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Kidney Donation after circulatory death: The Veneto Region experience in Italy

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A B S T R A C T

Donation after circulatory death (DCD) is a promising strategy for increasing organ supply worldwide. The Italian current legislative framework has represented a major barrier to the implementation of such program, given the 20-minute no-touch period required for donor death declaration.

In this study, we describe DCD reporting activity in Veneto, number of procurements and kidney transplants performed from DCD donors since the beginning of its application, in 2017. We considered donor characteristics (DCD Maastricht category, age, sex) and number of kidney grafts retrieved and transplanted for each donor.

All the procured kidney grafts underwent ex situ hypothermic perfusion and pre-implantation kidney biopsy according to Karpinski-Remuzzi score. Perfusion parameters were monitored in order to predict functional recovery after transplantation and the histological evaluation focused on evaluating the extension of the ischemic injury. In the Veneto experience, histological data and hypothermic perfusion have proven to be very useful tools to make a decision concerning whether a kidney is suitable for transplantation.

Considering logistical, clinical, ethical and technical issues related to DCD donor program in Italy, many resources had to be dedicated in Veneto to build adequate technical expertise and to develop dedicated care pathways. The Veneto Region Transplant Coordination has encouraged and supported the development of DCD activity, increasing kidney transplantation from DCD donors.

1. Introduction

Kidney transplantation represents the best therapeutic option for patients with end-stage renal disease (ESRD), providing optimal outcomes in terms of survival and quality of life. In the last decades, donor selection criteria progressively broadened in order to widen the available donor pool and to face the issue of organ shortage [1,2]. In Italy, the average waiting time for kidney transplantation is 3,4 years with a steady number of patients on the waiting list in the last years despite the increase in transplantation rate [3].

In the 1960s, when organ transplantation was firstly performed in Italy, organs were retrieved from donors after cardiac death [4,5]. It was only after the 1968 Harvard Report [6] that it was clarified the distinction between two types of donors: a) those who died for cardiac arrest (donor after cardiac death, DCD); b) those who died following complete loss of brain functions, in whom the heart continues to guarantee organ perfusion (donor after brain death, DBD).

Nowadays, in Italy, the vast majority of kidneys utilised for transplantation are retrieved from DBDs, but in recent years in many Countries donations after circulatory death (DCD) has remarkably increased the number of renal transplantations [7].

The prolonged warm ischemia time (WIT) of DCDs has been for years considered as an obstacle to transplantation. However, in the last decade, improvement in technologies considerably reduced the detrimental effect of WIT allowing DCD grafts to become useful resources to overcome organ shortage [8,9].

Cardiac death has been defined as the “irreversible cessation of circulatory and respiratory function”. In the first international workshop on non-beating heart organ donation held in Maastricht in 1994, [9,10] a classification into four donors’ categories was proposed. Based on onset of cardio-circulatory arrest, the Maastricht’s categories define “controlled” and “uncontrolled” donors. In uncontrolled DCD (uDCD), cardiac arrest is unexpected and fails to solve with resuscitation (Maastricht categories I, II, and IV). In controlled DCD (cDCD) the cardiac arrest is anticipated because it follows a planned withdrawal of life-sustaining treatments, considered to be of no overall benefit to a critically ill patient (Maastricht category III) [11].

The main difference between these two groups is represented by the duration of WIT, which is measurable in the cDCD, whereas it is only partially known in the uDCD. In the sixth conference, held in Paris in 2013, the original classification was changed adding some subcategories (Table 1).

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Table 1
Modified European Maastricht categories of donation after cardiac death (DCD) classification.

Category	Subcategory	Definition	Type
I	A (In hospital) B (Out of hospital)	Sudden, unexpected, irreversible CA; no attempt of resuscitation by a medical team. WIT to be considered according to national recommendations in place.	Uncontrolled
II	A (In hospital) B (Out of hospital)	Sudden, unexpected, irreversible CA; unsuccessful resuscitation by a medical team.	Uncontrolled
III	–	Planned, expected CA; withdrawal of life-sustaining treatment; Euthanasia excluded	Controlled
IV	A (While brain death)	Sudden* or planned** CA during or after brain death diagnosis process, but before retrieval	Uncontrolled* Controlled**
	B (During ECMO-ECLS)	Death determination by circulatory (DCD) or neurologic (DBD) criteria	Partially controlled

(DCD International Workshop, Paris, 2013, modified from Koostra et al., 1995).
CA: Cardiac Arrest.
DBD: Donation after Brain Death.
DCD: Donation after Cardiac Death.
ECLS: ExtraCorporeal Life Support.
ECMO: ExtraCorporeal Membrane Oxygenation.
WIT: Warm Ischemia Time.

It has been already demonstrated that transplant outcomes either from DBD or DCD are comparable [9,12–14]. Gavriilidis et al. published a meta-analysis showing that there are non-significant differences in graft survival rates between DCD and DBD donation [15].

Despite the excellent results of several studies, DCD kidney transplantation remains controversial. To overcome limitations related to DCD donation and optimize the results of transplantation from DCD donors, new technologies such as perfusion machines and targeted histological examinations are proposed to ascertain the good quality of the graft.

2. The Italian legislative framework

Numerous ethical challenges arise from DCD practice, upmost correlated with the concept of the “irreversibility” of death. The Dead Donor Rule establishes that nobody can be considered as a potential organ donor before the determination of his/her death and that no death can be accelerated or manipulated forecasting organ donation [16].

In Europe, the time interval required to define the irreversibility of death varies widely among Countries. In Italy, the time frame to ascertain death based on cardiopulmonary criteria is 20 min of cardiac arrest, demonstrated by the absence of activity in continuous electrocardiographic recording [17]. After this period, in fact, even if cardiopulmonary function would be artificially restored, no recovery of brain function can happen. This very long time interval places the Italian legislation at the top of the conservative approaches with respect to the certainty of death after stopping circulation and it is decisive in delaying the start of organ procurement programs from donors who died of asystole. The Italian ”20-minute no-touch period” is a time considerably longer than in other Countries’ legislations. This time negatively affects organ viability by causing prolongation of WIT, which increases the risk of non-functioning of the procured organs.

3. Material and methods

We describe DCD transplant activity in Veneto from the beginning of the program in 2017, with a focus both on procurement and transplant procedure.

In the setting of organ donation after cardiac death, in Veneto, two possible procedure have been developed according to the two different scenario that could take place.

Scenario A – uDCD: sudden unexpected irreversible cardiac arrest (in or out of hospital) – with unsuccessful resuscitation by the medical team (see Fig. 1).

Scenario B – cDCD: planned withdrawal of life-sustaining therapy and expected cardiac arrest in case of patients with unfavorable prognosis (see Fig. 2).

In both scenario, patient with a refractory and irreversible asystolia must meet the requirement inclusion criteria and not be presenting with an exclusion criteria (Table 2) to be eligible for donation.

3.1. Scenario A

When a witnessed, sudden, cardiac arrest occurs (out of hospital, or within hospital facilities), aCPR (advanced cardiopulmonary resuscitation) protocols are applied in order to restore circulation; in case of no ROSC, the patient is transferred to the Hospital. At the hospital, patient is evaluated for eligibility to ECLS/ECPR procedure (extracorporeal life support/cardiopulmonary resuscitation). If resuscitation is unsuccessful and ineffective intensive supports are stopped and death is confirmed according to the Italian legislation: 20-minute electrocardiogram recording (the so called “no-touch period”). During this time, the national registry must be consulted to assess if patient has expressed his will regarding organ donation. In case of registered opposition, any procedure for organ recovery is suddenly interrupted. In case of a positive registered consent, preservation measures are established to restore abdominal circulation with oxygenated blood in donor’s organs (cannulation of femoral vessels, heparin bolus (300 UI/Kg) and beginning of in situ normothermic regional perfusion through ECMO system: nrECMO).

In case of a non-registered willingness, a family approach is quickly required to eventually proceed with organ donation. Family is, firstly, informed about the irreversibility of the cardiac arrest and patient death, and then about the possibility of organ donation. While waiting for family decision, family consent is also required to start invasive maneuvers with the aim of preserving the possibility of organ donation (cannulation of femoral vessels and ECMO establishment for normothermic regional perfusion - nrECMO).

Family must be notified that:

- nrECMO does not influence patient death which has irreversibly taken place;
- nrECMO allows organs preservation while waiting for family consent and it allows not to frustrate ex-post the donative will of patient which can be verified later;
- nrECMO can be interrupted at any time in case of opposition to organ donation;
- nrECMO establishment respects patient’s dignity and it does not alter his integrity.

Technically, in order to guarantee a better abdominal organ perfusion, Arterial nr ECMO outflow is warranted by cannulation of one femoral artery, venous inflow for nr ECMO is gained through a femoral vein cannula placed till the right atrium. An aortic balloon is placed in the supra-diaphragmatic aorta, via femoral artery and inflated. In case of donation of available lungs, protective ventilation is warranted by tracheal intubation and mechanical ventilation.

Ideally, time from the cardiac arrest to nrECMO perfusion beginning, after death declaration, (the so-called Warm Ischemia Time) should be kept under 150 min.

According to negative or positive family consent, after a maximum of 2 to 3 h from regional perfusion beginning, abdominal organs recovery starts or not. Lungs are quickly retrieved in normothermic conditions:

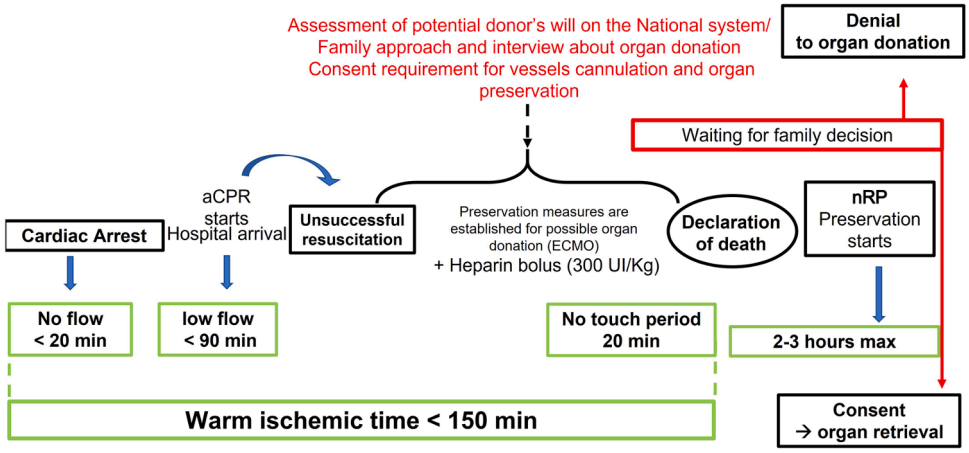

Fig. 1. Uncontrolled Donation after cardiac death (uDCD) donor pathway procedure.

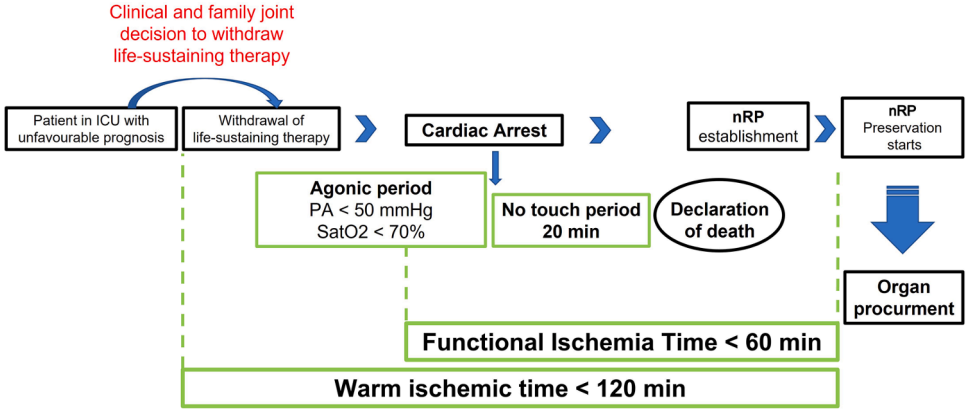

Fig. 2. Controlled Donation after cardiac death (cDCD) donor pathway procedure.

Table 2
Inclusion and Exclusion criteria for DCD protocol in Veneto.

Inclusion criteria for DCD protocol	Exclusion criteria for DCD protocol
Uniquely identifiability of patient	Evidence or suspicion of neoplastic disease
Witnessed CA	Past medical history of melanoma, malignant lymphoma, breast carcinoma or metastasis
Traceability of family members	Sepsis
Age between 18 and 65 years	Evidence of acute or chronic infectious and communicable diseases (HIV, HBV + HDV, DISSEMINATED TUBERCULOSIS)
Estimated Time from CA and aCPR < 20 min	Suspicion of spongiform encephalopathy
Estimated Time from CA and hospital arrival < 90 min	death requiring possible judicial jurisdiction
Estimated Time from CA and nrECMO post mortem < 150 min	

CA: cardiac arrest; aCPR: advanced cardiopulmonary resuscitation.

nrECMO support is prolonged until necessary.

3.2. Scenario B

In case of a patient with an unfavorable prognosis, who is usually receiving intensive care treatments without any positive life expectancy, a planned withdrawal of life-sustaining therapy causing an expected CA can take place in accordance with patient's will (if expressed in life) and/or family consensus and according to the guidelines of the Italian Society of Anaesthesiology and Intensive Care [18] and to the Italian Code of Ethics.

Usually, procedures for the assessment of patient willing to donate or family consent are carried out before the planned CA, as well as organ assessment for donation. Once a positive consent is obtained, life-supporting therapies are withdrawn leading to an imminent expected CA. Heparin bolus is administrated during the agonic period (defined by the presence of arterial blood pressure < 50 mmHg and/OR oxygen saturation < 70%): arteries and veins are cannulated with the Seldinger's technique only. A "Functional Ischemic Time" below 60 min is accepted, including also the no-touch-period. After declaration of death, ECMO is established in order to start nRP.

Time from the interruption of life-sustaining therapies and nRP beginning should be kept under 120 min, including the 20 min of ECG recording for death declaration.

After procurement, kidneys undergo ex situ hypothermic perfusion to optimize preservation and for the assessment of perfusion parameters. In this regard, a kidney biopsy is also performed to assess chronic lesions based on the Karpinski-Remuzzi score, to quantify the ischemic insult and identify the extent of ischemia-related alterations, which may lead to organ discard.

In this study, we report the number of DCD kidney procurements, characteristics of donors (DCD type, age, sex, expression of will), number of kidney transplants performed for each DCD donation, reasons for discard.

All the information was collected through the Veneto Regional Transplant Coordination system.

3.3. Theory

In Veneto, a DCD program was started in 2017; since then, the number of transplants and procurements from DCD donors has been increasing progressively.

In Italy, this activity has experienced a difficult expansion mainly due to the 20-minute of asystole period required by the Italian legislation to declare cardiac death. Concerns were related to the prolonged warm ischemia time in DCD organs and the subsequent ischemia-reperfusion injury which may be responsible for the increased rate of primary non function, delayed graft function (DGF) or poor renal function in DCD kidneys recipients. Therefore, DCD organs have been historically considered marginal organs and their utilization has been often discouraged by Italian transplant professionals.

Due to the persistence of the discrepancy between organ demand and availability, the Veneto Regional Transplant Coordination System has encouraged and supported the development of the DCD program. Considering organisational, clinical, ethical and technical issues related to DCD donor program in Italy, many resources have been dedicated in Veneto Region to grow adequate technical expertise among the transplant teams involved in the procedures and to build precise care pathways among the hospitals in the territory.

As shown in Fig. 3, there are 4 authorised Centres in Veneto Region for DCD activity; among them, 2 are only for lung donation from DCD type II. Uncontrolled DCD donor (category IIa from the modified Maastricht classification) is the most utilised DCD category in Veneto Transplant Centres. Only in Verona, an initial experience with a cDCD donor (category III) has been reported.

Following the global trend, DCD activity in Veneto has also been implemented by the utilization of tools for the pre-transplantation assessment of graft quality and prediction of renal function, combined with donor's clinical data. Among them, a particular attention is given to the histological evaluation, focused on the early recognition of ischemic irreversible alterations by dedicated and experienced pathologists and the analysis and monitoring of perfusion parameters (pressure, flow and vascular resistance) through the use of hypothermic perfusion machine.

4. Results

From 2017 to May 2022, 22 potential DCDs were reported. As noted in Fig. 4, the activity radically decreased in 2020, probably as a consequence of COVID-19 pandemic which negatively impacted solid organ transplantation and organ donation worldwide. Three Veneto Transplant Centres were involved in donor reporting: Padova, Verona and Vicenza, the latter active only in lung donation from DCD donors type II.

They were mostly uDCD donors (category IIa from the modified Maastricht classification), except for 6 cDCD (category III), reported between 2021 and 2022 (Fig. 5). The only Transplant centre in Veneto, which has gained experience with cDCD donors, is Verona.

Among the 22 reported potential DCDs, kidneys were utilised for transplantation in 12 cases: 6 from DCD type II and 6 from DCD type III (Fig. 6). 21/24 kidneys procured were transplanted: 10 from 6 cDCD donors and 11 from 6 uDCD donors. Donor age was 57,9+/−11,8 years. They were 18 males and 4 females. In two cases organ donation was denied after family interview during the no-touch-period.

Table 3 describes the details of the 22 DCD reported in Veneto: date of donor reporting, donor category, age, sex, expression of will and outcome of the procured grafts.

Main reasons for not utilization of kidneys for transplantation were: high vascular resistance during hypothermic perfusion, extensive ischemic damage on kidney histology, no suitable recipients, unacceptable donor infectious/neoplastic risk.

5. Discussion

The number of organ donations after circulatory death continues to grow in Italy and worldwide, being accepted universally as a strategy to widen organ procurement and as a viable option to serve the rising number of patients on the waiting list. However, DCD activity needs to face many issues including logistics, graft outcomes and ethical challenges, especially in the Italian scenario.

In Italy, a 20-minute period of observation is required after cardio-respiratory arrest before death declaration. This has long discouraged

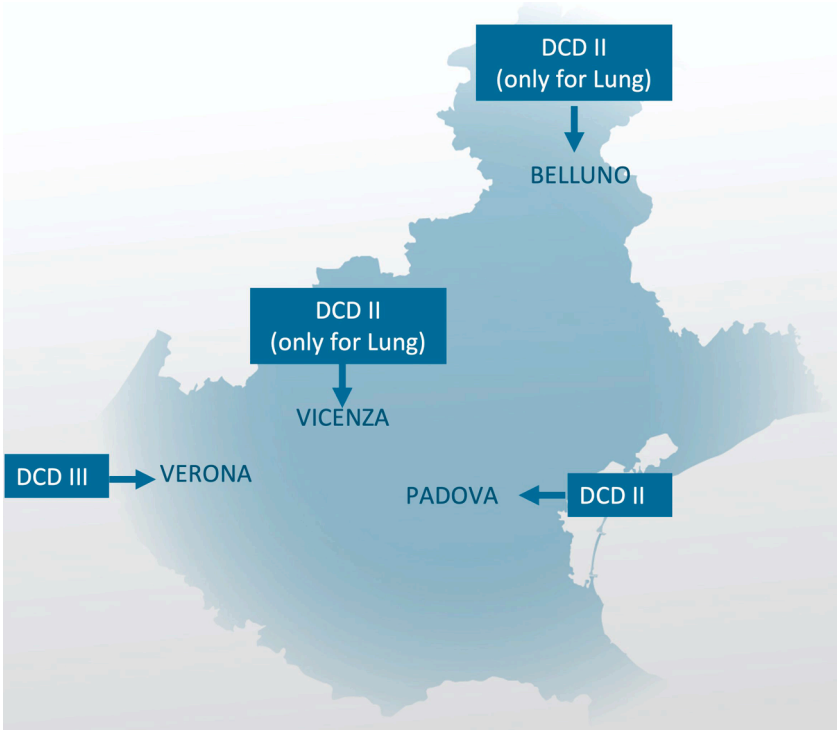

Fig. 3. authorized Transplant Centres in Veneto for donation after cardiac death (DCD) activity.

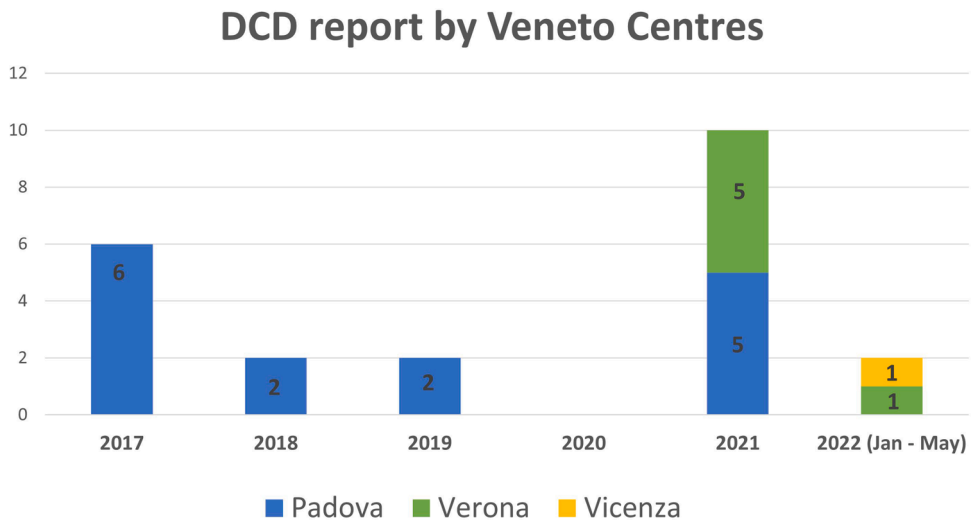

Fig. 4. Donation after cardiac death (DCD) report activity by Transplant Centres in Veneto.

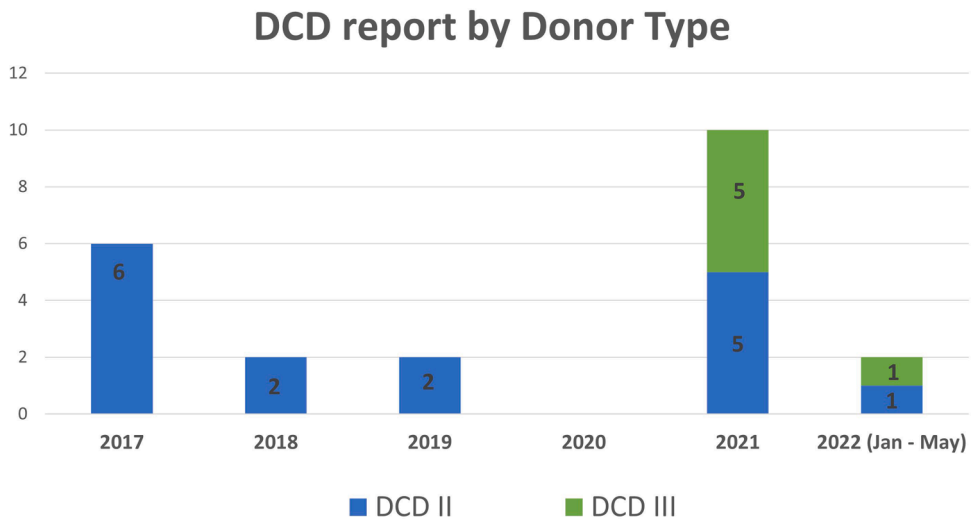

Fig. 5. Donation after cardiac death (DCD) report activity by Donor Type in Veneto.

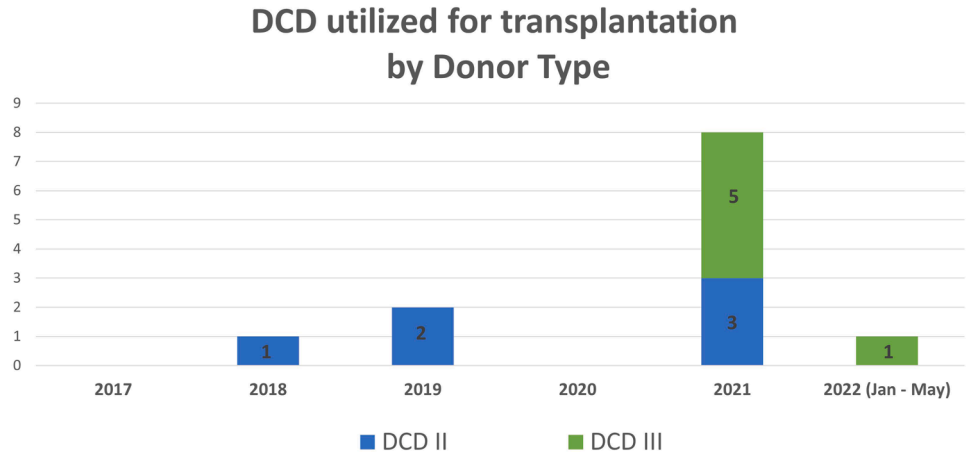

Fig. 6. Number of Donation after cardiac death (DCD) donors utilized for kidney transplantations by Donor Type in Veneto.

the introduction of DCD protocols in Italy. The Italian "20- minute no-touch period", currently required by the legislation, consists in continuous electrocardiographic recording of the absence of any cardiac electrical activity. As a consequence, a condition of prolonged WIT can become responsible for an increased incidence of primary non-function (PNF), DGF or poor graft function in kidney recipients from DCD donors

Table 3
DCD donor report in Veneto.

Date	Donor Type	Age	Sex	Expression of will	Kidneys	
					Retrieved	Transplanted
03/2017	DCD II	46	M	Denial	no	–
08/2017	DCD II	56	M	Denial	no	–
09/2017	DCD II	61	F	Consent	no	–
10/2017	DCD II	60	M	Consent	yes (right and left)	unsuitable
10/2017	DCD II	59	M	Consent	yes (right and left)	unsuitable
11/2017	DCD II	74	M	Consent	no	–
10/2018	DCD II	46	M	Consent	yes (right and left)	yes (right and left)
11/2018	DCD II	65	M	Consent	no	–
09/2019	DCD II	63	F	Consent	yes (left)	yes (left)
12/2019	DCD II	61	F	Consent	yes (right and left)	yes (right and left)
01/2021	DCD II	64	M	Not requested for unaccettable donor risk	–	–
01/2021	DCD II	56	M	Consent	yes (right and left)	yes (right and left)
03/2021	DCD II	48	M	Consent	yes (right and left)	yes (right and left)
04/2021	DCD III	81	M	Consent	yes (right and left)	yes (right)
05/2021	DCD III	69	M	Consent	yes (right and left)	yes (right)
08/2021	DCD II	50	M	Consent	yes (right and left)	yes (right and left)
09/2021	DCD III	28	M	Consent	yes (right and left)	yes (right and left)
11/2021	DCD III	62	M	Consent	yes (right and left)	yes (right and left)
12/2021	DCD II	44	M	Consent	no	–
12/2021	DCD III	63	M	Consent	yes (right and left)	yes (right and left)
01/2022	DCD II	48	F	Consent	no	–
02/2022	DCD III	75	M	Consent	yes (right and left)	yes (right and left)

M: male, F: female.

[7,19]. Moreover, kidneys from DCD donors are particularly vulnerable to the effects of cold ischemia time. It is well known that ischemia-reperfusion injury is a crucial factor in the development of endothelial damage which can trigger complement activation [20]. Therefore, this additional warm ischemic damage in DCD organs has represented an obstacle to the extensive diffusion of these programs for so long. DCD donors have been historically considered marginal donors for the assumption that their transplant outcomes could be poorer compared with ones from donors after brain death [21]. However, in recent years, donation after circulatory death is re-emerging as a promising option to expand the donor pool.

While there has been a significant increase in the number of transplants from DCD donors [22,23] worldwide, the development of DCD programs in Italy has been hurdled by the peculiar legal framework [24]. In the United States, organ procurement is potentially allowed after 2 min of respiratory and circulatory arrest [25], and after 5 min of asystole in the UK [25]. Hence, in Europe, the United Kingdom, the Netherlands, and Belgium, DCD programs provide 25% to 30% of the overall grafts [26].

The first Italian kidney transplant from a DCD donor was successfully performed in 2008 in Pavia and a real DCD protocol was established one year later: the “Alba Program” [27]. Since then, the utilization of DCD donors for transplantation has improved year by year in Italy 20. According to the Italian Informative System of Transplants (SIT) Annual Report, DCD donors have increased from 2 to 78 in the period 2008–2021 with a relative increase in DCD kidney transplants from 2 to 92 [28].

In Veneto, a DCD program was started in 2017 and 22 DCD donors have been reported up to May 2022. As many other transplant activities worldwide, which were negatively marked by the COVID-19 pandemic [29], DCD reporting in Veneto had to be completely reduced in 2020.

There have been almost exclusively uDCD donors (16 out of 22 DCD reported over the analysed period) and the activity is slowly but steadily growing with a total of 11 kidney transplants performed up to now. Excluding cases with lack of donor consent (2 in 2017) and one case of unacceptable donor risk in 2021, kidneys were considered unsuitable for transplantation and not harvested in 5 donors. In 2 cases, kidneys were procured but they were not transplanted in accordance with the histological result, the perfusion parameters and donor clinical data. In Verona a little experience with controlled DCD donors is gradually developing since 2021 and 10 kidney transplants have been performed to date, with the 6 donors reported.

In order to optimize outcome from DCD donation, a thorough technical preparation by medical staff and a precise organization of the health care system is required territorially as well as economic resources have to be dedicated. For these reasons, in Veneto, only two very experienced Transplantation Centres are involved in kidney procurement and transplantation from DCD: Padova and Verona. As a matter of fact, these two hospitals can provide all the essential medical services to improve kidney transplant outcome from DCD donors: intensive care specialists able to establish extracorporeal life support to preserve donor’s organs for transplantation, professional pathologist, well-experienced transplant surgeons and perfusion machines available at any time.

In these two donor service areas, when a DCD donor is reported, in situ preservation of abdominal or thoraco-abdominal organs with regional perfusion (RP) through the extracorporeal membrane oxygenation (ECMO) and ex situ preservation of kidneys with hypothermic machine perfusion are usually adopted. The choice of RP rather than in situ cooling (ISC), is driven by the demonstrated reduced risk for DGF and other post-transplant complications compared to ISC [30]. Moreover, in situ RP allows to maintain peripheral perfusion during the execution of the death assessment and to mitigate the effects of lack of cardiac activity. By restoring circulation, RP minimises the impact of warm ischemia, as ATP concentrations are restored, and ischemic events might be tempered [31,32].

Regarding ex situ preservation of kidneys with hypothermic machine perfusion, all kidneys retrieved from Veneto DCD donors were perfused before the potential transplantation by using the WAVES device (available in Padova and Verona). Many published papers have already demonstrated the overall superiority of perfusion preservation compared with simple cold storage [33,34]. Graft outcome is significantly improved when hypothermic machine perfusion is used by reducing the incidence of DGF after transplantation and its beneficial effect has been shown even in the long-term graft survival. The usage of machine perfusion in grafts from DCD donors has proved to be helpful not only for kidney preservation but also for the graft evaluation. The analysis of machine perfusion characteristics can help to predict functional recovery after transplantation [35]. The following parameters are generally monitored to make a decision concerning kidney suitability for

transplantation: mean perfusion pressure, vascular resistance during perfusion, mean flow and the average perfusate temperature.

The other useful tool to predict post-transplant renal function, in Veneto experience, has been the use of a pre-implantation kidney biopsy. When evaluated by experienced pathologists able to give additional information, beyond the Karpinski-Remuzzi score, the biopsy can be very accurate and specific in the assessment of ischemia-related alterations. As a matter of fact, the Karpinski scoring system does not consider the damage associated with the ischemic insult and it does not predict the functional recovery after transplantation [36–38]. Proximal tubule alterations have been identified as a pathological feature of the ischemia-reperfusion phenomena, being the proximal renal tubules extremely sensitive to the ischemic insult. These histological alterations are, in fact, more frequent in DCD than in DBD donors' graft biopsy [39]. Quantification of ischemic tubular lesions has represented a valid parameter for assessing the quality of the graft and, in selected cases, for discarding organs. For all these reasons, we believe it is essential to have a Pathology Service with transplant expertise in the hospital in order to initiate a DCD program.

The combination of pre-transplant renal biopsy results and perfusion parameters have always been integrated with clinical data such as donor's creatinine values, to predict transplantation outcome. However, the role of serum creatinine values in evaluating the ischemic injury in DCD kidneys, is still debated in the literature and has shown poor correlation and relevance [40].

6. Conclusion

Given the importance of increasing the number of organs available for transplantation, DCD donation should represent an additional resource for waiting list patients, and it should be more encouraged. A shortening of the "20-minute no-touch period", currently in place in Italy, would certainly support further development of DCD programs, by minimizing warm ischemia time and thus, improving kidney transplant outcomes from DCD donors. However, such an action is very time-consuming considering the actual Italian legal and ethical framework, much more focused on the safeguard of the dead donor rule. Meanwhile, the Italian Transplant Community should promote the usage of nrECMO, hypothermic perfusion and histological target data as tools to improve organ evaluation from DCD donors.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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