Uncontrolled Donation after Circulatory Death: European practices and recommendations for the development and optimization of an effective programme

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Abbreviations:
aCPR: Advanced Cardiopulmonary resuscitation.
CA: Cardiac Arrest
CPR: Cardiopulmonary resuscitation.
DBD: Donation /Donor after Brain Death.
cDCD: Controlled Donation/ Donor after Circulatory Death
DCD: Donation/ Donor after Circulatory Death
DGF: Delayed Graft Function.
DTC: Donor Transplant Coordinator
EMS: Emergency Medical Service
hRP: Hypothermic regional perfusion.
nRP: Normothermic regional perfusion.
ISP: In situ preservation.
PNF: Primary non function.
uDCD: Uncontrolled Donation/ Donor after Circulatory Death
WIT: Warm ischemia time
I. INTRODUCTION / BACKGROUND

Shortage of organs has made a global interest for donation after circulatory death (DCD) to re-emerge. While controlled DCD (cDCD) has been progressively increasing, uncontrolled DCD (uDCD) has only been developed in a few settings. This activity is quantitatively important in France and Spain, although it has also been reported in other European countries, as Austria, Belgium, Italy, the Netherlands, and recently in Russia. uDCD protocols have allowed the transplantation of a significant number of kidneys, livers and lungs at these countries. Excellent graft survival has been reported in kidney transplantation from uDCD, in spite of an increased incidence of delayed graft function (DGF). Albeit promising, results with liver transplants obtained in uDCD protocols do not consistently provide similar outcomes compared with livers from donors after brain death (DBD), mainly due to a higher incidence of primary graft dysfunction and non-function and biliary complications. Lung transplantation is still facing limited experience, but preliminary results are encouraging.

The development of uDCD does not only rely on technical knowledge and skills, but on important organizational efforts for a time-dependent process to be activated once the opportunity of donation is identified. This opportunity is represented by persons who suffer an unexpected and witnessed cardiac arrest (CA) and in whom advanced cardiopulmonary resuscitation (aCPR) has been exhausted, and resulted unsuccessful. The complexity of the process to follow - with protocols designed to minimize the duration and the impact of warm ischemia time (WIT) - may be fairly represented by the limited effectiveness of these programmes, in terms of the potential donors finally converted into actual donors. The figures available also describe that only about 65% of actual donors become utilized donors and that the number of organs transplanted per donor is below 1.5 in France or Spain.

The potential of uDCD in the United States has been estimated to be of up to 22,000 a year. Based on the availability of air ambulance teams and cases of witnessed CA transferred to the hospital during a 75 month period, uDCD was estimated to yield 300 potential donors per year in England and Wales. However, uDCD has remained confined within a few countries. Besides the technical and organizational difficulties, ethical dilemmas have been posed as other reasons for this constraint activity and have been the main difficulty encountered when trying to emulate this practice.

The objectives of this paper were: a) to describe consolidated uDCD programmes in Europe, including information on the underlying regulatory and ethical frameworks and on organizational and technical aspects; and b) to provide recommendations for the development and optimization of uDCD.

II. METHODS

A dedicated questionnaire was developed to collect information on the regulatory and ethical framework and the practice of uDCD in the European countries with the highest activity- France and Spain- and on the Dutch programme. Topics addressed were: a) general information; b) donor selection criteria; c) logistics of the protocol (out-of-hospital and in-hospital); d) determination of death; e) consent and authorization; and f) preservation. Information was obtained from the national transplant agencies (Agence de la Biomedecine-France, Dutch Transplant Foundation- the Netherlands, Organización Nacional de Trasplantes- Spain) and experts in the field.

An electronic search was performed in Medline and Pubmed, Cochrane library, ClinicalTrials.gov, and ControlledTrials.com. Keywords used: ['Cardiac arrest or 'Uncontrolled'] and ['Non Heart Beating Donation' or 'Donation after Circulatory Death' or 'Donation after Cardiac Death']. Articles written in English, French and Spanish were selected. Abstracts were first reviewed. If the article was identified as discussing key regulatory-ethical issues or describing logistic aspects of uDCD, then the manuscript was further reviewed and information was used for the preparation of this paper.
Recommendations were built based on the available evidence. Where possible, articles were ranked and recommendations graded as specified by the Oxford Centre for Evidence-based-Medicine (www.cebm.net). Recommendations on ethical aspects resulted from a deliberative approach among participants and consensus.

III. ETHICAL-REGULATORY FRAMEWORKS, PRACTICES AND EVIDENCE

1. General information

uDCD first started in Maastricht, the Netherlands, in 1981. The first procedures in Spain were described in the 80s. The programme started in 2006 in France. The number of active programmes in 2011 was 9 in France and Spain, and 4 in the Netherlands, with a number of actual uDCDs of 58, 112 and 1, respectively. Of note, more than 90% of these donors were persons who had suffered the CA in the out-of-hospital environment.

France, the Netherlands and Spain have specific legislation providing the framework for the practice of uDCD. The legal texts include provisions related to criteria for the determination of death, limitations to preservation— if any- and the consent to organ preservation-recovery, among others. In the three countries, national protocols/recommendations/guidelines have been issued, that deal with the ethical, technical and organizational aspects of uDCD. 

Dedicated action protocols defining roles and responsibilities in the process are in place at every Extrahospital Emergency Service (EMS) and hospital embarked on this type of donation. These protocols are adapted to the available material and human resources and the internal organization of the corresponding service and hospital.

The process of uDCD includes a number of phases, not necessarily sequential, graphically represented in figure 1. The practice of uDCD in the three studied countries, along with the available evidence, and their position with regards to some of the dilemmas that may arise at each of the phases are detailed below.

Reducing WIT and its potential impact as to ensure organ viability and optimal postransplant results is the underlying principle guiding the said practice, while respecting ethical standards, and ensuring the quality and safety of the procedure.

2. Donor identification and referral

The uDCD process is activated when a potential donor is identified, i.e., a person who fulfils all the criteria below:

- has suffered a witnessed CA, in the out-of-hospital or in the in-hospital setting;
- aCPR has been exhausted, according to national protocols, aligned with international professional standards;
- aCPR has been deemed unsuccessful by the attending team;
- a set of selection criteria is met, in terms of age, co-morbidities, circumstances of CA and WIT. A summary of the selection criteria applied in the evaluated programmes is shown in table 1.

With regards to persons in whom CA has occurred in the out-of-hospital setting, only persons who are transferred to the hospital with a therapeutic purpose and in whom aCPR is considered unsuccessful within the hospital are considered potential uDCDs in the Netherlands. In France and Spain, also persons in whom aCPR is deemed unsuccessful in the pre-hospital setting by medicalized EMS can be considered potential uDCDs and transferred to the hospital with that purpose.

1.1. Donor selection criteria
1.1.1. Unsuccessful CPR

CA is considered irreversible based on international standards if, despite a CPR being carried out correctly and without interruption for at least 30 minutes, return of spontaneous circulation is not achieved and the patient shows clinical signs of death -lack of consciousness and spontaneous movements, absence of spontaneous breathing, no detectable blood pressure, pulse or cardiac sounds-. In some circumstances, as pre-arrest hypothermia, suspected poisoning or metabolic derangement, CPR has to be prolonged and additional therapeutic options have to be considered, based on the mentioned standards.

1.1.2. Donor age

Most of the existing uDCD programmes have restriction criteria on age, but there is no strong evidence for age cut-offs. In a series of 242 kidney transplants, Mizutani et al reported lower graft survival for recipients of kidneys aged >60 years compared with the younger uDCD group. This result was confirmed by Hattori et al who, in a retrospective study of 706 kidney transplants from uDCDs, reported that donor age >55 years had a negative impact on long-term graft survival. In one of the largest series published, Sánchez-Fructuoso described that 1 and 5 year graft survival for kidneys from uDCDs with a maximum donor age of 60 years was similar to that of kidneys from DBDs <60 and significantly better than that of kidneys from DBDs ≥60 years. More recently, donor age ≥54 years was identified as a risk factor for primary non function (PNF) and decreased graft survival in a series of 135 kidneys from uDCDs. Based on these limited data, it appears appropriate to include in uDCD programmes young subjects ≤55-60 years, although some of the existing programmes are transplanting kidneys beyond this age cut-off value (Table 2).

1.1.3. Comorbidities

Some of the existing programmes exclude patients with a history of arterial hypertension or diabetes even if these diseases are controlled, kidney/liver diseases, some brain tumours or cancer. Sepsis, viral infection (HIV, HBV, HCV) and intravenous drug abuse are also contraindications for uDCD.

1.1.4. Circumstances of death

Suicide and homicide are contraindications for uDCD in some of the existing programmes, because of potential judicial obstacles. Major trauma is also a contraindication due to the risk of organ damage and hypoxia in case of haemorrhage. However, abdominal trauma does not preclude lung donation.

1.1.5. Warm ischemia time

Minimization of WIT is a critical factor. uDCD programmes in France and Spain recommend that a) the no flow period is <15-30 minutes for kidney and <15 minutes for liver; b) total WIT is <150 minutes. However, these recommendations are based on empirical grounds and require of further research and validation.

1.2. Donor referral

Communication of a possible uDCD to a pre-specified hospital implies the transmission of a minimum set of information to ensure selection criteria are met, and to activate and facilitate the transfer to the corresponding hospital or ward. An example of the list of items covered in this communication is shown in table 3. The identification and subsequent referral of the potential donor is necessarily performed by the team in charge of the aCPR. Different procedures are used for the communication, either through an intermediate and/or directly through radio or phone.

The effective referral of the potential donor requires of the availability of a Donor Transplant Coordinator (DTC) at the hospital, this being the case at the three studied countries. The DTC is 24/7 present at the hospital or on call and able to reach the hospital within a minimum time-frame of 20 minutes.
The DTC is in charge of: a) evaluating the referred potential donor, ensuring that selection criteria are met; b) authorizing the transfer to the hospital; c) alerting a first rapid team of professionals in charge of completing the evaluation, obtaining consent/authorization and initiating the preservation measures, and a second team in charge of organ recovery, arriving at a later stage; d) locating relatives, if not present at the scene of the CA, in cooperation with the relevant agencies, as appropriate.

3. Donor transfer

The transfer of a potential donor to the corresponding hospital/ward implies maintaining cardiac compression and mechanical ventilation as per CPR standards, but for the purpose of preserving organ viability, since aCPR has already been deemed unsuccessful and hence further care is considered futile.

The majority of the existing programmes use mechanical cardiac compression devices for donor transfer, although there is limited evidence on its superiority vs. manual cardiac compression in terms of organ viability and posttransplant outcomes. Preliminary results of the CIRC Trial show that return of spontaneous circulation and survival at hospital discharge for patients with a pre-hospital CA is similar with the use of Autopulse® compared with high-quality manual CPR. A similar randomized controlled trial is being conducted with LUCAS®. The use of mechanical devices also facilitates long-distance transportation with good quality cardiac compression. From the above, it could be derived that organ viability would be better preserved with mechanical devices. However, this is not consistently concluded from the available evidence. In a cohort study comparing the results of an uDCD programme with donor transfer performed with the LUCAS® device (n=91) vs. manual cardiac compression (n=112), the former was associated with a significant decrease in the number of kidneys discarded because of inappropriate organ perfusion (32.9% vs. 56.6%; p=0.026). Nonetheless, in another observational study, assessing the outcome of kidney transplants (n=39) from uDCD under mechanical vs. manual chest compression, the incidence of PNF was similar (5.1% vs. 9.1%; p=0.5). Data from a cohort of 50 uDCD also showed similar renal function at 6 and 12 months in kidney transplants from donors transferred with mechanical devices vs. manual chest compression.

On the other hand, it has been suggested that the use of mechanical devices for cardiac compression may cause lung injuries that could invalidate these organs for transplantation. This is not confirmed in dedicated studies comparing the LUCAS® device with manual chest compressions for the treatment of CA. Moreover, a recent series of 33 potential uDCDs under mechanical cardiac compression showed a limited number of mild and no severe thoracic and lung injuries, assessed by chest X-ray, tracheal and nasogastric tube examination and bronchoscopy.

The transfer of a potential uDCD from the out-of-hospital setting needs of a slow and constant speed of the corresponding vehicle to ensure an appropriate cardiac compression and an adequate perfusion of the organs. The transfer may be facilitated by the intervention of other agencies. In many occasions, the presence of the police is required. In addition, as in the transfer of critically ill patients, the use of security forces to regulate the traffic is common in order to avoid hemodynamic changes secondary to braking and acceleration. It is desirable that these agencies are familiar with the uDCD protocol.

4. Determination of death

Determination of death in current uDCD programmes takes systematically place in the in-hospital setting. Criteria are unanimous at the three evaluated countries:

- aCPR exhausted according to national protocols, aligned with international standards, and deemed unsuccessful is a pre-requisite. aCPR is identically applied, regardless of whether the person could be considered a potential donor or not.
- Cessation of circulation and respiration is assessed based on the absence of electrical activity by electrocardiography or the appropriate means (as
echocardiography or invasive blood pressure measurement) in case of electro-mechanical dissociation – if all its reversible causes have been discarded and treated.

- Irreversibility of the cessation of circulation (and respiration) is established after a minimum observation period of 5 minutes.

In France and Spain, determination of death preceding uDCD is based on the actual and demonstrated irreversibility of circulation, because aCPR has been exhausted and deemed unsuccessful, according to existing international standards and end-of-resuscitation rules. Based on this irreversibility concept, it would be arguable if an observation period is needed, although both countries respect a 5 minutes no-touch period. The possibility of an unperceived auto-resuscitation during donor transfer (after CPR has been deemed unsuccessful, but before determining death) is impossible the way protocols have been conceived. Potential donors remain monitored electrocardiographically during transfer, a period in which cardiac compression and mechanical ventilation are extended beyond the point of irreversibility of the CA, for the purpose of organ preservation. Because circulatory function is considered to have ceased irreversibly, the re-establishment of circulation after death with the aim of organ perfusion is considered ethically appropriate and is legally permitted and systematically performed at these two countries. These criteria for the determination of death are in contrast with standards developed in countries primarily focused on cDCD, where the permanent cessation of circulation (‘will not return’) is used as a surrogate of the irreversible cessation of circulation (‘cannot return’) for the diagnosis of death. In the views of countries with consolidated uDCD programmes and other commentators, the permanent cessation of circulation should not be the criteria applied to the determination of death under these very particular circumstances. These different approaches are however a matter of international debate.

Death by circulatory criteria in the three described programmes is systematically certified by a professional(s) independent of the donation and transplantation activity, in particular, by the team taking over the aCPR manoeuvres for cases transferred from the out-of-hospital setting and by the team in charge of the aCPR when CA has occurred within the hospital- usually intensive or emergency care professionals. The fact that a new evaluation of the irreversibility of the CA and death determination is performed by professionals independent from those who attended the CA in the pre-hospital setting is considered a control procedure in the assessment of the already discussed concept of irreversibility.

5. Preservation

After death is determined and certified, cardiac compression and mechanical ventilation is re-established routinely in France and Spain, with the purpose of organ preservation, this not being the case in the Netherlands. No dedicated studies have compared the results of re-establishing vs. not re-establishing cardiac compression until further preservation measures are initiated. However, the most consolidated uDCD programmes in terms of number of actual and utilized donors, and organs recovered and transplanted apply cardiac compression systematically after death. These programmes also offer the most promising results with regards to posttransplant outcomes, not only in kidney, but also in liver transplantation. (Table 4 and 5).

5.1. Preservation of abdominal organs

Preservation of abdominal organs is usually performed through hypothermic regional perfusion (hRP) or normothermic regional perfusion (nRP) in France and Spain, although in situ preservation (ISP) is also applied in some programmes just with the aim of kidney preservation. Of note, preservation with hRP/nRP in uDCD is a legal requirement for further proceeding with liver transplantation in France. Table 6 summarizes the main aspects of the different techniques.

There are variations in the maximum WIT allowed (usually 150 minutes). In the Netherlands, where cardiac compression is not restored after death, there is an additional no flow period following death allowed to be of a maximum duration of 30 minutes. There are also variations in the maximum time allowed under
preservation measures, before proceeding with organ recovery, but most of the programmes establish the limit of 240 minutes in case of hRP/nRP, with more restrictive times for ISP. Maximum WIT and preservation times allowed in the three programmes are graphically represented in figure 2. These maximum times are however based on empirical grounds.

Tables 4 and 5 show the results of kidney and liver transplantation in uDCD with different preservation strategies. In the setting of kidney transplantation, there is only one study directly comparing the three different techniques. Valero et al observed that the incidence of DGF and PNF was significantly lower when preservation was based on nRP (n=8) vs. hRP(n=8) and ISP (n=44) (p<0.01).57 Also, duration of DGF was significantly shorter with the use of nRP compared with ISP (p<0.05).

In the field of liver transplantation from uDCD, the early results published by the Pittsburgh group in 1995 were disappointing, with very poor graft and patient survival in a series of 6 cases.58 In 2003, a higher graft and recipient survival were reported in a Spanish series of 20 liver recipients from uDCD, with a heterogeneous use of preservation methods (chest-abdominal compression-decompression vs. hRP vs. nRP).20 A subsequent description of 10 liver transplants whose donors had been only subjected to chest-abdominal compression-decompression, raised survival to 90% after 57 months of follow-up.21 Later on, the use of nRP preceded by chest compressions by experienced centres has been related to optimal results in the short-term. Using this approach, in a prospective case-control study comparing liver transplantation from uDCD (n=20) vs. DBD (n=40), 1 year graft and patient survival was 80% and 85.5% vs. 87.5% and 87.5%, respectively. Although the incidence of PNF and ischemic cholangiopathy was higher in the uDCD group, the difference was not statistically significant.22 Combining chest compression with the LUCAS® device after death determination with nRP, Fondevila et al. reported the results of a series of 34 liver transplants from uDCD with one 1 year graft and patient survival of 70% and 82%, respectively.18

The superiority of nRP can be explained by the fact that re-establishing warm oxygenated reperfusion allows some repair for WIT to take place – something supported by experimental studies39,60,61 and provides a period for a better biochemical assessment of the liver – and hence a more appropriate selection of the liver donor. It is worth noting however that preservation with hRP/nRP has also been related to technical difficulties that may derive in potential donor losses. The Barcelona group reported that out of 400 potential uDCD placed under nRP, 72 (18%) were discarded due to inadequate venous return, resulting from unrecognized vascular trauma or internal hemorrhage or supposedly from the collapse of the inferior cava vein.18

Recently, a novel preservation approach for abdominal organs in uDCD has been described in San Petersburg, Russia.3 The protocol is applied to patients suffering an in-hospital CA unsuccessfully resuscitated. After death is determined, heparine is administered and distributed through the application of a limited number of cardiac compressions. This is followed by a no flow period of up to 90 minutes, when preservation of abdominal organs starts with nRP, combined with leukocyte depletion and fibrinolytics. Results with the transplantation of 20 kidneys from 10 uDCD show a 100% 3 month graft survival. These promising data may be guiding future preservation approaches in uDCD that allow longer acceptable WIT – something invaluable for overcoming key obstacles, as determination of death and consent.

5.2. Lung preservation

Lung recovery is about to start in France and the Netherlands. In Spain, the recovery of lungs is systematically performed in some of the uDCD programmes. Lungs are the only organs not requiring circulation to maintain the aerobic cellular metabolism, due to the mechanism of passive diffusion across the alveolar membrane. It has been shown an adequate gas exchange even after 2 hours of WIT in the absence of lung circulation, which could be extended to 4 hours in case of heparinization. The best method for the preservation of non-ventilated lungs is topic cooling.

After mechanical ventilation is interrupted and the preservation of abdominal organs has been started, where appropriate, bilateral thoracic drains are placed via transthoracic insertion, through the second intercostal space, midclavicular line. Cold preservation solution (Perfadex®) is infused at 4°C (5-6 l per hemithorax) to
allow for a topic cooling and lung collapse. Oesophageal temperature is maintained at 20°C. In case of abdominal preservation with nRP or to better ensure the cooling of the lungs, some groups place a system for the recirculation of the lung preservation solution, to keep this target temperature. For such purpose, two additional thoracic drains are placed in the sixth intercostal space, midaxilar line. However, the usefulness of this approach has not been shown yet. Before the procedure is started, approximately 300 mL of venous blood from the potential donor are recovered and preserved at 4°C for the ulterior functional evaluation of the lung. The maximum preservation time varies according to the team, but – based on empirical grounds – the usual criteria applied is 240 minutes.

6. Donor evaluation

Donor evaluation is a continuum which already starts in the phase of donor identification. In uDCD, inclusion and exclusion criteria are similar to those applied in DBD, with some peculiarities, as specified in section 1.1.

As for a DBD, donor and organ evaluation are based on the review of the past and present medical history and risk behaviours of the potential uDCD, a physical examination and complementary tests. Available medical records and charts must be carefully reviewed. A dedicated and guided interview with the relatives always should take place for the assessment of donor’s suitability.

Donor evaluation can be facilitated by the EMS in several ways. Usually, blood samples are taken once death has been determined. Of note, potential uDCD are frequently haemodyluted when CA occurs in the pre-hospital setting and has been followed by the transfer to the hospital. To ensure that non haemodyluted samples are available for a proper donor evaluation, e.g. serology, some Spanish programmes have incorporated to the EMS protocol the recovery of blood samples once the uDCD procedure is activated. These early samples are also of value when potential donors have exsanguinating lesions, preserving the option of lung donation. On the other hand, some EMS are able to discard potential uDCD at the scene of the CA through using rapid drug tests and strip-based HIV testing. This practice avoids the unnecessary activation of the protocol and the related use of resources.

7. Consent and authorization for organ donation

Consent to proceed with organ donation is assessed differently in the three evaluated countries, based on the dissimilar practicalities of uDCD and legislation, particularly when the potential uDCD suffers the CA in the out-of-hospital setting.

With an opt-in system, the practice in the Netherlands is to assess if the person has expressed his/her will about organ donation after death. A national registry must be consulted by the DTC or emergency room staff to assess the person’s wishes. Even in the case of an expressed consent in the said registry, a dedicated interview is held with the relatives before proceeding with organ recovery. In the uDCD process, the registry may be consulted as early as when the EMS announces that a potential donor is being transferred to the hospital. In case of registered opposition, the process is not continued. If no opposition towards donation or positive consent is identified, it is allowed by the national Law to start with preservation measures after death. However, this is not continued with organ recovery if the family oppose or if the family interview cannot be held within the first 2 hours following the initiation of the preservation measures.

France and Spain hold an opting-out policy, so obtaining consent is focused on checking any expressed opposition towards donation during lifetime- there is a specific national registry in France, and an advanced directives registry in Spain. In both countries though an interview with the relatives is held. However, facilitating donation until opposition is encountered is eased by the existing legal framework. In this context, consent may be obtained at different time points along the process: as soon as when the irreversibility of the CA is established by the EMS, or until preservation measures have started. In France, checking the donor registry is mandatory before preservation is initiated, but not in Spain. Organ recovery will never proceed before consent is obtained.
Principles guiding the information to relatives in uDCD have been a matter of international debate. The three countries hold transparency in information as a paramount principle. Messages are provided progressively and adapted to the emotional situation of the relatives and their understanding of the situation. Particular emphasis must be performed on cases transferred to the hospital for the purpose of organ donation.

With regards to the judicial authorization procedure, specific protocols are in place in Spain to facilitate a rapid communication with the coroner and a rapid authorization, first for preservation and later on for organ recovery. Although in principle limited to judicial cases, in practice, these protocols are applied in most of the cases with a prehospital CA. The reason is that frequently professionals in charge of determining death lack of the necessary information to specify the cause of the CA, further to be determined through a judicial autopsy.

8. Resources of EMS and uncontrolled DCD

In the experience of existing programmes, the implementation of uDCD does not entail an increase in material or human resources on the EMS side. As for any time-dependent process, the essentials are a dedicated action protocol that reduces variability and ensures quality in practice, the smooth coordination and communication with the receiving hospital and the fast transfer of the potential donor. Table 7 summarizes three levels of participation of an EMS in uDCD based on the availability of resources.

For a basic implementation of the programme, additional means to those already available at any EMS are not necessary, since all are equipped with material for advanced-life-support. Additional resources may however facilitate the selection and evaluation of potential donors, avoiding unnecessary activations of the protocol if contraindications to donation are already identified at the scene.

As previously specified, the use of mechanical cardiac compressors can facilitate the transfer of potential uDCD and the safety of those in charge of cardiac compression, but it is not an essential. The use of rapid screening tests for certain diseases (e.g. HIV,) and drugs, helps to a better early selection of the cases.

If possible within the organization of the EMS, the presence of another vehicle can be very useful for enabling logistic support and helping in the cardiac compression and mechanical ventilation measures. When is not feasible to transfer potential uDCD by road, the use of helicopters is a possible solution. This allows expanding the pool of potential donors, by including those from areas with a complicated orography or with a long distance from the receiving hospital.

With regards to additional human resources at the scene, the presence of a senior professional who coordinates all external and internal participants and guarantees the adequate compliance with the operating procedure may be considered. This figure may help to ensure a quality control in the compliance with the procedure. The presence of a psychologist at the scene may be useful for the information and to assist and accompany the family until the hospital.

Finally, the composition of the EMS teams may be critical. The presence of physicians at the scene of the CA does not only improve the quality of assistance, but also facilitates this particular donation process - the existence of medicalized EMS may be one of the underlying reasons for the important expansion of uDCD in France or Spain.

IV. RECOMMENDATIONS
1. uDCD is a necessary practice in the pursuit of self-sufficiency in transplantation, in particular, in maximizing donation from the deceased. It represents the culmination of systematically placing donation at the end-of-life in all possible circumstances of death. Efforts must be undertaken to overcome the ethical, legal, technical & logistical barriers that avoid uDCD to be possible at the European level and at each Member State reality. *(Expert opinion)*

2. uDCD needs vision, dedication and institutional support. An unambiguous national regulatory framework should exist to facilitate uDCD and its time constrained related-practice. *(Expert opinion)*

Regulatory aspects should cover, at a minimum, issues related to:

- **Determination of Death** – criteria to define the cessation of the cardiac-circulatory (and respiratory) functions and when such cessation is to be considered irreversible, along with the pre-conditions for the determination of death – aCPR applied and optimized as specified in national CPR protocols, aligned with international professional standards.
- **Preservation measures** – establishing any limitations to its practice, if deemed appropriate within a given jurisdiction.
- **Consent and authorization criteria to proceed with organ preservation and recovery**, adapted to the corresponding general consent framework of a given jurisdiction.

3. Respectful with the national regulatory framework, a specific action protocol should be established at every EMS and hospital engaged in an uDCD programme, where roles and responsibilities are clearly defined, and which is adapted to the available human and material resources and to the internal organization of the corresponding service. *(Expert opinion)*

A dedicated protocol sets the basis for consistency in the development of the process, avoiding personal interpretations, and ensuring quality in practice. This protocol should be developed by a multidisciplinary team with the representation of all relevant professional groups engaged – in smooth cooperation with the EMS, where appropriate. The protocol should be continuously reviewed, updated and subjected to quality control. Continuous training and education, as well as information on the results of the implementation of the protocol should be provided periodically to all relevant stakeholders and professional groups directly or indirectly participating in the development of the uDCD activity.

4. uDCD will only be considered in persons who have suffered a witnessed and appropriately documented CA (either in the pre-hospital or in the in-hospital setting) and in whom CPR has been exhausted according to national protocols, aligned with international standards, and deemed unsuccessful by the attending team. *(Recommendation grade C)*
5. Selection criteria for uDCD represent an important area for research in the future, particularly with regards to the limits in donor age and in WIT, which have been established based on empirical grounds. The following set of criteria describes the current practice in most of the existing programmes and may be proposed as the recommended profile (Recommendation grade C):

- Time of CA known
- ≤55-60 years
- No evidence of:
  - Arterial hypertension – relative contraindication for kidney.
  - Diabetes – relative contraindication for kidney
  - Kidney disease
  - Liver disease
  - Malignancies
  - Intravenous drug abuse
  - Sepsis and viral infection (HIV, HBV, HCV)
  - No major trauma – relative contraindication– abdominal trauma does not preclude lung donation.
  - No homicide or suicide – relative contraindication.
- Time between CA and CPR initiation (no flow period) <15-30 min for kidney transplants, <15 min for liver transplants.
- Total WIT <150 min.

6. A mechanism for the activation of the uDCD protocol by the team in charge of the CPR should be enabled. (Expert opinion).

   Smooth communication between the attending team and the receiving hospital is paramount.

7. A key donation person / DTC should be 24/7 present at the relevant hospital or be able to reach the hospital at a maximum time of 20 minutes. (Expert opinion).

   In case of programmes that may be activated by the EMS, the DTC should be checking the selection criteria and authorizing the potential uDCD transfer, where appropriate, and should be always present at the arrival of the potential uDCD at the hospital. In every single case, the activation of a rapid alert team and the transplantation team should follow. In checking the selection criteria, special emphasis should be performed in the WIT (time since CA until the initiation of aCPR and estimated time of initiation of the preservation measures).

8. As for the purpose of the transfer of the potential uDCD, mechanical cardiac compressors are not essential, although its use improves the quality of cardiac compression and the safety of participating professionals and may improve organ viability (Recommendation grade C).
9. The transfer of a potential uDCD from the out-of-hospital setting needs of a slow and constant speed of the corresponding vehicle to ensure an appropriate cardiac compression and an adequate perfusion of the organs *(Recommendation grade C)*.  

An appropriate transfer may be facilitated by the coordination with other agencies.

10. Death determination should always be the responsibility of a professional(s) independent of the donation and transplantation team *(Expert opinion)*. Death determination preceding uDCD is based on the irreversible cessation of cardiac-circulatory and respiratory functions. *(As per international recommendations on CPR- Recommendation grade A)*.  

- The cessation of the cardiac-circulatory function should be based on the absence of electrical activity by ECG or the appropriate means (as echocardiography or invasive blood pressure measurement) in case of electromechanical dissociation, when reversible causes have been discarded and treated.  
- The irreversibility of the loss of circulation is derived from the inability to restore spontaneous cardiac activity and circulation after aCPR has been applied and fully optimized according to national protocols, aligned with international standards. Still, an observation period is recommended to be set down as a minimum in 5 minutes. There is no solid basis to recommend extending this period of observation beyond this time.

11. There is a need to review some of the already existing national standards on the determination of death based on circulatory criteria, by also capturing the clinical specificities of uDCD. *(Expert opinion)*.  

There is controversy with regards to the validity of death determination after the re-establishment of systemic (and cerebral) circulation with oxygenated blood. In the context of uDCD, this controversy is unfounded in the long lasting experience of consolidated programmes due to the particular clinical characteristics of potential donors. Firstly, the permanent cessation of circulation as a surrogate of the irreversible cessation of circulation is not applicable in this setting- because irreversibility has been already proven. Secondly, because potential uDCD have been exposed to prolonged low-flow periods (aCPR and cardiac compression during donor transfer) and to at least two periods of complete absence of circulation, with previous aCPR deemed unsuccessful by the attending team. The possibility of restoring brain function following the re-establishment of circulation is expected to be clinically negligible due to the profound ischemic injury to the brain. The applicability of the permanent cessation of circulation as a surrogate of the irreversible cessation of circulation in uDCD is not accepted in countries with consolidated programmes of this kind, which base the determination of death on the irreversible loss of cardiac-circulatory functions.

12. Although the practice of re-establishing systemic circulation with cardiac compression after death is determined with the purpose of organ preservation is not applied in all existing programmes, this practice is considered to profoundly impact organ viability and post-transplant outcomes – especially for liver-, a conclusion that may also be derived from the results of the most successful uDCD protocols. *(Recommendation grade C)*.
13. The effectiveness of the different preservation procedures for abdominal organs in the context of DCD, and in the context of uDCD in particular, is still to be compared in randomized controlled trials. However, preclinical and cohort studies suggest the superiority of nRP, compared to hRP, and that of hRP compared with ISP in kidney transplantation and makes nRP (preceded by cardiac compression) to be the advisable preservation method for the liver. *(Recommendation grade C).*

However, ISP may be considered as an option in kidney transplantation, as long as stricter criteria are used in donor selection – e.g. age and WIT. Additionally, the non-realization of the uDCD process when hRP/nRP is used is a matter of concern. The possibility of converting the preservation procedure to ISP in cases where the former fails may be seen as an option, e.g. when the integrity of the vascular structure is not ensured.

Research is needed for the objective establishment of the maximum times for abdominal preservation techniques, but current protocols establish the limit of 180 min for ISP and 240 min for RP. The role of leukopheresis combined with nRP is to be determined. *Each programme should select the preservation method that is better adapted to the local reality and resource availability,* but the principles of reducing potential donor losses as much as possible, while ensuring organ viability and optimal post-transplant results are paramount.

14. Preservation of the lungs should be based on topic cooling. The recirculation of the lung preservation solution allows for the simultaneous normothermia for abdominal organs. *Further research should help establish the maximum times for preservation in terms of organ viability and post-transplant outcomes,* but existing programmes set down the limit of 240 minutes. *(Recommendation grade C).*

15. Donor evaluation is based on the same principles than the evaluation of any deceased organ donor. As for a DBD, donor and organ evaluation is based on the review of the past and present medical history and risk behaviors of the potential uDCD, a physical examination and complementary tests. Available medical records and charts should be carefully reviewed and a dedicated and guided interview with the relatives should always take place for the assessment of donor’s suitability. *(Expert opinion).*

16. For potential uDCD in whom CA takes place in the pre-hospital scenario, donor evaluation can be facilitated by the EMS in several ways, particularly through the collection of blood samples (avoiding potential donor losses due to haemodilution or exanguination- lung transplantation still possible) or the performance of dedicated screening tests at the scene (ie. HIV rapid strip test). *(Expert opinion).*

17. Information to the relatives and the procedure for obtaining consent to proceed with organ preservation and organ recovery should be respectful with the consent system in place at a given jurisdiction. The principle of transparency should be preserved, while maintaining the spirit of an appropriate family care *(Expert opinion).*
<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>18.</td>
<td>A dedicated judicial procedure should be enabled for judicial cases due to the time constraints of the process. <em>(Expert opinion).</em></td>
</tr>
<tr>
<td>19.</td>
<td>An EMS fully implemented in society does not need any additional equipment for the development of uDCD. The essentials are a clear protocol and a smooth communication system with the receiving hospital. <em>(Expert opinion).</em></td>
</tr>
</tbody>
</table>
Figure 1: The process of uncontrolled Donation after Circulatory Death.
Table 1: Selection criteria of uncontrolled donors after circulatory death in France, the Netherlands and Spain.

<table>
<thead>
<tr>
<th></th>
<th>France</th>
<th>Netherlands</th>
<th>Spain</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (Min-Max), years</strong></td>
<td>18-55</td>
<td>12-65</td>
<td>Min: 1 –18; Max: 55-65</td>
</tr>
<tr>
<td><strong>Weight (Min), Kgs</strong></td>
<td>No limit</td>
<td>One programme excludes cases &lt;12 Kg.</td>
<td>One programme excludes &lt;15 Kg and other programme excludes morbid obesity</td>
</tr>
<tr>
<td><strong>Cause of Cardiac Arrest</strong></td>
<td>Excluded cardiac arrest due to hypothermia or cardiotropes (aCPR has to be prolonged) and violent deaths (eventual legal problems).</td>
<td>No limit.</td>
<td>Violent deaths excluded in some programmes.</td>
</tr>
<tr>
<td><strong>Time of cardiac arrest, before aCPR is started</strong></td>
<td>&lt; 30 min for kidney / &lt; 15 min for liver.</td>
<td>&lt; 20 minutes .</td>
<td>&lt; 15 -20 min (depends on the programme).</td>
</tr>
<tr>
<td><strong>External aspect</strong></td>
<td>Excluded cases with signs of intravenous drug addiction.</td>
<td>Excluded cases with signs of intravenous drug addiction.</td>
<td>Excluded cases with signs of intravenous drug addiction.</td>
</tr>
<tr>
<td><strong>Traumatism</strong></td>
<td>Excluded multiple trauma with hemorrhagic shock, kidney and liver injuries and aortic dissection</td>
<td>Excluded hemorrhagic shock or aorta dissection.</td>
<td>Excluded exsanguinating lesions in thorax or abdomen, since they may avoid an appropriate oxygenation and preservation.</td>
</tr>
<tr>
<td><strong>Time goal until arrival into the hospital</strong></td>
<td>120 min</td>
<td>90 min</td>
<td>90 min (120 min in one programme).</td>
</tr>
<tr>
<td><strong>Other (Please, specify)</strong></td>
<td>For kidney, exclusion criteria are renal disease, arterial hypertension or diabetes even if treated, all cancer types, severe sepsis, violent polytrauma, and homicide.</td>
<td>Maximum mechanical CPR (besides 20 min of basic life support) of 70 minutes if &lt; 55 years and 45 minutes if 55-65 years.</td>
<td>Unknown cause of death, unknown identity, untreated sepsis, malignancy, active viral infections, active tuberculosis. Kidney: primary kidney disease</td>
</tr>
<tr>
<td></td>
<td>For Liver: the 3 first renal criteria are replaced by a liver disease.</td>
<td></td>
<td>No tumor or systemic diseases.</td>
</tr>
</tbody>
</table>

aCPR: Advanced Cardiopulmonary Resuscitation.
Table 2: Selected studies addressing donor age in uncontrolled donation after circulatory death.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Grade</th>
<th>Level</th>
<th>Study design</th>
<th>Trial</th>
<th>N</th>
<th>W</th>
<th>Preservation</th>
<th>PNF</th>
<th>DGF</th>
<th>Graft survival</th>
<th>Patient survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hoogland et al (2013), the Netherlands⁵</td>
<td>B</td>
<td>2b</td>
<td>Cohort study</td>
<td>Identification of risk factors for PNF and graft survival in KTx uDCDs</td>
<td>135</td>
<td>&lt; 45 min WIT</td>
<td>ISP</td>
<td>22%</td>
<td>62%</td>
<td>63% (5 yr)</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt; 5 yr if donors ≥54 yr vs 16% if &lt; 54 yr ** Donor age ≥54 yr independently associated with PNF **</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt; 45 min WIT</td>
<td>ISP</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Sánchez-Fructuoso et al (2006), Spain⁹</td>
<td>B</td>
<td>2b</td>
<td>Cohort study</td>
<td>Comparison of results of KTx from uDC (maximum 60 yr) vs DBD &lt;60 yr vs DBD ≥60 yr</td>
<td>320</td>
<td>&lt; 15 min no flow; &lt; 120 WIT (CA-hRP)</td>
<td>Cardiac compression* + hRP</td>
<td>4.4% vs 1.1% vs 4%**</td>
<td>60.9% vs 20.4% vs 27.4%**</td>
<td>82.1% vs 85.5% vs 73.3%**</td>
<td>90% (5 yr) vs 85.5% vs 73.3%**</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>ISP</td>
<td></td>
<td></td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>Hattori et al (2003), Japan⁶</td>
<td>C</td>
<td>4</td>
<td>Poor case series</td>
<td>Identification of risk factors for graft failure in KTx from uDCD donor age &lt; 55 vs ≥ 55 yr (univariate analysis)</td>
<td>706</td>
<td>-</td>
<td>ISP</td>
<td>-</td>
<td>-</td>
<td>53% (10 yr)</td>
<td>82% (10 yr)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Mizutani et al (2001), Japan⁷</td>
<td>B</td>
<td>2b</td>
<td>Cohort study</td>
<td>KTx from uDCD comparing donors &lt; 60 yr vs ≥60 yr</td>
<td>252</td>
<td>WIT (does not specify calculation)</td>
<td>ISP</td>
<td>1% vs 6%**</td>
<td>73.8%</td>
<td>43% (10 yr)</td>
<td>87% (10 yr)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>9.5 min vs 7.9 min</td>
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</tbody>
</table>

*Not specified in the paper; but per protocol. **p<0.05
CA: Cardiac arrest; DBD: Donors after Brain Death; DGF: Delayed graft function; hRP: Hypothermic Regional Perfusion; ISP: In situ preservation; KTx: Kidney Transplant; PNF: Primary non function; uDCD: Uncontrolled donors after circulatory death; WIT: Warm ischemia time; Yr: Years.
Table 3: List of items to communicate during the referral of a potential uDCD as reflected in the 2012 Spanish National Consensus Document.34

<table>
<thead>
<tr>
<th>Close relatives, availability and information provided</th>
</tr>
</thead>
<tbody>
<tr>
<td>Timing:</td>
</tr>
<tr>
<td>▪ Exact time of the cardiac arrest</td>
</tr>
<tr>
<td>▪ Time aCPR was started</td>
</tr>
<tr>
<td>▪ Time of transfer to the hospital</td>
</tr>
<tr>
<td>Past and present medical history (if known)</td>
</tr>
<tr>
<td>Cause of the cardiac arrest</td>
</tr>
<tr>
<td>Possible haemorrhagic lesions</td>
</tr>
<tr>
<td>Venous accesses</td>
</tr>
<tr>
<td>Status of the endotracheal tube (blood, remains)</td>
</tr>
<tr>
<td>Blood gas analysis</td>
</tr>
<tr>
<td>Drug tests, rapid strip HIV test (if tests available)</td>
</tr>
<tr>
<td>ECO Fast (if tests available)</td>
</tr>
<tr>
<td>Use of mechanical cardiac compressor devices</td>
</tr>
</tbody>
</table>

aCPR: Advanced Cardiopulmonary Resuscitation.
Table 4: Selected studies addressing preservation strategies and results with kidney transplantation from uncontrolled donors after circulatory death.

**KIDNEY TRANSPLANTATION FROM UNCONTROLLED DCD: nRP PROVIDES SUPERIOR OUTCOMES COMPARED TO hRP AND hRP COMPARED TO ISP, PARTICULARLY WITH REGARDS TO THE INCIDENCE OF PRIMARY NON FUNCTION (GRADE C)**

Very heterogeneous studies, and only one targeted to study differences in outcomes depending on the preservation method used

<table>
<thead>
<tr>
<th>Reference</th>
<th>Grade</th>
<th>Level</th>
<th>Study design</th>
<th>Trial</th>
<th>N</th>
<th>Times</th>
<th>In situ Preservation</th>
<th>PNF</th>
<th>DGF</th>
<th>Graft survival</th>
<th>Patient survival</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Miranda-Utrera et al (2013), Spain</td>
<td>C</td>
<td>4</td>
<td>Case series</td>
<td>Description of results of KTx from uDCD</td>
<td>156</td>
<td>-</td>
<td>Cardiac compression* + nRP</td>
<td>8.6%</td>
<td>85%</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Abboud et al (2012), France</td>
<td>C</td>
<td>4</td>
<td>Case series</td>
<td>Description of results of KTx from uDCD</td>
<td>58</td>
<td>&lt;30 min CA-CPR; &lt;150 min total WIT; preservation time &lt;180 min (ISP) or &lt;240 min (nRP)</td>
<td>Cardiac compression + ISP or nRP</td>
<td>5%</td>
<td>95%</td>
<td>91.4% (1 yr)</td>
<td>98% (1 yr)</td>
<td>Ex situ kidney preservation with pulsatile preservation</td>
</tr>
<tr>
<td>De Gracia et al (2012), Spain</td>
<td>C</td>
<td>4</td>
<td>Case series</td>
<td>Description of results of KTx from uDCD</td>
<td>27</td>
<td>&lt;120 min total WIT</td>
<td>Cardiac compression* + ISP or nRP</td>
<td>0%</td>
<td>85.2%</td>
<td>85% (2 yr)</td>
<td>100% (2 yr)</td>
<td>-</td>
</tr>
<tr>
<td>Hanf et al (2012), France</td>
<td>B</td>
<td>2b</td>
<td>Cohort study</td>
<td>Description of results of KTx from uDCD vs ECD vs SPK</td>
<td>27 vs 30 vs 24</td>
<td>&lt; 30 min CA-CPR</td>
<td>Cardiac compression* + ISP</td>
<td>0% vs 0% vs 0%</td>
<td>81.5% vs 27.6% vs 0%</td>
<td>100% (3 yr) vs 82% vs 94%</td>
<td>100% (3 yr) vs 100% vs 100%</td>
<td>Pulsatile preservation used for kidney selection in uDCD</td>
</tr>
<tr>
<td>Hoogland et al (2011), the Netherlands</td>
<td>B</td>
<td>2b</td>
<td>Cohort study</td>
<td>Comparison of results of KTx from uDCD vs cDCD</td>
<td>128 vs 208</td>
<td>&lt; 45 min of CPR; &lt; 45 min CPR-ISP</td>
<td>ISP</td>
<td>22% vs 21%</td>
<td>61% vs 56%</td>
<td>50% (10 yr) vs 46%</td>
<td>61% (10 yr) vs 60%</td>
<td>Pulsatile preservation used in 82% vs 84%</td>
</tr>
<tr>
<td>Reznik et al (2011), Russia</td>
<td>C</td>
<td>4</td>
<td>Case series</td>
<td>Description of results of KTx from uDCD</td>
<td>20</td>
<td>45-92 min no flow after cessation of CPR</td>
<td>Leukopheresis + fibrinolytics + nRP</td>
<td>0%</td>
<td>70%</td>
<td>100% (3 mo)</td>
<td>100% (3 mo)</td>
<td>-</td>
</tr>
<tr>
<td>Sánchez-Fructuoso (2006), Spain</td>
<td>B</td>
<td>2b</td>
<td>Cohort study</td>
<td>Comparison of results of KTx from uDCD vs DBD &lt; 60 yr</td>
<td>320 vs 458 vs 126</td>
<td>&lt; 15 min CA-CPR; &lt; 120 min total WIT</td>
<td>Cardiac compression* + hRP</td>
<td>4.4% vs 1.1% vs 4%**</td>
<td>60.9% vs 20.4% vs 27.4%**</td>
<td>82.1% (5yr) vs 85.5% vs 85.5%</td>
<td>90% (5yr) vs vs vs</td>
<td>-</td>
</tr>
<tr>
<td>Study</td>
<td>Country/Cohort Study</td>
<td>Comparison of results</td>
<td>CA Preservation</td>
<td>Mean: 23.7 min CA-Preservation</td>
<td>ISP</td>
<td>51% vs 24% vs 42%**</td>
<td>73.3%**</td>
<td>73.3%**</td>
<td>53% (10 yr) vs 62% vs 29%**</td>
<td>82% (10 yr)</td>
<td>Mean: 23.7 min CA-Preservation</td>
<td>51% vs 24% vs 42%**</td>
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<tr>
<td>Gagandeep et al (2006), United States</td>
<td>B 2b  Cohort study</td>
<td>Comparison of</td>
<td>-</td>
<td>Mean: 23.7 min CA-Preservation</td>
<td>-</td>
<td>-</td>
<td>73.3%**</td>
<td>73.3%**</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>results of KTx from uDCD vs DBD vs cDCD</td>
<td>216 vs 75,865 vs 1,814</td>
<td>Mean: 23.7 min CA-Preservation</td>
<td>-</td>
<td>-</td>
<td>73.3%**</td>
<td>73.3%**</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Hattori et al (2003), Japan</td>
<td>C 4  Poor case series</td>
<td>Identification of</td>
<td>-</td>
<td>ISP</td>
<td>-</td>
<td>-</td>
<td>53% (10 yr) vs 62% vs 29%**</td>
<td>82% (10 yr)</td>
<td>-</td>
<td>-</td>
<td>ISP</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>risk factors for</td>
<td>-</td>
<td>ISP</td>
<td>-</td>
<td>-</td>
<td>53% vs 6%**</td>
<td>73.8%</td>
<td>43% (10 yr) vs 47% vs 30%**</td>
<td>87% (10 yr)</td>
<td>ISP</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>graft failure in KTx</td>
<td>-</td>
<td>ISP</td>
<td>-</td>
<td>-</td>
<td>53% vs 6%**</td>
<td>73.8%</td>
<td>43% (10 yr) vs 47% vs 30%**</td>
<td>87% (10 yr)</td>
<td>ISP</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>from uDCD-donor age &lt; 55 vs ≥ 55 yr (univariate analysis)</td>
<td>706 vs 192 (≥ 55 yr) vs 411 vs 192 (≥ 55 yr)</td>
<td>ISP</td>
<td>53% (10 yr) vs 62% vs 29%**</td>
<td>82% (10 yr)</td>
<td>-</td>
<td>-</td>
<td>ISP</td>
<td>-</td>
<td>53% vs 6%**</td>
<td>73.8%</td>
</tr>
<tr>
<td>Mizutani et al (2001), Japan</td>
<td>B 2b  Cohort study</td>
<td>Comparison of results</td>
<td>-</td>
<td>ISP</td>
<td>-</td>
<td>-</td>
<td>53% vs 6%**</td>
<td>73.8%</td>
<td>43% (10 yr) vs 47% vs 30%**</td>
<td>87% (10 yr)</td>
<td>ISP</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>of KTx from uDCD ≤60 yr vs ≥60 yr</td>
<td>252 vs 200 vs 52</td>
<td>ISP</td>
<td>53% vs 6%**</td>
<td>73.8%</td>
<td>43% (10 yr) vs 47% vs 30%**</td>
<td>87% (10 yr)</td>
<td>-</td>
<td>-</td>
<td>ISP</td>
<td>-</td>
</tr>
<tr>
<td>Valero et al (2000), Spain</td>
<td>C 4  Poor cohort study</td>
<td>Comparison of results</td>
<td>-</td>
<td>ISP</td>
<td>-</td>
<td>-</td>
<td>53% vs 6%**</td>
<td>73.8%</td>
<td>43% (10 yr) vs 47% vs 30%**</td>
<td>87% (10 yr)</td>
<td>ISP</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>of KTx from uDCD with ISP vs hRP vs nRP</td>
<td>44 vs 8 vs 8</td>
<td>&lt;30 min CA-CPR vs 150 min total WIT</td>
<td>22.5% vs 0% vs 0%**</td>
<td>55% vs 75% vs 12.5%** &amp; significantly shorter duration with nRP</td>
<td>56% (5yr) No statistically significant differences between the groups</td>
<td>89.3% (5yr)</td>
<td>No statistically significant differences between the groups</td>
<td>-</td>
<td>&lt;30 min CA-CPR vs 150 min total WIT</td>
<td>22.5% vs 0% vs 0%**</td>
</tr>
</tbody>
</table>

*Not specified in the paper, but per protocol. **p<0.05
CA: Cardiac arrest; CPR: Cardiopulmonary resuscitation; cDCD: Controlled Donors after Circulatory Death; DBD: Donors after Brain Death; DGF: Delayed graft function; hRP: ECD: Expanded Criteria Donors; Hypothermic Regional Perfusion; ISP: In situ preservation; KTx: Kidney Transplant; nRP: Normothermic Regional Perfusion; PNF: Primary non function; SPK: Simultaneous Pancreas Kidney; uDCD: Uncontrolled donors after circulatory death; WIT: Warm ischemia time; Yr: Years.
Table 5: Selected studies addressing preservation strategies and results with liver transplantation from uncontrolled donors after circulatory death.

<table>
<thead>
<tr>
<th>Grade</th>
<th>Level</th>
<th>Study design</th>
<th>Trial</th>
<th>N</th>
<th>Times</th>
<th>Preservation-after death determination</th>
<th>Graft survival</th>
<th>Patient survival</th>
<th>Biliary complications</th>
<th>PNF</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fondevila et al (2012), Spain</td>
<td>C</td>
<td>4</td>
<td>Case series</td>
<td>Outcomes of LTx from uDCD. Compares with cohort of LTx from DBD</td>
<td>34 vs 538</td>
<td>&lt; 15 min CA-CPR; &lt; 150 min total WIT</td>
<td>Cardiac compression + nRP</td>
<td>70% (1 yr) vs 87%**</td>
<td>82% (1 yr) vs 90%</td>
<td>8% (IC)</td>
<td>-</td>
</tr>
<tr>
<td>Jiménez-Galanes et al (2009), Spain</td>
<td>C</td>
<td>3b</td>
<td>Case-control study</td>
<td>Outcomes of LTx from uDCD. Comparison with LTx from DBD before and after</td>
<td>20 vs 40</td>
<td>&lt; 15 min CA-CPR; &lt; 150 min total WIT</td>
<td>Cardiac compression* + nRP</td>
<td>80% (1 yr) vs 87.5%</td>
<td>85.5% (1 yr) vs 87.5%</td>
<td>1 vs 0</td>
<td>10% vs 2.5%</td>
</tr>
<tr>
<td>Suárez et al (2008), Spain</td>
<td>C</td>
<td>4</td>
<td>Case series</td>
<td>Describe biliary complications with LTx from uDCD. Compares with a large population of LTx from DBD</td>
<td>27 vs 471</td>
<td></td>
<td>Cardiac/abdominal compression and cardiac compression + hRP/nRP*</td>
<td>49% (5 yr) vs 68%**</td>
<td>62% (5 yr) vs 74%</td>
<td>41.7% vs 16.8%</td>
<td>NAS 25% vs 2.3%%</td>
</tr>
<tr>
<td>Otero et al (2003), Spain</td>
<td>C</td>
<td>4</td>
<td>Poor case-control study</td>
<td>Outcomes of LTx from uDCD. Comparison with with DBD before-after. Comparison Cardiac/abdominal compression vs. hRP /nRP</td>
<td>20 vs 40</td>
<td></td>
<td>Cardiac/abdominal compression vs cardiac compression + hRP/nRP*</td>
<td>55% (2yr) vs 73% vs 83% vs 43%</td>
<td>80% (2yr) vs 73% vs 100% vs 71%</td>
<td>30% vs 8%**</td>
<td>25% vs 3%</td>
</tr>
</tbody>
</table>

*Not specified in the paper, but per protocol. **p<0.05. CA: Cardiac arrest; DBD: Donation after Brain Death; IC: Ischemia colangiopathy; CPR: Cardio-pulmonary resuscitation; hRP: Hypothermic Regional Perfusion; LTx: Liver transplant; NAS: Non anastomotic strictures; nRP: Normothermic Regional Perfusion; uDCD: Uncontrolled Donation after Circulatory Death; WIT: Warm ischemia time; Yr: years.
Table 6: Technical aspects related to the preservation of abdominal organs in uDCD

<table>
<thead>
<tr>
<th>In situ preservation</th>
</tr>
</thead>
<tbody>
<tr>
<td>▪ Double-balloon-triple-lumen catheter inserted via the femoral artery, one balloon placed at the aortoiliac bifurcation and the other balloon placed over the superior mesenteric artery.</td>
</tr>
<tr>
<td>▪ Drain in femoral vein to allow the clearance of the hematic content,</td>
</tr>
<tr>
<td>▪ Control of pressure of perfusion of preservation liquid (70-80 mmHg).</td>
</tr>
<tr>
<td>▪ Variable preservation solutions used (HTK, Wisconsin, Celsior, IGL-1).</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>hRP</th>
</tr>
</thead>
<tbody>
<tr>
<td>▪ Use of an extracorporeal circuit: femoral vessels cannulated and connected with a module for temperature exchange and with a membrane oxygenation module: blood is oxygenated and cooled at 4-15°C.</td>
</tr>
<tr>
<td>▪ The contralateral femoral artery is cannulated with a unique balloon catheter. The balloon is advanced into the supraceliac aorta and is inflated with saline and X-ray contrast. Proper positioning on the balloon is confirmed by simple Rx.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>nRP</th>
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<tbody>
<tr>
<td>▪ Similar to hRP, except for blood maintained at 32-37°C and kept until the macroscopic visualization of liver and kidneys in the surgical room and ulterior cold perfusion with preservation solution.</td>
</tr>
<tr>
<td>▪ Pump flow is maintained at 1.7-2.5 L/min/m².</td>
</tr>
<tr>
<td>▪ Blood is sampled at baseline and throughout nRP to determine biochemical and haematological parameters and acid-base status.</td>
</tr>
<tr>
<td>▪ Additional heparin administered every 90 minutes (1.5 mg/kg i.v.).</td>
</tr>
</tbody>
</table>
**Table 7: Levels in the participation of EMS in uDCD based on the availability of resources**

<table>
<thead>
<tr>
<th>Application Procedure Basic Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>a) Advanced Life Support Ambulances and/or helicopters, electromedical equipment, medication and equipment needed for resuscitation.</td>
</tr>
<tr>
<td>b) Possibility of arrival at the receiving hospital within 120 minutes after the PCR.</td>
</tr>
<tr>
<td>c) Communication system with the receiving hospital/donor transplant coordinator.</td>
</tr>
<tr>
<td>d) Specific protocol for uDCD at the EMS.</td>
</tr>
<tr>
<td>e) Training EMS staff in the uDCD protocol.</td>
</tr>
<tr>
<td>f) Regular quality control of the implementation of the uDCD protocol.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Process Development Level: Donor selection and evaluation optimized and better results achieved.</th>
</tr>
</thead>
<tbody>
<tr>
<td>a) Support Basic Life Support units in each process.</td>
</tr>
<tr>
<td>b) HIV test strips and drug detection kit.</td>
</tr>
<tr>
<td>c) Mechanical cardiac compressors.</td>
</tr>
<tr>
<td>d) Work-procedures with non-health-care agencies (i.e. police) for locating family members and escorting ambulances during donor transfer.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Optimal Development Level: Optimal performance in donor selection/evaluation and better quality of preservation of donor’s organs.</th>
</tr>
</thead>
<tbody>
<tr>
<td>a) Presence of a second doctor on the scene with a coordinating role with other agencies and with the receiving hospital and the Coordination Center.</td>
</tr>
<tr>
<td>b) Presence of a logistics support vehicle at the scene that facilitates the work of cardiac massage and provides the necessary material.</td>
</tr>
<tr>
<td>c) Presence of an Emergency Psychologist at the scene, to facilitate the communication with the relatives and for the purpose of family care.</td>
</tr>
<tr>
<td>d) Analytical stage, in order to evaluate and correct electrolyte imbalances and consider time of cardiac arrest.</td>
</tr>
<tr>
<td>e) Medical helicopter for long distance potential uDCD.</td>
</tr>
</tbody>
</table>
Figure 2: Times in uncontrolled DCD in France, the Netherlands and Spain.

*This limit is only established in the Netherlands, where cardiac compression is not re-established after death determination.
20. REFERENCES


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