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Review

UNCONTROLLED DONATION AFTER CIRCULATORY DEATH: A BY-PRODUCT OF THE CONTROLLED? A NARRATIVE REVIEW

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Summary

Uncontrolled DCD (uDCD) refers to donation from persons who die because of an unexpected and sudden cardiac arrest after unsuccessful resuscitation. This type of donation pathway has important organizational issues since it can be considered part of the out of hospital cardiac arrest resuscitation bundle. Two are the main challenges of an uDCD program. The first is represented by legal, ethical and, mostly, organizational issues. Secondly, on a pathophysiologic view and strictly concerning to organ transplantation, the ischemia/reperfusion injury is the main factor able to affect organ function in the uDCD donor. *In vivo* and *ex-vivo* perfusion represent, to date, the chief treatment believed to counteract the deleterious effects of ischemia-reperfusion injury in the uDCD donor (normothermic regional perfusion -NRP- for abdominal organs) and in the single organ (*ex-vivo* machine perfusion), as well as to permit the assessment organ viability during perfusion. Peculiarities of the uDCD pathway in respect to cDCD will be also summarized.

Key word: uncontrolled donation after circulatory death, ischemia-reperfusion injury, normothermic regional perfusion, *ex-vivo* perfusion, transplantation

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Uncontrolled DCD (uDCD) refers to donation from persons who die because of an unexpected and sudden cardiac arrest after unsuccessful resuscitation. This type of donation pathway has important organizational issues since it can be considered part of the out of hospital cardiac arrest resuscitation bundle.

uDCD is being recognized as a potential donor pool even if not all European countries have developed this program due to its organizational, ethical and legal issues [1-5]. According to the overview of the European landscape reported by Lomero et al. [4], eight European countries have both uDCD and controlled DCD (cDCD) programs, six countries only uDCD programs and 4 countries only cDCD ones.

Two are the main challenges of an uDCD program. The first is represented by legal, ethical and, mostly, organizational issues. On an organizational view, for the implementation of this program it is pivotal a synergistic interplay between the hospital (mainly the emergency physicians and the Extracorporeal Membrane Oxygenation -ECMO- team) and the emergency medical system, which timely alerts the emergency department (ED) in the presence of a person aged 65 years or less with a witnessed refractory out-of-hospital cardiac arrest (OHCA). The uDCD program is in effect a time-dependent program. It can be considered the "last ring" of the survival

chain since it may give the chance to donate organs to all the persons deemed not eligible for extracorporeal cardiopulmonary resuscitation (eCPR) who have given their consent for organ donation or after the consent of their next to kin. Secondly, on a pathophysiologic view and strictly concerning to organ transplantation, the ischemia/reperfusion injury is the main factor able to affect organ function in the uDCD donor. *In vivo* and *ex-vivo* perfusion represent, to date, the chief treatment believed to counteract the deleterious effects of ischemia-reperfusion injury in the uDCD donor (normothermic regional perfusion -NRP- for abdominal organs) and in the single organ (ex vivo machine perfusion), as well as to permit the assessment organ viability during perfusion.

So far, many questions are still unanswered, while uDCD programs are becoming feasible in an increasing number of Italian Regions and organs from uDCD donors are being increasingly transplanted with acceptable results. These questions mainly concern whether the "cardiac arrest itself" (organizational issue) is able to affect organ function in the uDCD donor (i.e. no/low flow times, the presence/absence of mechanical chest compression, metabolic factors, *in primis* lactate values) [6,7].

The present narrative review will focus on the two main challenges of uDCD programs: organizational issues and the ischemia reperfusion injury in the uDCD donor. Peculiarities of the uDCD pathway in respect to cDCD will be also summarized.

ISCHEMIA-REPERFUSION INJURY IN THE UDCD DONOR

The ischemia-reperfusion phenomenon is the main mechanism able to affect organ function in the uDCD donor and distinguishes it from donors after brain death (BD) and cDCD donors.

Organs from BD donors are mainly subjected to a systemic inflammatory response, BD-induced neurohumoral and hemodynamic effects and factors strictly linked to ICU stay (I.e duration of mechanical ventilations, and nosocomial infections, duration and dosages of vasoactive drugs). During BD development till organ retrieval, each organ may be able to face these "injury mechanisms" mainly on the basis of donor age and comorbidities, but treatments, timely and tailored administered, has been documented to facilitate and, more often, achieve organ recovery [8,9]. In organ transplantation from BD donors two are the forms of ischemia: surgical warm ischemia, when the organ is obtained and cold ischemia.

In cDCD donors, mechanisms of organ damage can be related to age, comorbidities, ICU stay (i.e. nosocomial infections) and ischemia/reperfusion injury, the latter being quantified in minutes and through identified parameters (i.e. systolic blood pressure decrease) during the withdrawal of life supporting therapies (WSLT). Both in BD and cDCD donors, there is "time" for a more complete donor assessment and risk stratification even by means of further diagnostic and laboratory tests. Controlled DCD and BD processes can be considered both time-dependent (since WLST and the beginning of BD ascertainment, respectively) but with a wider time window than the uDCD process.

ISCHEMIA-REPERFUSION PHENOMENON IN THE UDCD DONOR

Potential uDCD donors are exposed to at least 2 no-flow periods (that of the CA and that of the no-touch period) and to prolonged periods of low-flow [10]. In Italy, the declaration of death based on circulatory criteria requires a no-touch period of at least 20 min, that is much longer compared to the 5 min accepted in other European countries.

Ischemia starts with cardiac arrest. That is why witnessed cardiac arrest is mandatory for the identification of a potential uDCD. In brief, the "ischemia-reperfusion clock" starts with the time of witnessed cardiac arrest. Ischemia is a systemic process, and it sets the stage for reperfusion injury. It is known that shorter periods of ischemia do not cause any reperfusion injury at all while the opposite is seen, since short intervals of complete ischemia can produce ischemic preconditioning, a state of protection and decreased injury [11].

Obviously, this is not the case of an uDCD donor in whom ischemia lasts for at least more than an hour. Indeed, in most protocols, a period of less than 60 minute (since cardiac event) is considered a mandatory requisite for eligibility for extracorporeal cardiopulmonary resuscitation (eCPR).

After a more prolonged ischemic period the cells cross a threshold of metabolic derangement, and reperfusion injury develops. In the uDCD process, a measure for the ischemic injury is the so called warm ischemic time that is the time from cardiac arrest to normothermic regional perfusion (NRP) start which has been identified as up to 150 min since cardiac arrest.

Recent and growing evidence strongly supports the notion that mitochondria is "where everything happens" that is where ischemia-reperfusion begins within the cell. Research in this topic is still in its infancy, since most data come from animal models and similar clinical conditions, *in primis* cardiac arrest [12-17].

Investigations on uDCDs most often focus on ex-vivo reperfusion (mainly liver) and results are too often difficult to compare due to differences in protocols from one transplant center to another (i.e. inclusion donor criteria,

parameter for organ assessment during NRP and type of *ex-vivo* machine perfusion).

We report in brief the main events accounting for the development of the ischemia-reperfusion injury, a multifactorial, though not completely understood process.

Ischemia and diminished availability of oxygen are known to induce a rapid reduction of ATP production and ATP levels. Within the mitochondria, due to the absence of oxygen, there is a rapid intracellular REDOX shift toward reduction within the cell. The mitochondrial compartment will begin to "leak" electrons directly to molecular oxygen which although reduced in level (due to ischemia) is still present in sufficient quantities for this radical generating reaction. It follows an elevation in superoxide and other reactive oxygen species (ROS) and, simultaneously, the cell membranes lose their ability to control ionic gradients (in primis Ca, K, and Na).

This generates an important shift in calcium concentration into the typically low-calcium cytosolic compartment with the result of cell swelling. While it is generally acknowledged oxidative stress as a major factor in the etiology of reperfusion injury, there is debated around which sources of ROS among whom the cytosolic NADPH-linked NOX enzymes and mitochondrial dysfunction.

An amplifying cascade of oxidative damage is set into motion where ROS causes damage, which in turn generated more ROS. Cellular targets mainly comprise include nuclear DNA (nDNA) damage, cytosolic proteins, and mitochondrial DNA (mtDNA).

When cells are injured or die, mtDNA can be released from lytic organelles to induce an inflammatory response, mainly by activating Toll-like receptors [18]. mtDNA is being considered a new biomarker, able to assess the ischemia/reperfusion injury, though data in uDCDs are so far lacking. Overall, the mitochondria exert a pivotal role in both the generation of ROS and as a target for the functional disruption of the cell by ROS-induced reperfusion injury. Evidence on this topic is growing, though to date investigations are mainly based on animal models.

ORGANIZATIONAL ISSUES

Two are the essential requirements for the implementation of an uDCD program. Firstly, a network between the emergency medical system (EMS) and the emergency department of the hospital equipped with a 24 h ECMO team, with early alert by the EMS, so the ECMO team is already at the First Aid when the patient arrives [5]. The availability of an experienced ECMO team allows the NRP implantation in a short time with a low incidence of complications.

Secondly, the transplantation coordinator has a key role since he/she (together with the physician in charge) communicates with the potential donor's family discussing death and donation. This moment is stressful and quite challenging. In such a difficult and painful moment for the family, the transplant coordinator should be able to create an interview mode that is as serene as possible as to give the family the opportunity to evaluate the possibility of giving consent for organ donation. This interview is particularly difficult both on a human and professional level even because it has to be conducted in a limited time. Training programs specifically focused on communication are needed.

An adequate setting within the emergency department and experienced and properly trained professionals (possibly including a psycologist) who will be able to devote time to relatives are desirable. Transparency is a fundamental principle of communication with family. Information to the family, provided in a compassionate manner and at the appropriate timing, needs to be decoupled: in other words, donation should be presented as an option only when the family has accepted and understood the death of their loved one.

In order limit the impact of the prolonged warm ischemia time inherent to the uDCD, it is advisable that uDCD program should be defined by each tertiary center and/or Region according to the locally available healthcare resources. Ethical issues should be also addressed, among whom defining moment to approach families to discuss donation opportunities.

uDCD has been recognized to substantially contribute to increasing organ availability [19-24], even if the number of uDCD programs in European countries is limited. This is quite surprising considering the strong recommendation of the European Resuscitation Guidelines, that uDCD should be considered when advanced cardiopulmonary resuscitation (eCPR) is terminated. A European survey-based study aimed to comparatively assess the evolution of resuscitation/end-of-life practices and emergency care organization from 2015 to 2019 (25 countries) [25] reported a significant improvement in the 2019 emergency care organization. An apparent decline in organ donation practices was observed in two countries and, though a steady increased in DCD practice was present in United Kingdom, the Netherlands, Belgium and Spain, the survey was not able to detect this country-specific increases in organ donation.

The utilization rate of the process and the number of organs recovered and transplanted per donor are lower compared with cDCD and DBD. In an European investigation (2016), the overall utilization of uDCD donors was 75%, lower than that observed in cDCD (91%) and DBD (93%). Similarly, the number of organs transplanted per donor was 1.6 in uDCD *versus* 2.6 and 3.5, respectively. This phenomenon may be related to several factors including logistical factors (time needed by the recovery

team to reach the hospital) and differences among transplant centers in criteria for organ suitability.

IN VIVO PERFUSION

Abdominal normothermic regional perfusion (NRP) can be viewed as a perfusion bridge between cardiac arrest and organ recovery since it allows the repletion of cellular energy stores after warm ischemia and an early assessment of organ function.
The combined use of in-situ and ex-situ perfusion offers potential advantages for DCD transplantation, including organ reconditioning, viability testing and improved preservation times which favour transplant logistics.
A long no touch period necessary for death declaration (20 min) together with logistical factors (distance between DCD protocols hospitals and transplant centers) make DCD programs in Italy inseparable from NRP.
Recently a systematic review and meta-analysis of NRP in DCD reported outcomes of solid transplantation after NRP [26].
Livers and kidneys from uDCD submitted to NRP showed inferior graft and patient survival compared to DBD.
Nevertheless, some kidney registry analyses suggest that NRP was associated with decreased PNF and DGF risks compared with in situ cold preservation (ISP) in uDCD.
The lack of studies comparing NRP with ISP in uDCD for liver strongly suggest hesitancy to transplant uDCD livers without some form of perfusion.
In Italy the DCD donation activity showed an increase in the overall numbers compared to 2020 with a growth of 50.9% of utilized donors. Even comparing the numbers of 2019, the year before the pandemic COVID-19, there is a 25% increase in utilized donors.
The growth, compared to 2020, is evident for both controlled DCD (cDCD) and uDCD, even if the latter results slightly down.
There has been a notable increase in the number of centers with uDCD programs with 8 hospitals more than 2020. To date in Italy, there are 49 centers that made at least one DCD report in 7 Regions compared to 14 centers active in 2017, when the "National Perfusion Program" was launched [27].

CONCLUSIONS

uDCD is a complex procedure from a logistical point of view (with certain physio-patological impact) and can only be developed under an appropriate regulatory framework that deals with the ethical challenges that it poses. uDCD can significantly contribute to increase transplantation activities and leads to acceptable post-transplant outcomes, that can improve if modifiable and well-identified factors are controlled. Making uDCD possible after an unsuccessfully resuscitated CA not only improves patient access to transplantation therapies, but it also provides more patients with the unique opportunity to donate organs upon their death, if donation is consistent with their wishes and values.

WHAT DISTINGUISHES CDCD FROM UDCD?

This question arises since a greater number of European countries, as well as Italian hospitals, have implemented controlled DCD instead of uDCD [4,27]. We are going to focus on the peculiar elements of a cDCD pathway.
On an organizational point of view, a cDCD "starts" in the Intensive Care Unit while a potential uDCD may be identified outside the hospital with the involvement of a greater number of healthcare resources and pathways [1-3].
cDCD concerns to organ donation after circulatory death following the planned withdrawal of life-sustaining therapies (WLST). The latter is taken in a multi-disciplinary approach (according to local/national protocols), by the ICU treatment team together with the family (or, rarely, the patient), whenever further treatments are considered futile [1,4].
A mandatory ethical and legal issue is the fact that the process of WLST is taken by the ICU physician who is independent from the transplant coordinator and the transplant team.
The term "controlled" means that the ischemia time is short enough to considered organ retrieval but, also, in a broader perspective, the cDCD pathway may be "controlled" by a well-organized procurement and transplant networks. National and local protocols are pivotal in defining role and responsibilities of each professional figure (since the cDCD is a multidisciplinary process) and the optimal organization and utilization of the local healthcare resources. Thanks to defined local protocols, mobile ECMO teams can implant NRP in peripheral hospitals, where an ECMO team is not available, to implement the cDCD program. This organizational strategy proved to be effective in strengthen the cDCD program even during resource constrains in time of pandemic in Emilia Romagna [28].
Briefly, the main steps of an cDCD process are as follows, and each of them should be clearly defined in the local/national protocols. The more accurate the protocol, the less likely it is the occurrence of unforeseen events that could negatively affect organ suitability for transplantation. One the decision of WLST has been taken by the ICU team, the transplant coordinator is contacted [29]. Whenever the patient has not already given his/her consent/refusal to donation, the transplant coordinator has an interview with the family in which he/she informs her about the possibility of organ donation. This interview may require several meetings since the family, whenever there is consent to donation, has to be informed about

all phases of the procedure and may need time to understand and accept it.
Only after family consent to organ donation, the assessment for the eligibility of the cDCD donor can begin and it may include further non-invasive imaging examinations and bio-humoral tests. National second opinion consultations may be needed, mostly to estimate the risk of neoplastic and/or infection disease transmission to recipients. This time window, which may last even 24 hours, does represent a concrete opportunity for the procurement/transplant networks to make a through and complete donor assessment and minimize ("control") the unexpected.
The allocation process is being performed simultaneously and the allocation policy is within the Region but it may extend over the whole national territory. Differently from the uDCD process, retrieval teams from other Regions may have time to reach the cDCD hospital when WLST is planned. Each organ should be evaluated individually because of different susceptibility of age, comorbidities, and ischemia-reperfusion injury.
The WLST is planned in accordance with the family and with the Regional Transplant Center who has the task of organizing the timely arrival of the mobile ECMO team, if needed, and of all the retrieval teams (if more than one).
The WLST is generally planned in the theatre and is managed by the ICU physicians. It can start only when the ECMO team and the retrieval teams are present, even if none of them are allowed to take part to the WLST procedure. The simultaneous presence of the ECMO team and the retrieval teams is necessary mainly for two reasons. Firstly, because most protocols include ante mortem procedures such as heparin administration and wire positioning. Secondly because "the controlled ischemia time" that is functional warm ischemia is monitored by the retrieval team. There may be a third reason. Whenever, after death declaration, ECMO implantation is not feasible and/or a procedural complication occurs (such as rupture of a vessel), a "quick retrieval procedure" may be performed by the retrieval teams.
A controlled DCD cannot be considered simpler in respect to uDCD, since donors are quite often older (frequently older than 65 years) and with comorbidities. Longer ICU stay may predispose to the development of infections such as ventilatory associated pneumonia and catheter-related blood stream infections.
Nevertheless, differently from the uDCD donor, NRP implantation occurs generally in more controlled conditions; wires are positioned before death declaration and ultrasound imaging of vascular beds is generally available before WLTS.
While in an uDCD donor repeated corrections of acidosis and volume replenishment are frequently needed to maintain stable NRP flows, in a cDCD donor NRP flows are generally higher and more stable, with a lesser need for interventions.
In cDCD donors, *ex-vivo* perfusion is necessary to assess organ suitability for transplantation since potential transplantable organs are exposed to a warm ischemia time during the cDCD process. The total period of warm ischemia is defined from the moment of the WLST to organ perfusion, while functional ischemia extends from the agonal phase (during cardiorespiratory deterioration and collapse) to organ perfusion [30].
In an cDCD pathway, the presence of "controlled factors" (mainly shorter warm ischemia time) may account for better outcome of organs (liver and kidneys) transplanted from cDCD donors compared to uDCD donors [1,27].

Conflict of interest statement

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Authors' contributions

CL, AP: equally contributed to the writing and revision of the manuscript.

Ethical consideration

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