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Evaluating Islet Cell Isolation and Transplantation From Donors Following Medical Assistance in Dying

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Background. Limited information is available regarding outcomes of islet cell isolation (ICI) and transplantation (ITx) using medical assistance in dying (MAiD) donors. We aimed to assess the feasibility and outcomes of ICI and ITx in MAiD donors. **Methods.** ICI and ITx from MAiD were compared with donation after circulatory death (DCD) type III between 2016 and 2023. Differences of isolated islet equivalents (IEQs), numeric viability and other quantitative in vitro metabolic measures were assessed. **Results.** Overall, 81 ICIs were available of whom 34 (42%) and 47 (58%) from MAiD and DCD-III, respectively. There were no differences of pancreas and digested tissue weight and islets viability among the 2 groups; however, cold ischemic time was longer in MAiD (11.5 versus 9.1 h; $P = 0.021$). The IEQ ($P < 0.001$) and percent trapped ($P < 0.001$) were higher in the DCD-III; however, MAiD islets demonstrated a higher purity ($P = 0.020$). Overall, 15 ITx were performed of whom 3 (8.8%) and 12 (25.5%) from MAiD and DCD-III, respectively ($P = 0.056$). Patients had a median fasting C-peptide of 0.51 ng/mL (interquartile range, 0.30–0.76 nmol/L), with no differences between groups (MAiD = 0.52 versus DCD-III = 0.51; $P = 0.718$). The median HbA1c was 6.2% (interquartile range, 5.7%–7%) (MAiD = 6.3% versus DCD-III = 6.1%; $P = 0.815$) and BETA2 scores (MAiD = 7.4 versus DCD-III = 12.8; $P = 0.229$) did not differ. **Conclusions.** ICI from MAiD donor pancreas may be successfully transplanted with comparable outcomes to DCD-III and may be used for research. These results justify additional efforts to consider MAiD as another valuable source of grafts for ITx. Further multi-center studies and larger clinical experience are needed to validate our findings.

(*Transplantation Direct* 2024;10: e1667; doi: 10.1097/TXD.0000000000001667.)

Several countries have accepted the practice of medical assistance in dying (MAiD) where the physician, after appropriate counseling and consent, administers approved and standardized medications to a patient to intentionally cease the life. As of 2023, donation after MAiD has been legalized in few countries, namely Belgium, the Netherlands, Canada[1] and, recently, Spain and Australia. Given the process of MAiD, these types of donors have been classified as donation after circulatory death (DCD) category V. The possibility of organ donation after MAiD with the expected short agonal period before declaration of death has garnered attention among the transplant community as an additional source of organs to increase the donor pool. Some studies have reported satisfactory outcomes for liver, kidney, and cardiothoracic organs.[1-3]

Received 8 March 2024. Revision received 8 May 2024.

Accepted 10 May 2024.

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The authors declare no funding or conflicts of interest.

A.P., K.V., and A.M.J.S. were involved in study concept, study design, project administration and resources, and writing – original draft. All authors were involved in data curation, investigation, and collection and in writing – review & editing. A.P. and K.V. were involved in data analysis and interpretation and resources, validation, and visualization.

Supplemental digital content (SDC) is available for this article. Direct URL citations appear in the printed text, and links to the digital files are provided in the HTML text of this article on the journal's Web site (www.transplantationdirect.com).

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ISSN: 2373-8731

DOI: 10.1097/TXD.0000000000001667

In Canada, the process of organ donation following MAiD is regulated by the law since June 2016 to outline the procedures and eligibility criteria. Between 2016 and 2021, 31 664 MAiD procedures were reported, but only 155 patients donated their organs and tissues.[4] Briefly, after MAiD eligibility has been confirmed, the patient is referred to organ donation organization and informed consent must be obtained. Organs are therefore allocated, and the MAiD process is generally commenced in hospital, although organizations have been able to accommodate patients' wishes to die at home and pursue donation.[5] After the administration of drugs, the individual undergoing MAiD must be pronounced dead before organ procurement. Death is determined using circulatory and respiratory criteria and a 5-min "no-touch period" is required to determine that the loss of circulation is permanent.[6,7]

Islet cell transplantation (ITx) is an effective treatment for selected people with type 1 diabetes and intractable hypoglycemia with satisfactory long-term outcomes.[8] Recently, the Belgium group demonstrated feasibility of islet cell isolation (ICI) after DCD-V, showing a better in vitro outcome with a 50% higher average β-cell number before and after culture and a higher average beta cell purity compared with selected DCD category III (DCD-III) organs.[9] That report was limited to an experience with 13 isolations and a single clinical transplant with DCD-V islets. Despite this report, limited information is currently available regarding outcomes of ICI and ITx with organs recovered from DCD-V.

In this single-cohort study, the ICI and ITx with DCD-V grafts were analyzed with the aim to assess isolation and transplantation outcomes and to compare them with the results of the more commonly performed transplantation with DCD-III grafts.

MATERIAL AND METHODS

Study Design

A retrospective review of a prospectively maintained database was performed. Donation after MAiD was legalized in Canada in 2016 and, therefore, all DCD pancreata category V undergoing ICI at University of Alberta Hospital Clinical Islet Transplant Program and University of Alberta IsletCore between January 2016 to September 2023 were included. As a comparative cohort, all ICIs from pancreata obtained by the University of Alberta Clinical Islet Transplant Program following DCD category III (DCD-III) were reviewed in the same period. Data collected included information about donors' and recipients' characteristics, such as gender, age, body mass index (BMI) in kg/m^2 were collated. ICI data, including pancreas weight, isolated islet equivalents (IEQs), islet purity and viability were collected. For patients undergoing ITx, the clinical outcomes were collected. Reduced insulin was defined as a reduction in the total daily dose of insulin that patients were requiring. Values for BETA score, C-peptide and insulin have previously been described by our group.[10] This study was approved by our institutional health research ethics board (PRO0000001120 and PRO00087040).

Procedure of Islet Isolation

All pancreata were assessed for suitability of ICI. The isolation was routinely performed according to previously published protocols.[8,10,11] Notably, islet isolations were completed at 2 unique sites including the University of Alberta Clinical Islet Transplantation Laboratory and the University of Alberta IsletCore.[11] Techniques, materials, and technicians are similar between both islet isolation sites; however, pancreata are first offered to the clinical islet laboratory for isolation and, if deemed not suitable for clinical use, they are subsequently offered to the IsletCore for islet isolation for research distribution. In view of of the differences in organ quality, comparisons in this study focus on the clinical islet isolations, with secondary analysis including ICI completed for research purposes.

Study Comparisons

We compared the differences between DCD-V and DCD-III in terms of IEQs, numeric viability, and other quantitative in vitro metabolic measures of function, static insulin/c-peptide release.

Statistical Analysis

Continuous values are presented as medians with interquartile range (IQR) and discrete values are presented as absolute numbers with percentages because of data being nonnormally distributed. Cohorts are described according to donor type (DCD-V versus DCD-III) with donor demographics, ICI, and clinical ITx outcome comparisons made using Mann–Whitney U testing for continuous variables and chi-square testing for discrete variables.

Because of ICI being conducted at 2 sites with differing acceptance criteria 2 additional subgroup analyses were planned a priori. The first subgroup compared demographics and ICI outcomes for islet isolations completed by the IsletCore compared with the University of Alberta Clinical Islet Transplantation Laboratory. The second subgroup compared all DCD-V and DCD-III islet isolations including those completed at the University of Alberta IsletCore and the Clinical Islet Transplantation Laboratory. Statistical analysis was performed using Stata 17 (STATA Corp LP, College Station, TX) with the alpha set to a P value of <0.05.

RESULTS

Baseline Characteristics of the Clinical Donor Cohort

Data were available for 81 ICI (34 DCD-V and 47 DCD-III) with 16 (19.8%) being isolated for research purposes by the University of Alberta IsletCore, all of which were DCD-V. Donors with islets isolated by the University of Alberta Clinical Islet Transplantation Laboratory had a median age at procurement of 49.0 y (IQR, 26.0–58.0 y), a median BMI of 26.3 kg/m^2 (IQR, 22.4–30.0 kg/m^2), and 24 (36.9%) were female (Table 1). There were no significant differences between the sex, HbA1c, and BMI between DCD-V and DCD-III (Table 1). The age of patients (P = 0.003), their minimum glucose (P = 0.002), and maximal glucose (P < 0.001) were significantly higher in DCD-III compared with DCD-V.

Cause of death was significantly different between donor cohorts (P < 0.001) with DCD-V donors having more primary neurologic conditions (35.3% versus 2.1%), spinal cord injuries (5.9% versus 0%), and not reported (47.1% versus 0%). DCD-III donors were more likely to have anoxic brain injury (51.1% versus 0%), cerebral vascular accidents (25.5% versus 0%), spontaneous intracranial hypotension (4.3% versus 0%), and traumatic brain injuries (14.9% versus 0%).

TABLE 1.

Characteristics of islet donors comparing DCD-V and DCD-III for donor islets collected for clinical use (excluding those collected for research)

	Clinical Donors, n = 65	DCD-V, n = 18	DCD-III, n = 47	*P*
Female	24 (36.9)	6 (33.3)	18 (38.3)	0.448
Age, y	49.0 (36.0–58.0)	55.5 (50.0–60.0)	47.0 (29.0–55.0)	0.003
HbA1c	5.4 (5.2–5.7)	5.4 (5.2–5.7)	5.4 (5.2–5.7)	0.600
BMI	26.3 (22.4–30.0)	27.2 (22.4–30.1)	26.0 (22.3–30.0)	0.563
Minimum basal glucose before isolation*	6.7 (5.6–7.6)	5.6 (5.0–6.1)	6.9 (6.4–8.0)	0.002
Maximum basal glucose before isolation*	8.3 (6.1–9.9)	5.6 (5.0–6.1)	9.2 (7.9–12.0)	<0.001
Underlying disease				<0.001
Anoxic brain injury	25 (30.9)	1 (2.9)	24 (51.1)	
Primary neurologic condition	13 (16.0)	12 (35.3)	1 (2.1)	
CVA	12 (14.8)	0 (0)	12 (25.5)	
Spontaneous intracranial hypotension	2 (2.5)	0 (0)	2 (4.3)	
Spinal cord injury	2 (2.5)	2 (5.9)	0 (0)	
Traumatic brain injury	7 (8.6)	0 (0)	7 (14.9)	
Other	3 (3.7)	2 (35.9)	1 (2.1)	
Not reported	16 (19.8)	16 (47.1)	0 (0)	
Transplanted	15 (23.1%)	3 (16.7%)	12 (25.5%)	0.448

*Data for minimum and maximum basal glucose only available for 18 of the 34 DCD-V cases. Not available from cases collected for research.
Values are presented in median (IQR).
BMI, body mass index; CVA, cerebrovascular accident; DCD, donation after circulatory death; IQR, interquartile range.

Characteristic of Islet Isolates

Comparison of ICI completed for clinical purposes demonstrated that DCD-V and DCD-III isolated islets had similar outcomes across all isolation criteria including cold ischemia time ($P = 0.229$), pancreas weight ($P = 0.975$), digested tissue weight ($P = 0.275$), isolated IEQ ($P = 0.179$), percent trapped islets ($P = 0.262$), purity ($P = 0.331$), viability ($P = 0.326$), and glucose-stimulated insulin secretion ($P = 0.09$) stimulation index (Table 2).

Additionally, perifusion of isolated islets demonstrated similar characteristics between DCD-V and DCD-III. During exposure to low glucose, DCD-V islets (n = 4) produced 14.71 uU/mL (IQR, 12.1–23.2 uU/mL) insulin compared with 24.9 uU/mL (IQR, 12.5–48.8 uU/mL) insulin for DCD-III (n = 8; $P = 0.513$). When stimulated with high glucose, DCD-V islets also produced a similar amount of insulin as DCD-III islets (354.1 versus 187.8 uU/mL; $P = 0.513$). Therefore, during perifusion, they achieved a similar low-glucose to high-glucose stimulation index (24.1 versus 14.5; $P = 0.827$). Additionally, the insulin stimulation rate per IEQ was also similar between DCD-V and DCD-III at low insulin (Table 2).

Subgroup analysis comparing islets isolated by the IsletCore for research to those isolated by the Clinical Islet Laboratory demonstrated that donors who had islets isolated for research were older (56.0 versus 49.0 y; $P = 0.005$), had a lower HbA1c (5.4% versus 5.2%; $P = 0.019$), but other baseline characteristics were similar (**Table S1, SDC**, http://links.lww.com/TXD/A671). In terms of islet isolation outcomes of this subgroup, research-based donors had a nonstatistically significantly longer cold ischemia time (12.5 versus 9.2 h; $P = 0.092$), with a nonstatistically significant

TABLE 2.

Islet isolation outcomes for donor islets collected for clinical use (excluding those collected for research)

	Clinical Donors, n = 65	DCD-V, n = 18	DCD-III, n = 47	*P*
Cold ischemia time (h)	9.2 (6.5–13.0)	10.4 (8.0–13.6)	9.2 (5.8–12.8)	0.229
Pancreas weight (g)	92.8 (81.0–103.7)	93.5 (76.4–103.7)	92.5 (81.3–105.1)	0.975
Digested tissue weight	52.5 (37.1–66.1)	45.1 (31.1–65.2)	53.8 (42.0–66.8)	0.275
Isolated IEQ	288 205 (181 330–464 114)	211 106 (115 900–451 774)	321 583 (209 111–516 282)	0.179
Percent trapped	17.7 (8.8–29.5)	14.3 (8.6–27.6)	19.5 (9.1–36.5)	0.262
Purity	37.5 (30.0–55.0)	31.3 (30.0–47.5)	38.8 (30.0–55.0)	0.331
Viability	89.5 (82.5–94.0)	87.8 (79.5–92.5)	90.0 (85.0–94.0)	0.326
GSIS stimulation index	2.2 (1.5–3.4)	1.5 (1.4–2.0)	2.7 (2.1–3.6)	0.093
Insulin produced in low glucose (perifusion)*	23.0 (13.6–43.8)	14.7 (12.1–23.2)	24.9 (12.5–48.8)	0.513
Insulin produced in high glucose (perfusion)*	190.4 (157.2–704.1)	354.1 (218.7–512.3)	187.8 (132.5–1054.0)	0.513
Perifusion stimulation index*	19.3 (4.1–27.4)	24.1 (12.1–28.6)	14.5 (2.0–27.6)	0.827
Metabolic rate at low glucose (uU/IEQ/16 min)*	0.61 (0.49–1.17)	0.45 (0.38–1.07)	0.66 (0.52–1.25)	0.275
Metabolic rate at high glucose (uU/IEQ/16 min)*	4.38 (3.07–10.64)	6.29 (3.77–8.66)	4.27 (2.1–15.0)	0.513

*Perifusion was completed for n = 4 DCD-V and n = 8 DCD-III.
Values are presented in median (IQR).
DCD, donation after circulatory death; IEQ, isolated islet equivalents; IQR, interquartile range; GSIS, glucose-stimulated insulin secretion.

lower isolated IEQ (249 327 IEQs versus 288 205 IEQs; $P = 0.138$) but fewer trapped islets and greater purity (**Table S1, SDC**, http://links.lww.com/TXD/A671).

The second subgroup analysis comparing all DCD-V and DCD-III including both donors isolated by the IsletCore (for research) and the University of Alberta Clinical Islet Transplant Program was completed. There were no differences of pancreas weight, digested tissue weight, viability of islets among the 2 groups. The isolated IEQ ($P = 0.041$) and percent trapped ($P < 0.001$) were higher in the DCD-III; however, the islets obtained from DCD-V demonstrated a nonstatistically significant higher purity ($P = 0.093$). The glucose-stimulated insulin secretion stimulation index was similar between the 2 groups ($P = 0.502$). These results are summarized in **Table S2** (**SDC**, http://links.lww.com/TXD/A671).

Clinical Outcomes of Patients Undergoing Islet Transplantation

Overall, 15 ITx were performed, of whom 3 and 12 were from organs obtained following DCD-V and DCD-III, respectively. Accordingly, 8.8% of islets isolated from DCD-V donors and 25.5% of DCD were used for clinical transplant ($P = 0.056$).

Recipient demographics demonstrated an age at transplant of 54.3 y (IQR, 46.5–59.8 y), with 10 (66.7%) being female. All but 4 (26.7%) of recipients had previously undergone ITx, with a median ITx number of 2.0. Of patients with prior ITx, 4 (26.7%) had 2 prior, 4 (26.7%) had 3 prior, and 3 (20.0%) had ≥3 prior ITx. One patient had received a ITx because their DCD-III transplant and their outcomes were censored at the point of this transplant. Patients received a median of 7538 (IQR, 5477–8857) IEQ/kg with viability of 87.5% (IQR, 83.0%–94.0%), purity of 55.0% (IQR, 47.5%–60.0%), and trapped percentage of 1.0%. Islet culture time before transplant was 30.5 h (IQR, 27.8–32.8 h). All recipient demographics including age at transplant, sex, and number of ITx were similar between those with DCD-V and DCD-III donors (Table 3).

Recipient follow-up was a median of 2.0 y, with similar duration for patients receiving DCD-V islets (2.1; IQR, 1.6–4.2 y) and DCD-III islets (1.6; IQR, 0.4–3.2 y; $P = 0.471$). All recipients had a reduction in their insulin use with 1 patient in the DCD-V group and 6 in the DCD-III group being insulin independent. Patients had a median fasting C-peptide of 0.51 nmol/L (IQR, 0.30–0.76 nmol/L), and there was no statistically significant difference between groups (0.52 versus 0.51; $P = 0.718$). Additionally, the median HbA1c was 6.2% (IQR, 5.7%–7.0%), with no difference between cohorts (6.3% versus 6.1%; $P = 0.815$). Finally, BETA2 score between cohorts was similar (7.4 versus 12.8; $P = 0.229$). The follow-up data are summarized in Table 4.

DISCUSSION

We describe herein a comparison of human pancreatic islet isolation from a total of 34 DCD-V donors, compared with 47 standard DCD-III donors, which although limited, still represents the largest collective experience with medical

TABLE 3.

Characteristics and outcomes of ITx recipients

	ITx recipients, n = 15	DCD-V, n = 3	DCD-III, n = 12	*P*
Age at transplant, y	54.3 (46.5-59.8)	46.9 (36.4-48.8)	55.8 (48.3-61.5)	0.083
Female	10 (66.7)	3 (100)	7 (58.3)	0.171
Prior ITx	11 (73.3)	1 (33.3)	10 (83.3)	0.299
1	4 (26.7)	0 (0)	4 (33.3)	
2	4 (26.7)	0 (0)	4 (33.3)	
3+	3 (20.0)	1 (33.3)	2 (16.7)	
No. ITx	2 (1–3)	1 (1–5)	2.5 (2–3)	0.504
IEQ/kg	7538 (5477–8857)	7918 (5477–10 026)	7464 (5482–8440)	0.773
Viability	87.5 (83.0–94.0)	83.0 (81.0–87.0)	90.3 (84.8–95.5)	0.112
Purity	55.0 (47.5–60.0)	50.0 (35.0–72.5)	55.0 (48.8–60.0)	0.662
Trapped percent	1.0 (0.3–3.0)	2.5 (1.0–3.0)	1.0 (0.5–5.3)	0.712
Culture time	30.5 (27.8–32.8)	30.5 (22.0–32.8)	30.6 (28.3–32.4)	0.665

Values are presented in median (IQR).
DCD, donation after circulatory death; IEQ, isolated islet equivalents; ITx, islet cell transplantation.

TABLE 4.

Follow-up data of clinical islet cell recipients comparing DCD-V and DCD-III

	ITx recipients, n = 15	DCD-V, n = 3	DCD-III, n = 12	*P*
Follow-up	2.0 (0.5–3.5)	2.1 (1.6–4.2)	1.6 (0.4–3.2)	0.471
Reduced insulin	15 (100)	3 (100)	12 (100)	N/A
Fasting C-peptide	0.51 (0.30–0.76)	0.52 (0.10–0.70)	0.51 (0.30–0.78)	0.718
HbA1c, %	6.2 (5.7–7.0)	6.3 (5.6–9.6)	6.1 (5.7–7.0)	0.815
BETA2	12.4 (6.6–25.5)	7.4 (2.3–23.9)	12.8 (8.1–26.7)	0.229

Values are presented in median (IQR).
DCD, donation after circulatory death; ITx, islet cell transplantation; N/A, not applicable.

assistance in dying donation to date. Such practice is not currently approved in the United States but is accepted in Canada, Belgium, and the Netherlands, Spain and Australia. This study confirms that islets from DCD-V donors may be isolated successfully and potentially transplanted.

The results show that ICI with DCD-V pancreas grafts have satisfactory purity, viability and isolated IEQ rates that are comparable to those of the more commonly utilized with DCD-III when we compare outcomes of clinical-intent isolations. In addition, ITx with islet isolated after DCD-V appears to achieve similar outcomes to the DCD-III in terms of reduction of insulin, C-peptide, and HbA1c levels and BETA2 score. However, our clinical outcome experience with only three isolations remains limited thus cannot be overinterpreted and is further confounded by functional outcomes that are mixed with prior or subsequent isolations. These findings appear to be of relevance given the possibility to increase the donor pool using islets donated after DCD-V.

DCD-V procurement represents a minority (<10%) of all DCD procedures even in countries where it has been legalized for decades like Belgium, but it has been demonstrated that organ donation in following DCD-V has the potential to double the total number of donor organs available for transplantation.[12] Donation after brain death is followed by cytokine storm which have been shown to have a negative impact on ICI and in vivo function.[13] On the other hand, a prolonged agonal phase in DCD-III could impair in vitro islet function,[14] although good outcomes of ITx after DCD-III are reported.[15] Theoretically, these issues are not present during DCD-V given the absence of brain death cytokine storm and the shorter agonal phase; thus, these donors should yield better grafts.

Considering the benefits of ITx in the treatment of type 1 diabetes,[8,16] the applications of ITx after DCD-V are potentially relevant to increase the donor pool. This led our clinical islet program to consider these grafts for ITx because MAiD was legalized in Canada in 2016. In this study, we have shown that ICI from DCD-V had slightly higher purity, which was not statistically significant ($P = 0.093$); however, we observed less isolated IEQ ($P = 0.041$) and less percentage of islets trapped ($P < 0.001$) when comparing total isolations (clinical intent and research combined). In the clinical setting, only 3 of 34 (8.8%) DCD-V preparations were used for ITx, which is considerably lower compared with 12 of 47 (25.5%) DCD-III ($P = 0.056$). This difference could be explained by the limited experience with DCD-V ICI which led to a more conservative clinical decision to proceed. Nevertheless, we have observed satisfactory outcomes of ITx from DCD-V compared with DCD-III. However, levels of C-peptide were lower in the DCD-V and patients had higher HbA1c. In addition, BETA2 score was lower in DCD-V without statistical differences ($P = 0.229$). Although none of these factors reached statistical significance when comparing with DCD-III, these positive results need to be interpreted with caution given the small sample size.

We found that ICI from DCD-V have higher purity compared with DCD-III and our cohort of patients had reduction on insulin requirement after ITx. These encouraging results are in line with the only other case reported in the literature, where authors found that the patient decreased insulin need.[9] These findings are promising; however, they need to be interpreted carefully given the small number of patients involved.

This study has several limitations which need to be acknowledged when evaluating its results. First, because of the retrospective nature of our study, some data might have been inherently lost. This could have introduced bias, as there could be other unmeasured factors which would result in confounding. Notably, data on the warm ischemic times of donors were not available and their correlation with isolation and clinical outcomes could not be assessed. Second, although donation after DCD-V is not commonly performed, the sample size presented here is relatively small, and it makes it difficult to provide robust conclusions. In particular, data on the discard reasons following isolation for those which did not proceed to transplantation were not available. Finally, the results of this study are based on data from a single center in Canada, thus the findings might not be generalizable to other population or countries, particularly those where healthcare system and population demographics differ considerably from Canada. In addition, at the time of writing, MAiD is legalized only in Canada, Belgium, the Netherlands and recently in Spain and Australia; therefore, this limits the broader applicability of our data.

Notwithstanding several limitations, this study has demonstrated that ICI after DCD-V is feasible and ITx may be performed safely and successfully, albeit with limited clinical experience to this point. ICI from pancreata donated after DCD-V seems to yield promising results with regards to in vivo islets function. Moreover, the clinical outcomes after ITx of these grafts in terms of insulin reduction, BETA2 score and HbA1c levels are similar to the more commonly used DCD-III. The results of our study justify any additional efforts to increase the number of ICI and ITx following DCD-V which could potentially increase the donor pool available. This limited data suggest that we should continue to pursue donation after MAiD and to consider these organs suitable for ICI and ITx, but further multicenter studies are warranted to validate these preliminary findings.

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