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ORIGINAL ARTICLE

Graft utilization after normothermic regional perfusion in controlled donation after circulatory death—a single-center perspective from France

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SUMMARY

Normothermic regional perfusion (NRP) in controlled donation after circulatory death (cDCD) is a promising procurement strategy. However, a detailed analysis of graft utilization rates is lacking. This retrospective study included all cDCD donors proposed to a single center for NRP procurement of at least one abdominal organ from 2015 to 2020. Utilization rates were defined as the proportion of transplanted grafts from proposed donors in which withdrawal of life sustaining therapies (WLST) was initiated. In total, 125 cDCD donors underwent WLST with transplantation of at least one graft from 109 (87%) donors. In a total of 14 (11%) procedures NRP failure led to graft discard. Utilization rates for kidney and liver grafts were 83% and 59%, respectively. In 44% of the discarded livers, the reason was poor graft quality based on functional donor warm ischemia >45 min, macroscopic aspect, high-transaminases release, or pathological biopsy. In this study, abdominal NRP in cDCD lead to transplantation of at least one graft in the majority of cases. While the utilization rate for kidneys was high, nearly half of the liver grafts were discarded. Cannulation training, novel graft viability markers, and *ex-vivo* liver graft perfusion may allow to increase graft utilization.

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Key words
donation after circulatory death, extended criteria donor, graft utilization, normothermic regional perfusion, organ donation

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Introduction

Normothermic regional perfusion (NRP) is a promising procurement strategy in controlled donation after circulating death (cDCD) [1]. During NRP, future grafts undergo in-situ perfusion at normothermic temperatures with an extra-corporeal membrane oxygenation (ECMO) perfusion [2]. Several cDCD programs worldwide have opted for the use of NRP as an alternative to super-rapid organ procurement [3,4]. France, Italy, and Norway have implemented a mandatory use of NRP for every cDCD procurement [1,5]. While studies report excellent outcomes after NRP in cDCD liver and kidney transplantation, this strategy requires additional logistics, donor cannulation training, and raises specific ethical questions [6-10]. In addition, a detailed analysis of utilization rates and reasons for graft discard including technical failures after NRP are currently lacking [3]. In the context of an increasing liver and kidney graft shortage, these data are urgently needed to optimize the use of available grafts, improve procurement and preservation strategies and further expand cDCD organ transplantation [11].

Materials and methods

Study design

This is a retrospective cohort study including all consecutive cDCD donors proposed for transplantation of at least one abdominal organ to our center and for whom withdrawal of life sustaining therapies (WLST) was initiated. The study period covers 6 years (01.01.2015–31.12.2020).

Donor and recipient selection criteria

The French cDCD program started in 2015 with mandatory use of NRP for every procurement [5]. Strict donor and recipient selection criteria apply in order to select low-risk combination and achieve optimal post-transplant outcomes (Table 1). Of note, donor age limit was modified from <61 years until 2018 to <71 years in 2020. In addition, allocation of cDCD grafts was regional in contrast to DBD grafts, which are allocated at a national level to reduce static cold storage duration and facilitate coordination of the cDCD procedure. There were no cDCD lung or pancreas procurements performed in our study population.

Abdominal NRP and organ procurement

Abdominal NRP was applied to the donor after circulatory arrest, with the aim of reconstituting blood flow at physiological temperatures to the donor organs prior to procurement. Heparin (300 UI/kg) was routinely administered to the donor upon start of WLST. Once circulatory arrest occurred, a donor "no-touch" period of 5 min was mandatory before death could be

Table 1. Donor and recipient selection criteria for cDCD kidney and liver transplantation in France.

	Liver transplantation	Kidney transplantation
Donor criteria		
Age	<71 years	<71 years
Comorbidities	No chronic disease AST/ALT ≤ 4N	No chronic disease Normal renal function
NRP	AST/ALT ≤ 4N	No defined selection criteria
Biopsy after NRP	Steatosis ≤ 20%, Fibrosis < F2	No routinely performed biopsies
Ex-vivo hypothermic perfusion	–	No defined selection criteria
TDWI	≤3 h	≤3 h
FDWI	≤45 min	–
AWI	≤30 min	If <66 years: ≤45 min If 66–71 years: ≤30 min
Recipient criteria		
Age	≥18 and ≤65 years	≥18 years
Hepatic/renal disease	Primary transplant, no PV thrombosis, MELD ≤25, no super-urgent transplantation	Primary transplant
Comorbidities	No major surgical history No ventilation, no inotrope UNOS 1	To consider but not mandatory: Vascular disease, surgical history

ALT, alanine aminotransferase; AST, aspartate aminotransferase; AWI, asystolic warm ischemia time, FDWI, functional donor warm ischemia time; NRP, normothermic regional perfusion; TDWI, total donor warm ischemia.

declared. Once death was declared, arterial, and venous cannulas for NRP were inserted over preplaced guidewires into femoral vessels by an anesthesiologist (postmortem vessel cannulation). The minimal required duration of NRP before procurement could proceed was 60 min with a maximum of 4 h (details in Appendix S1). Once NRP was terminated, organs were cold flushed and a standard organ procurement was performed. Liver grafts underwent static cold storage while kidney grafts underwent *ex-vivo* hypothermic machine perfusion until implantation (Appendix S1; Fig. S1).

Endpoints and definitions

Proposed donors included all donors who were screened by the national donor agency (Agence de la Biomédecine) and who were inside the aforementioned French cDCD selection criteria with consent by the donor and family (Table 1). Only once a donor was proposed for procurement, transplant teams were able to accept or decline the proposition.

The primary endpoint of the study was utilization rates for cDCD kidney and liver grafts defined as the proportion of transplanted organs procured from donors initially proposed for cDCD donation of the respective. Secondary endpoints included reasons and characteristics of discarded grafts, technical failures of NRP and graft and recipient survival after NRP cDCD kidney and liver transplantation at our center. We also investigated the impact of the time period on utilization rates and adverse events after NRP. For this purpose, we divided the cohort in two time periods, prior and after the change in donor age limit (2015–2018 vs. 2019–2020), and performed a subgroup analysis.

Functional Donor Warm Ischemia Time (FDWI) was defined as the duration from systolic blood pressure below 45 mmHg to initiation of NRP (Fig. S1). Asystolic Warm Ischemia (AWI) was defined as the period from occurrence of cardiac arrest until initiation of NRP (Fig. S1). Extended criteria for cDCD liver donors (EDCD) were based on the UK-DCD Risk score and included donor age >60, donor BMI >25 and FDWI >30 min [12]. A donor presenting at least 2 of these criteria was considered EDCD. Extended criteria for cDCD kidney donors were defined as a donor age >60 years or between 50 and 59 years with at least two of the three following criteria: cerebrovascular cause of death, renal insufficiency, and hypertension [13].

Data collection and ethical approval

All data for the present study were extracted from a prospective national database (CRISTAL) administered by the Agence de la biomédecine. Our center has signed a specific data sharing agreement to participate in this database. For the present study, nominative password protected access was limited to center-specific and anonymized data only. The study was conducted in accordance with French legislation and local ethics committee approval was obtained.

Statistical analysis

Categorical variables are expressed in quantities and percentages while continuous variables are expressed as median with interquartile range (IQR). Continuous variables were compared using the Mann–Whitney *U*-test. Categorical variables were compared using the chi-square test or the Fisher's exact test. Survival rates were calculated by Kaplan-Meier estimates. *P*-values <0.05 were considered statistically significant. Statistical analysis was performed using SPSS software version 23 (Armonk, NY, USA) and GRAPHPAD PRISM 8.

Results

During the study period, a total of 125 cDCD donors were proposed for procurement of at least one kidney or liver graft (Fig. 1). Median donor age was 55 years and 68% had a cardiac arrest with a median of 30 min of no flow/low flow prior to ICU admission (Table 2). The delay from ICU admission to WLST was 9 days (IQR: 7–16 days). Overall, 20% of liver and 32% of kidney donors were EDCD donors (Table 3).

Donation process and normothermic regional perfusion

After WLST, cannulation was attempted in 118 donors (94%; Fig. 1). Successful initiation of NRP was followed by procurement and transplantation of at least one abdominal organ in 109 donors (87%). A median of two grafts per donor were transplanted. The median duration for postmortem vessel cannulation for NRP initiation was 12 min (IQR: 10–17 min). We registered 14 (11%) adverse events during NRP leading to discard of at least one potential graft (Table 4). The majority of adverse events were cannulation failures ($n = 7$, 54%). During the study period, the number of NRP cDCD procedures increased by 5× ($n = 7$ in 2016 to $n = 36$ in

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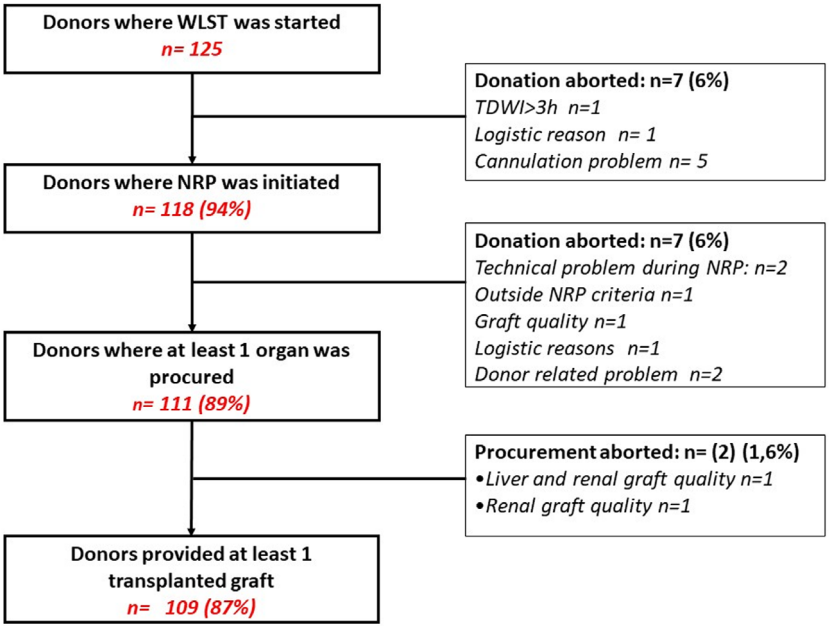

Figure 1 Study flow chart.

Table 2. Donor characteristics.

	All cDCD donors *n = 125*	Donor provided transplanted liver graft *n = 58*	Donor provided no transplanted liver graft *n = 41*	*P*	French cDCD Selection criteria
Donor characteristics					
Donor age, year	*	53 (45–61)	55 (47–61)	0.997	<71 years
Donor gender, male, n (%)	88 (70) [0]	41 (71)	25 (38)	0.313	
Donor BMI, kg/m2	25 (22–29) [0]	25 (21–28)	25 (21–28)	0.428	
Cardiac arrest prior to ICU, n (%)	85 (68) [0]	44 (76)	21 (51)	0.011	
Duration of no flow/low flow, min	30 (20–39) [7]	30 (25–45)	26 (14–40)	0.180	
Peak donor serum lactate, mmol/l	2.1 (1.5–4.6) [2]	1.9 (1.5–4.1)	1.9 (1.3–2.6)	0.451	
Donor ICU stay					
Cause of ICU admission, n (%)					
Cerebrovascular accident	23 (18) [0]	6 (10)	12 (29)	0.016	
Hypoxic brain injury	78 (62) [0]	43 (74)	20 (49)	0.010	
Trauma	24 (19) [0]	9 (16)	9 (22)	0.414	
Donor ICU stay, days	9 (7–16) [0]	9 (7–16)	10 (7–21)	0.618	
Transfusions, n (%)	31 (25) [0]	15 (26)	9 (22)	0.655	
Donor serum Na, mmol/l	142 (138–145) [0]	141 (138–145)	142 (138–144)	0.806	
Donor serum Hb, g/l	8.7 (9–11) [1]	9.6 (9–10.9)	9.7 (9.1–10.6)	0.943	
Donor serum Hct, %	30 (28–34) [0]	30 (27–32)	30 (28–33)	0.428	
Donor serum AST, UI/l	59 (26–85) [1]	54 (32–71)	56 (33–78)	0.432	
Donor serum ALT, UI/l	51 (35–94) [1]	40 (29–60)	61 (36–83)	0.115	
Donor serum GGT, UI/l	120 (60–253) [1]	92 (49–158)	120 (62–204)	0.145	
Donor serum creatinin, µmol/l	61 (43–76) [0]	63 (48–74)	58 (42–80)	0.621	
Donor creatinin clearance, ml/min	126 (96–168) [0]	126 (97–157)	115 (89–167)	0.707	

AST, aspartate aminotransferase; ALT, alanine aminotransferase; BMI, body mass index; GGT, gamma-glutamyl transferase; Hb, hemoglobin; Hct, hematocrit.

* Numbers between brackets indicate missing values.

Table 3. Procurement and NRP characteristics.

	All cDCD donors n = 125	Donor provided transplanted liver graft *n = 58*	Donor provided no transplanted liver graft *n = 41*	*P*	French cDCD Selection criteria
WLST characteristics					
Total donor warm ischemia, min	33 (28–43) [0]*	32 (28–38)	36 (28–52)	0.118	≤180 min
Functional donor warm ischemia, min	22 (18–29) [0]	21 (18–25)	27 (19–36)	0.01	≤45 min
Asystolic donor warm ischemia, min	17 (14–23) [0]	16 (15–20)	19 (14–25)	0.073	≤30 min for livers, ≤45 min for kidneys
Donor risk profile					
FDWI >30 min, n (%)	8 (6)	0 (0)	4 (10)	0.015	
Donor age >60 years, n (%)	34 (27)	16 (28)	11 (27)	0.934	
BMI >25 kg/cm^2, n (%)	62 (50)	25 (43)	22 (53)	0.300	
EDCD liver donors, n (%)	25 (20) [0]	30 (52)	26 (63)	0.248	
EDCD kidney donors, n (%)	40 (32) [0]	n.a.	n.a.	–	
NRP characteristics					
Donor vessel cannulation duration, min	12 (10–17) [0]	11 (10–15)	14 (9–20)	0.074	
NRP duration, min	204 (178–226) [0]	212 (195–229)	192 (142–229)	0.015	min 60 min and max 240 min
Mean arterial flow, l/min	2.6 (2.5–3) [2]	2.7 (2.5–3)	2.5 (2.5–3)	0.963	

EDCD, extended donation after circulatory death criteria; FDWI, function donor warm ischemia; NRP, normothermic regional perfusion; WLST, withdrawal of life sustaining therapies.

*Numbers between brackets indicate missing values.

2020) and the number of centers performing NRP increased from 1 to 11 (Fig. 2). Utilization rates for donors in 2015–2018 were 89% and in 2019–2020 were 86% ($P = 0.790$). Utilization rates for liver grafts in 2015–2018 were 57% and in 2019–2020 were 60% ($P = 0.831$). NRP adverse events decreased from 15% in 2015–2018 to 7% in 2019–2020 ($P = 0.263$; Fig. 2).

Graft specific utilization rates

Of the initially proposed 99 liver and 243 kidney grafts, a total of 58 liver and 201 kidney grafts were successfully transplanted resulting in graft utilization rates of 59% for livers and 83% for kidneys (Table 5). Overall, 1-year recipient and graft survival rates at our center were 93% respectively after liver transplantation and 97% and 96%, respectively, after kidney transplantation (Fig. 3). Donors in whom a liver graft was discarded had longer FDWI (21 min vs. 27 min, $P = 0.01$) but did not differ in age (55 years vs. 53 years, $P = 0.10$) nor EDCD criteria (63% vs. 52%, $P = 0.25$; Tables 2 and 3). In contrast, kidney donors in whom the kidney graft was rejected were more frequently EDCD donors (45% vs. 26%, $P = 0.022$) with a higher donor age (59 years vs. 53 years, $P = 0.026$) and higher rates of arterial hypertension (48% vs. 26%, $P = 0.005$) and diabetes (21% vs. 6%, $P = 0.005$; Table S1). Nearly half of all liver grafts discards (44%) were due to poor graft quality based on either subjective evaluation ($n = 4/41$, 10%), transaminase increase during NRP >4× baseline ($n = 4/41$, 10%) or pathological liver biopsy (8/41, 20%; Table 5).

Discussion

This study presents graft specific utilization rates after cDCD procurement with the use of abdominal NRP at a single center from France. The study shows that the use of NRP in low-risk cDCD donors led to transplantation of a median of two abdominal grafts per donor with excellent post-transplant outcomes. However, while utilization rates for kidney grafts were 83%, liver grafts presented a significantly lower utilization rate of 59%. Technical failure of NRP leading to discard of at least one potential graft occurred in 11% of all cDCD procedures in the study.

The regulations, which apply to cDCD dependent on each country's legal and ethical framework and thus display important differences [3]. For instance, the *no-touch period* after cardiac arrest of the donor ranges

Table 4. Details of technical problems with NRP procedures resulting in discard of at least one proposed graft.

N	Adverse event during NRP	CVF in donor	Cause of death CVA	NRP initiation	NRP completion	Procurement of at least one organ	Kidney grafts	Liver graft
1	45 min for cannulation, prolonged AWI	No	No	Yes	Yes	Yes	Procured and transplanted	Liver not procured due to AWI >30 min
2	Arterial perforation during cannulation	No	No	No	No	No	Not procured	Not procured
3	Delayed occlusion balloon inflation, prolonged AWI	No	No	Yes	Yes	Yes	Procured and transplanted	Liver not procured due to AWI >30 min
4	Occlusion balloon failure	No	No	Yes	No	No	Not procured	Not procured
5	Low flow, addition of 1 l of saline	Yes	No	Yes	Yes	No	Not proposed	ALT/AST >4N, Liver not procured
6	Cannulation failure	No	No	No	No	No	Not procured	Not procured
7	Cannulation failure, venous perforation	No	No	No	No	No	Not procured	Not procured
8	Cannulation failure by percutaneous and surgical approach, anatomical variation	Yes	Yes	No	No	No	Not procured	Not procured
9	Occlusion balloon failure	Yes	No	Yes	No	No	Not procured	Not procured
10	Low flow, donor hemodynamic instability	Yes	No	Yes	Yes	Yes	Procured and transplanted	Liver not procured due to quality
11	Percutaneous cannulation impossible, surgical cannulation but prolonged AWI	No	No	Yes	Yes	Yes	Procured and transplanted	Liver not procured due to AWI >30
12	Aortic dissection during cannulation	Yes	No	Yes	Yes	Yes	Not procured	Procured and transplanted
13	Delayed occlusion balloon inflation	Yes	No	Yes	Yes	Yes	No decoloration of right kidney	Procured and transplanted
14	Arterial perforation during cannulation	Yes	Yes	No	No	No	Not procured	Not procured

AWI, asystolic warm ischemia times; CVA, cardiovascular accident; CVF, cardiovascular risk factors includes arterial hypertension, diabetes, history of smoking or peripheral vascular disease.

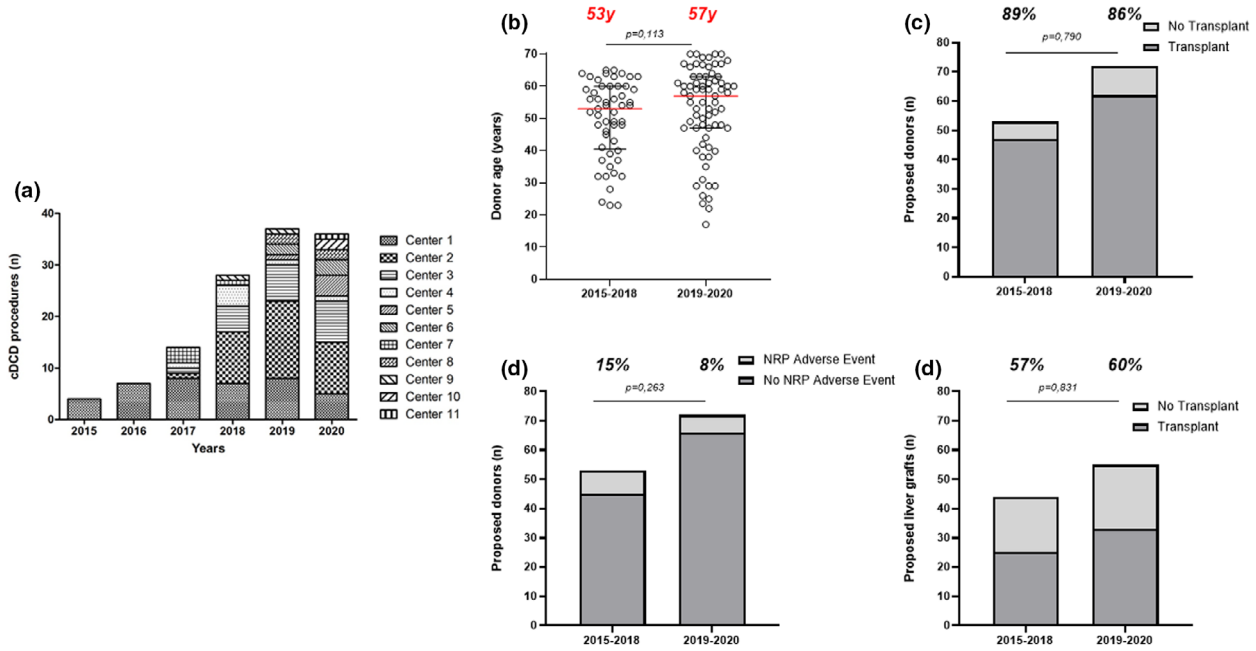

Figure 2 cDCD procedures and utilization rates according to volume and time period. (a) cDCD volume per center and year; (b) donor age, (c) donor utilization rate, (d) adverse events during NRP and (e) liver graft utilization rates according to the time period.

Table 5. Graft specific discard rates and reason for graft discard.

Reason for graft discard	Liver graft discarded 41/99 (41%)	Kidney graft discarded 42/243 (17%)
TDWI >3 h	*n* = 1	*n* = 2
FDWI >45 min	*n* = 2	–
Technical failure of NRP	*n* = 10	*n* = 16
Pathological biopsy*	*n* = 8	*n* = 4
AST/ALT >4 × *N* during NRP	*n* = 4	–
Graft quality concern†	*n* = 4	*n* = 2
Logistic reason‡	*n* = 4	*n* = 3
Donor history	*n* = 4	*n* = 6
Unexpected finding in donor	*n* = 2	*n* = 5
Adverse event during *ex-vivo* perfusion	–	*n* = 4
Unknown	*n* = 2	–

*Biopsy after NRP was mandatory for livers but not for kidneys. Pathological biopsy for livers was defined as cirrhosis, fibrosis >F1, macrosteatosis >20%; pathological biopsy for kidneys was based on the appreciation of the transplant team.

†Based on macroscopic aspect.

‡Adverse event or no-show of the recipient without an available backup recipient, no transfer of graft possible.

widely across countries from 5 min in France to 20 min in Italy. Furthermore, in Spain premortem cannulation for NRP is permitted while in France only premortem placement of guidewires is allowed and cannulation must be performed postmortem [3]. These legal differences must be considered when analyzing donor selection and procurement techniques.

Since the beginning of the cDCD program in France, efforts were made to optimize post-transplant outcomes in order to promote acceptance of cDCD procedures among transplant professionals and other stakeholders. First, mandatory and strict donor and recipient selection criteria were established to achieve optimal post-transplant outcomes (Table 1). In liver transplantation

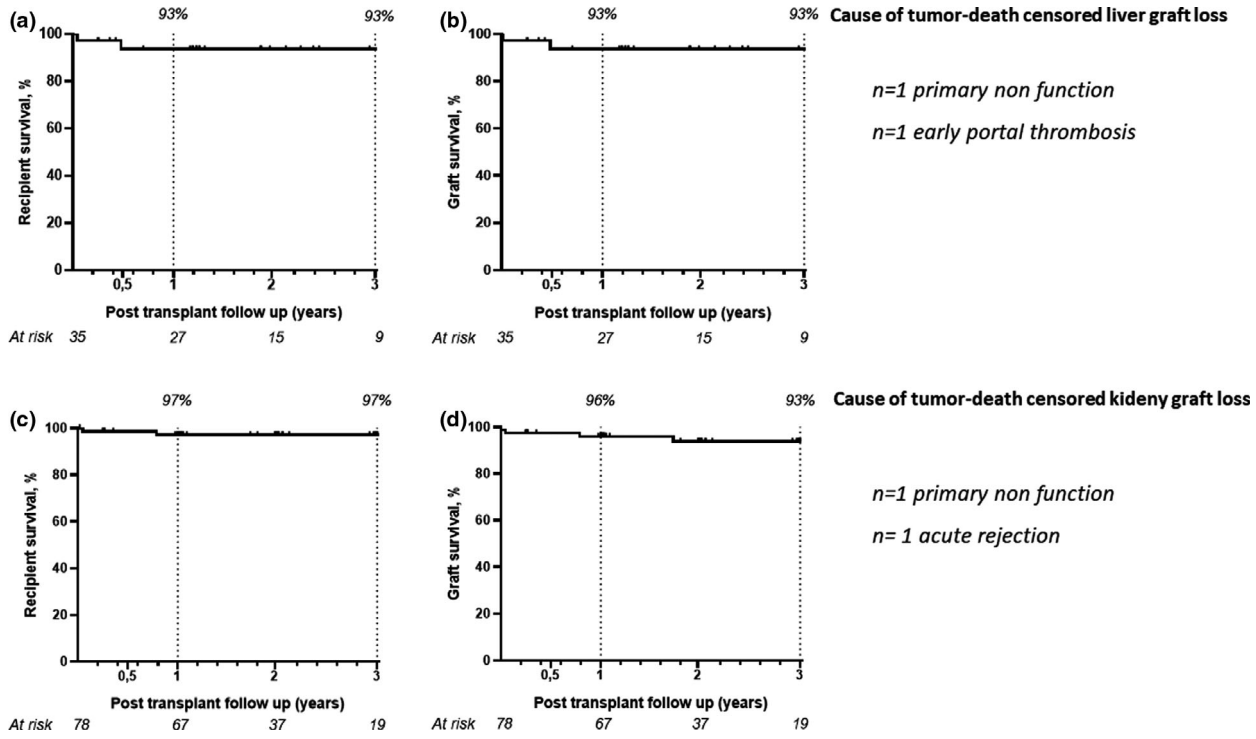

Figure 3 Recipient and graft survival after NRP cDCD kidney and liver transplantation at a single center. (a) Tumor-death censored recipient and (b) graft survival after liver transplantation; (c) overall recipient and (d) graft survival after kidney transplantation.

for example, these strict selection resulted in low-risk donor-recipient combinations with a median donor age of 50 years, FDWI of 22 min and a UK-DCD risk score of six points [14]. Other cDCD LT programs, for example, in Switzerland present significantly higher donor-recipient risk combinations with a median donor age of 61 years, FDWI of 31 min and UK-DCD risk score of nine points, resulting in higher liver graft utilization rates [15]. Second, allocation of cDCD grafts in France was regional instead of national as for DBD grafts, to shorten cold ischemia times and facilitate organization of cDCD procedures. It is in this context of optimal donor selection, that we present single-center data on cDCD kidney and liver graft utilization after abdominal NRP.

Currently, several countries use NRP for cDCD procurement but a detailed analysis of utilization rates is lacking [6,15,16]. A recent systematic review by van de Leemkolk *et al.* [16] identified 14 cohort studies on NRP in cDCD mostly focusing on either liver or kidney grafts in a single-center setting. Graft utilization rates were only reported in seven studies and definitions were very heterogeneous. For instance, Oniscu *et al.* defined utilization rates as grafts transplanted from donors who successfully completed NRP while Watson *et al.* [2,17] included all donors where NRP was initiated. Another large study on NRP in cDCD kidney transplantation only included transplanted grafts in the analysis [7]. Reported graft utilization rates after NRP for cDCD kidneys range from 62.7% to 92.7% and for cDCD livers range from 61.4% to 62.5%, depending on the definition [16].

Given the heterogeneity in definitions of utilization rates in the literature, we propose a broader definition of utilization rates: The proportion of transplanted grafts procured from donors in whom the respective graft was proposed. This allows to identify adverse events at every step of the donation and propose pragmatic solutions to increase utilization rates, for example, by reducing cannulation failures (Fig. 1). Of note, in France donor screening is performed by the national donor agency and transplant centers are unable to interfere with the decision to propose donors. To prevent conflict of interest, transplant centers may accept or decline an organ offer once a proposition from the national agency is received. Conclusively, we opted to start the count from the moment a donor was proposed to our transplant center. Future randomized trials and cohort studies on marginal graft transplantation or novel preservation strategies should clearly state definitions and report utilization rates [1,18].

Regarding donor characteristics, an interesting finding was that significantly more cardiac arrests prior to ICU admission occurred in donors with successful graft utilization compared to those where grafts were discarded. The available literature and guidelines on cDCD donation only rarely report cardiac arrest prior to ICU admission and consequently its impact on graft quality and outcomes is not well studied [19]. A possible explanation for high utilization rates in this subgroup of donors is that donors with cardiac arrest have fewer comorbidities compared to donors with a cerebrovascular accident (CVA) in terms of age, smoking and arterial hypertension [20]. Indeed, in our study EDCD kidney donors had a 2× higher rate of CVA than non EDCD donors (data are not shown). This overall lower donor risk profile may increase utilization rates in this subgroup of donors.

We identified two major modifiable causes of graft discard in NRP cDCD: technical problems with NRP and poor quality after NRP, especially for liver grafts. First, technical issues with NRP were due to cannulation failure and balloon occlusion failure in the majority of the cases (Table 4). Donor cannulation in this study was performed by an anesthesiologist at the donor center using the Seldinger technique over preplaced guidewires in the femoral vessels. Of note in a few cases, a surgical approach of the femoral vessels or abdominal vessel was used in the case of failure of the Seldinger technique or as primary approach (data are not shown). In contrast to our data, Oniscu *et al.* [2] reported the preliminary UK experience (34 cases) with a 6% failure rate using surgical cannulation of the abdominal vessels in the operating room for all cases. Reports from Spain show even lower cannulation failure rates with premortem cannulation, which reduces the time constraint and even allows to perform cannulation in an interventional radiology facility [6]. In France, cannulation by the Seldinger technique was chosen as the standard technique to allow end-of-life accompaniment of the donor and family in the intensive care unit. However, beyond those ethical considerations, our data raise the question of a tailored cannulation strategy based on specific donor criteria. For example, donors with peripheral vascular disease may present additional difficulty for percutaneous cannulation and a surgical approach in the operating room may have a higher success rate. In this study, we did however not observe a higher rate of cardiovascular risk factors or cerebrovascular cause of death in cases where femoral vessel cannulation failed (Table 4). Larger studies are needed to identify robust predictive criteria for difficult femoral vessel cannulations, which may assist the choice of the cannulation strategy. We conclude from our data that percutaneous premortem cannulation has several logistical advantages but remains a technically challenging procedure and requires appropriate training and experience to overcome the learning curve [7,21]. In this study, 5 centers performed all the NRP procedures during the first 3 years with six centers joining thereafter and thus having less experience (Fig. 2). Similarly, from the 30 centers in the French cDCD program, half performed ≤15 NRP procedures from 2015 to 2019 [22]. Given the very small number of cases performed by some centers included in the study (<4 cases), we were unable to identify a significant correlation between center volume and adverse events during NRP (data are not shown). A larger data set is needed to confirm the center volume hypothesis. However, we did observe a trend toward a lower rate of NRP adverse events from 2018–2019 compared to 2015–2018 (Fig. 2) which further supports the importance of experience in the use of NRP.

The issue of NRP experience raises the question if local teams at the donor hospital should perform cannulation for NRP or if a specialized mobile NRP team should be dispatched to each regional donor hospital to perform cannulation? In our study the majority of NRP procedures were performed by local teams, even in low volume centers. Feasibility of setting up a mobile team to allow hospitals without NRP experience to participate in cDCD programs have been reported [23]. However, this strategy presents additional logistical challenges, which may hamper broader acceptability of cDCD procurement.

A second major reason for graft discard, which was predominantly observed in liver grafts, was poor graft quality after initiation of NRP. Definitions for poor liver graft quality vary widely and assessment of graft viability is often based on visual assessment by the procurement surgeon or indirect markers such as transaminases [24]. A large series by Hessheimer *et al.* [6] including 152 cDCD liver grafts undergoing NRP reported a 21% discard rate due to poor macroscopic aspect on visual assessment. Interestingly in our cohort, other than FDWI included in the selection criteria, we did not find any significant differences in donor characteristics which differentiate transplantable from non-transplantable liver grafts. In this context, we see an urgent need for liver graft viability markers prior to transplantation. Such biomarkers may be identified by metabolomic analysis ideally focusing on mitochondrial metabolism [25–27]. A recent publication by Wang

et al. [28] suggests that a real-time assessment of a mitochondrial marker flavin mononucleotide during NRP is possible. A recent study from France on cDCD liver transplantation after NRP showed a 1-year graft survival of 68% for liver grafts with FDWI >30 min and prolonged cold storage >8 h [29]. Such marginal cDCD liver grafts may benefit from additional ex-vivo perfusion after NRP. Several Italian teams have proposed a sequential strategy with NRP followed by hypothermic oxygenated perfusion (HOPE) to rescue marginal cDCD liver and kidney grafts with FDWI up to 52.5 min for livers and 325 min for kidneys [30–32]. In the absence of validated biomarkers during NRP and following the positive results of two recent randomized trials on HOPE in cDCD liver and kidney transplantation, we suggest adding a period of HOPE after NRP in high-risk grafts to assess mitochondrial viability prior to implantation [12,24,33–36]. Of note in the French cDCD program, all kidney grafts already undergo mandatory hypothermic perfusion after NRP.

While this study is the largest to date to comprehensively report on utilization rates after abdominal NRP, it has certain limitations. The present study analysis discard rates from a single-center perspective which has the advantage of reflecting on a standardized practice. However, the reported discard rates need to be validated in a future study based on national data to capture all the discarded grafts in all the donor centers. Second, in order to perform a more precise statistical analysis of donor characteristic associated with graft discard and identify robust prediction factors, a larger cohort is needed.

In conclusion, the use of abdominal NRP in highly selected cDCD donors allowed transplantation of at least one graft in the majority of procedures resulting in excellent post-transplant outcomes. However, while utilization rates for kidneys were >80%, liver grafts had higher discard rates due to presumably poor quality after initiation of NRP. Dedicated training for NRP, development of graft viability markers and the use of ex-vivo perfusion strategies for additional graft assessment may allow to further increase utilization rates.

Authorship

XM and GR: designed the study, acquired the data, performed the statistical analysis, interpreted the data and wrote the manuscript. JYM, KM and ML: interpreted the data, critically reviewed the data and drafted a final version of the manuscript. SD, AG, XMA, EM, and LB: analyzed, interpreted and verified the individual center data and approved the final manuscript.

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Conflict of interest

The authors declare that there is no conflict of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1: Donation Flow Chart for the French cDCD Procedure

Appendix 1: The French Normothermic Regional Perfusion Protocol

Table S1: Characteristics of Donors in which a Kidney Graft was Transplanted vs. Discarded.

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