *in situ* cooling, including the use of a double balloon catheter, is derived from that used in DCD kidney transplantation [19]. The cannulation technique used during *in situ* cooling is important with respect to the pancreas. Perfusion of the abdominal organs by cannulation of the superior mesenteric vein as well as the aorta results in poor perfusion of the pancreas, because this increases the pressure on the venous side of the organ and causes congestion. The pancreas should be perfused via an aortic cannula and, whenever possible, vented via a portal venotomy. If portal perfusion to the liver is required, a cannula should be placed via a portal venotomy without compromising pancreatic venous outflow. Adequate flushing and cooling are likely to be important in minimizing subsequent preservation and ischaemia–reperfusion damage. Topical cooling of the pancreas with ice slush placed into the lesser sac during *in situ* perfusion greatly improves the efficiency of cooling and has been shown to improve islet yield and function [20]. A particular advantage of topical ice is that it prevents pancreas rewarming during the liver recovery time. A standardized organ retrieval technique is recommended, which (i) avoids venous congestion of the pancreas and (ii) stipulates the use of ice slush within the lesser sac.

Normothermic regional perfusion (normothermic extra-corporeal membrane oxygenation) of the donor is increasingly used in a number of countries (Spain, France, USA, UK) as a means to replenish the energy stores of donor organs before retrieval and thereby reduce the ischaemia–reperfusion injury at the time of transplantation. The technique involves placing the

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donor onto a cardio-pulmonary bypass circuit after the declaration of death, with an aortic balloon or clamp used to prevent reperfusion of the brain or heart. There is little published evidence of the benefit of this technique in the context of the pancreas. Farney *et al.* [21] published four cases of SPK transplantation for DCD donors managed in this way, all with good outcomes, and Magliocca *et al.* [22] published a single case within a multi-organ DCD series. Although the results from kidney and liver transplantation are encouraging [23], the lack of published information regarding the pancreas precludes any recommendation. This is likely to be a productive area for research.

The use of thrombolysis has been shown to be beneficial in DCD kidney retrieval, at least in terms of machine preservation parameters [24], and has been used in DCD pancreas retrieval (unpublished data). However, this has not been formally tested in the context of multi-organ DCD retrieval, and the evidence does not currently support its recommendation for routine use. This may usefully, however, be the basis for a multi-centre trial.

Preservation of DCD pancreases is based on the same protocols and preservation solutions as preservation of DBD organs. University of Wisconsin (UW), IGL-1, Celsior and HTK solutions are all used, and there is no consistent evidence that any is superior. It is recommended that attempts should be made to minimize storage times by organ allocation algorithms that reduce transport times and (possibly) prioritize patients eligible for virtual cross-matching.

There is very limited clinical experience in the use of hypothermic machine perfusion (HMP) of the pancreas. The first report of four perfused organs and subsequent islet isolation showed good islet yields [25]. Experimental evidence suggests that this technique may have value in islet isolation, in which the moderate oedema associated with prolonged HMP of the pancreas may be beneficial for enzymatic dissociation [26].

The 'two-layer method' (TLM) places the preserved organ at the interface between cold UW solution and an oxygen carrier (perfluorocarbon). Although early studies in rodents were positive, implying effective oxygen diffusion throughout the organ, and early clinical experience seemed to show a benefit for marginal organs, this has not been corroborated in porcine studies and a large clinical study has failed to confirm islet outcome benefit [27]. This probably results from poor penetration of oxygen to the core of pancreases larger than rodents' [28]. Meta-analyses show at best limited interest of the TLM for the preservation of pancreases in view of islet transplantation [29,30]. There is no published evidence in favour of the TLM for clinical DCD pancreas transplantation.

Oxygen persufflation of organs was developed as a means to minimize ischaemia–reperfusion injury and thus improve transplant outcomes [31]. In the case of the pancreas, it consists of the perfusion of gaseous oxygen through the arterial tree, via the superior mesenteric and splenic arteries [32]. The technique has been utilized in a DCD pig model, and shown to decrease islet cell death and increase islet cell ATP levels [32,33]. ATP levels were also increased in human DBD pancreases [32]. Although cumbersome, this promising technology may render more DCD pancreases suitable for successful islet or even vascularized pancreas transplantation.

Postoperative management

Ischaemia–reperfusion injury is manifested by graft pancreatitis and a higher incidence of venous thrombosis [34]. Many patients with diabetic renal failure are hypercoagulable, and a rigorous policy of coagulation and monitoring may be beneficial [35]. The range of strategies used includes heparin, dextran, aspirin, and monitoring in some units requires regular thromboelastography. There is little evidence to support any individual protocol over any other.

Postoperative surveillance is a major challenge in pancreas transplantation with few biomarkers to allow the clinician to detect problems at a time when effective therapy can be instituted. However, early investigation of any functional abnormality (a spike in blood glucose or abnormal glucose tolerance result) can sometimes allow detection of partial venous thrombosis that can be treated effectively by therapeutic anticoagulation [16,36].

Strategies to mitigate ischaemia–reperfusion are likely to find a place in DCD pancreas transplantation, but there is insufficient evidence to recommend any one of these currently.

Overview of current DCD vascularized pancreas transplantation activities and outcomes

The short list of countries that have used DCD donors for vascularized pancreas transplantation currently comprises the US, the UK, The Netherlands, Belgium, Japan and Australia [37]. In the Eurotransplant zone and in the UK, the vast majority of DCD donors are controlled Maastricht Class III donors [5].

Few studies on activities and outcomes have been published. The UW in Madison has been the pioneering centre in the utilization of DCD donors for vascularized pancreas transplantation [38–41]. This group has published its experience in DCD pancreas transplantation in a series of articles over the past decade [38,39,41]. The latest update of this centre compares 72 DCD with 903 DBD pancreas transplants performed between 1993 and 2008 [41]. No distinction was made between recipients of pancreases from DCD versus DBD donors [39]. Donor characteristics were similar in both groups, with the obvious exceptions of longer WIT (17.5 min vs. naught) and vasopressor requirement in 80% vs. 30%.

Occurrence of delayed graft function (DGF) of the pancreas, technical failure and length of hospital stay were similar in both groups. Pancreas graft function was 83% and 72% at 1 and 5 years in the DCD group, as compared with 89% and 79% in the DBD group, these differences failing to reach significance. Mean HbA1c was normal and near-identical in both groups up to 5-year follow-up [41].

Other US publications include a country-wide registry study [40], in which the bulk of the subjects were transplanted at the UW and are included in the above-described publications. DCD donor selection may have been more stringent on a national basis than in Madison, due to the use of the PDRI [10]. Similar outcomes are reported in terms of pancreas graft survival. The main difference resides in the observation of higher rates of pancreatic thrombosis (12.8% vs. 6.1%; $P = 0.06$) and of DGF (28.2% vs. 7.6%; $P < 0.01$) in the DCD group. It should be noted, however, that DGF seemed to occur only in the kidney graft, although time to insulin discontinuation is not reported [40].

In Europe, the UK has led the field for vascularized pancreas transplantation [3,16]. Since 2005, the UK, under the leadership of the University of Oxford, has overtaken the US in numbers of pancreas transplants performed from DCDs [2,3,16]. A recent publication reporting the British experience compares 134 pancreas transplants from DCDs with 875 from DBDs performed between 2006 and 2010 [16]. This represents the largest DCD pancreas transplant activity worldwide. Pancreases were procured from Maastricht Class III and Class IV donors. DCD pancreases were preferentially allocated to local recipients in order to limit cold ischaemia time as much as possible. Recipient selection criteria were otherwise identical for both groups. There was no significant difference in the occurrence of technical failure between both groups. Pancreas graft survival at 1 year was 88% vs. 87% for SPK, and 73% vs. 76% for PAK/PTA, for DCD versus DBD pancreases, respectively.

Another UK, single-centre, study reports the experience of the University of Cambridge over a slightly prolonged period [42]. Remarkably, one-third of SPK transplants were performed with pancreases from DCDs (20 vs. 40). Outcomes were similar in the DCD versus DBD groups in terms of 2-day and 30-day serum amylase and lipase levels, operative morbidity (30-day reoperation rate: 4/20 vs. 11/40; $P = 0.75$), length of hospital stay (17 days vs. 17 days; $P = 0.54$), 1-year pancreas graft survival (84% vs. 95%; $P = 0.18$), and HbA1c at 1 year (5.4% vs. 5.4%; $P = 0.9$). A report of the first case series of pancreas transplantation from DCDs in the Eurotransplant zone was recently published by the Leiden group in the Netherlands [43]. There were five recipients (four SPK, one PAK) from Maastricht Class III donors. Donor selection was not particularly stringent, as shown by a PDRI = 2.45 in one donor. WIT calculated from life support withdrawal to start of cold perfusion was rather high (mean = 32 min; range 22–39), but CIT could be kept short (mean = 9.6 h). The authors emphasize the need for consistency in the definition of WIT and report excellent outcomes, all 5 pancreases being fully functional at 1 year [43].

Overview of current DCD islet transplantation activities and outcomes

Transplantation of islets of Langerhans isolated from DCD donor pancreases is almost anecdotal and has been performed at least in the US, Japan, the UK, the Netherlands and Belgium.

The only available published data of clinical islet transplantation from DCD pancreases are from the US and Japan. The first consistent attempts at isolating islets from DCD pancreases were made in Leicester, UK [44]. The authors compared the results of 8 islet isolations from DCD pancreases with those of 9 from DBDs. No data were given on the Maastricht category of donors. This study merely demonstrated similar islet yields and *in vitro* glucose-stimulated insulin release (static incubation assay), but these islets were not clinically transplanted. More recently, the University of Pennsylvania repeated the experience and compared *in vitro* and *in vivo* islet function of islets isolated from 10 DCD and 10 DBD donors [45]. Maastricht Class III donors were utilized. There were no differences in *in vitro* function assessed in static incubation or glucose perifusion assays. *In vivo*, DCD and DBD islets were equally efficient in reversing diabetes in immunodeficient diabetic mice. One DCD islet preparation was transplanted into a patient with type 1 diabetes and

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hypoglycaemia unawareness and resulted in insulin independence up to at least 3 months after islet transplantation with normalization of HbA1c. No follow-up data are available for this recipient [45].

In Japan, where there is near-unavailability of DBD donors, an initial publication reported the results of eight islet isolations from DCD donors performed over a few months in the Japanese consortium. Maastricht category is not described. Excellent islet yields (mean > 400 000 IEQ) were obtained in all 8 isolations, which all met criteria for transplantation in terms of viability, purity, endotoxin contents, and *in vitro* function in static incubation assays [46]. Seven of these preparations were transplanted into type 1 diabetic recipients, with outcomes reported in a follow-up publication. The Japanese Pancreas and Islet Transplantation Association reported a few years later the outcomes of 65 DCD islet isolations that resulted in 34 transplantations performed between 2004 and 2007 in 18 patients [47]. This represents the largest experience in DCD islet of Langerhans transplantation worldwide. Uncontrolled donors were used, probably consisting of Maastricht Class II, although this is not explicitly indicated. Remarkably, more than half the islet preparations were deemed appropriate for clinical transplantation, although release criteria are not indicated in the publication. Multiple islet infusions were administered in 10 patients and single infusions in 8. The mean number of transplanted preparations was 427 000 IEQ or 7500 IEQ/kg body weight. Insulin independence was achieved in 3/10 patients who completed the islet transplant protocol, that is who received two or three islet infusions. Islet graft survival, defined as basal C-peptide >0.3 ng/ml, was 77%, 47% and 34% at 1, 2 and 3 years for the whole cohort, and 100%, 80% and 57% for patients who had received multiple islet infusions [48]. Because of the lack of DBD donors in Japan, there is no control group in this study.

Donor selection criteria

In terms of Maastricht category, it seems that only Class III DCD donors were used in the US and that mostly Class III and some Class IV DCD donors were used in the UK for vascularized pancreas transplantation. The Australian case report was from a Class III DCD donor [37]. Although there is no published data, it is likely that Class II donors were also used in the Japanese vascularized pancreas transplantation experience. Identical donor selection criteria have been reportedly used for DCDs and DBDs and are similar in the UW and in the UK series. They include an age range of 5–60 years, BMI < 30 kg/m^2, absence of general contraindications such as malignancies, intra-abdominal infection, acute or chronic pancreatitis, abdominal trauma, history of diabetes and history of pancreatic surgery [16,39]. In the UK publication, technical criteria are added, namely a time from withdrawal of cardio-respiratory support to circulatory arrest <60 min (WIT) and adequate *in situ* perfusion with preservation solution as assessed by the procurement surgical team [16].

The pancreas is highly vulnerable to ischaemia–reperfusion injury, which may lead to graft pancreatitis and/or graft thrombosis and result in early technical graft loss. The major determinants of technical failure are old donor age, high donor BMI, non-trauma CVA and prolonged cold ischaemia time [7,10,34]. It is reasonable to assume that the threshold for acceptance in terms of other risk factors should be more conservative in DCD organs and that this is particularly the case for age. This reflects practice in many units in which there is a lower age cut-off for DCD organs. Indeed in the UK, there is good evidence of a more stringent approach to age (28 years vs. 37 years; $P < 0.001$). A cerebro-vascular cause of donor death is a significant prognostic factor with a risk ratio of 1.23 [10]. This is reflected in clinical practice: DCD pancreas donors were less likely to have died of vascular causes (33% vs. 60%; $P < 0.001$) than DBD pancreas donors in the UK cohort [16]. In the UW series, DCD pancreas donors also were less likely to have died of vascular causes (19% vs. 30%; $P = 0.03$). WITs were remarkably short and well within the set limits. Median WIT was 13 min (range 0–30) in the UK series [16], and mean WIT was 17.5 min (range 6–48) in the UW series [39].

It is logical to minimize cold ischaemia time in an organ that has sustained a warm ischaemic injury prior to cold storage. However, there was no difference between DCD and DBD groups in the UK multi-centre study [16]. This may reflect the logistic aspects of DCD transplantation (shorter time between notification and organ retrieval leading to delays waiting for patient preparation, cross-match, etc.). The Cambridge group achieved shorter CITs in the DCD group (8.2 vs. 9.5 h $P = 0.004$) as a result of a policy of selecting patients suitable for virtual cross-match for DCD organs [42].

Consequences of ischaemia–reperfusion injury are much less dramatic in the setting of islet of Langerhans transplantation. The main risks incurred are a failed isolation or islet graft dysfunction, two events that do not expose patients to the life-threatening consequences of pancreas graft thrombosis or pancreatitis. Accordingly, in addition to Maastricht Classes III and IV, Class II DCDs have been successfully used for islet transplantation.

Table 1. Recommendation on utilization of DCD organs for pancreas and islet transplantation.

Recommendation	Grade	References
Warm ischaemia time (WIT) should be minimized for vascularized pancreas transplantation. A WIT limit of 30 min is acceptable for transplantation	B	[17,18]
WIT should be minimized for islet of Langerhans transplantation. A WIT limit of 60 min is acceptable for transplantation	D	[17,18]
In the absence of direct evidence, normothermic regional perfusion (NRP/NECMO) is appropriate in the context of a clinical trial for pancreas procurement from uncontrolled DCD donors both for vascularized pancreas and islet of Langerhans transplantation	D	[21,22]
Rapid laparotomy and direct cannulation of the aorta is the preferred technique in controlled DCD donors both for vascularized pancreas and islet of Langerhans transplantation	D	[19,20]
The pancreas should be perfused via an aortic cannula and, whenever possible, vented via a portal venotomy, for both vascularized pancreas and islet of Langerhans transplantation	D	[9,19]
Topical cooling of the pancreas should be done by placing ice slush into the lesser sac during *in situ* perfusion, both for vascularized pancreas or islet of Langerhans transplantation	C	[9,20]
Every effort should be made to minimize cold ischaemia time and to transplant DCD vascularized pancreases as soon as possible after explantation, for example by favouring allocation to local recipients or those eligible for virtual cross-matching	D	[10,16]
The use of the two-layer method is not recommended	D	[27–30]
Hypothermic machine perfusion (HMP) of DCD pancreases may be appropriate in donors for islet isolation only in the context of a clinical trial. The use of HMP for vascularized pancreas transplantation is not recommended	D	[25,26]
In recipients of DCD pancreases, close monitoring of the vasculature of the graft by ultrasound or cross-sectional imaging, monitoring of coagulation status and assessment of pancreatic enzyme serum levels is advised in the post-operative period	D	[16,34–36]
Maastricht Class III and IV DCD donors can be reasonably used for vascularized pancreas transplantation	B	[16,38–43]
Maastricht Class I and II DCD donors should be used with caution for vascularized pancreas transplantation	D	[46]
DCD donors from Maastricht Classes II-IV can be reasonably used for islet of Langerhans transplantation	D	[46]
Transplantation of vascularized DCD pancreases from donors aged >50 years should be approached with caution and only if other risk factors are favourable	C	[10,16,39]
Transplantation of vascularized pancreases from DCD donors with BMI>30 kg/m^2 should generally be avoided and preferentially proposed for islet isolation/transplantation	C	[10,16,39]
Donor hypertension and death from vascular causes should be taken into account in the context of other risk factors in the allocation of DCD pancreases for vascularized organ transplantation	C	[10,16,39]

Donor selection criteria are not described in the published series, but are unlikely to differ from selection criteria for DBD islet donors. Mean WIT was 8.3 ± 1.0 min in the Japanese series [47] and 22.9 min (range 15–47) in the University of Pennsylvania series [45]. Differences in WITs are explained by the predominant use of Class II donors in Japan, as opposed to Class III in Pennsylvania, and possibly to differences in WIT definitions [44]. Interestingly, the outcome of the islet isolation procedure in terms of islet yields was found to correlate with the function of kidney grafts procured from the same DCD donors [48] (Table 1).

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Conflicts of interest

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