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Expanding controlled donation after the circulatory determination of death: statement from an international collaborative

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Abstract

A decision to withdraw life-sustaining treatment (WLST) is derived by a conclusion that further treatment will not enable a patient to survive or will not produce a functional outcome with acceptable quality of life that the patient and the treating team regard as beneficial. Although many hospitalized patients die under such circumstances, controlled donation after the circulatory determination of death (cDCDD) programs have been developed only in a reduced number of countries. This International Collaborative Statement aims at expanding cDCDD in the world to help countries progress towards self-sufficiency in transplantation and offer more patients the opportunity of organ donation. The Statement addresses three fundamental aspects of the cDCDD pathway. First, it describes the process of determining a prognosis that justifies the WLST, a decision that should be prior to and independent of any consideration of organ donation and in which transplant professionals must not participate. Second, the Statement establishes the permanent cessation of circulation to the brain as the standard to determine death by circulatory criteria. Death may be declared after an elapsed observation period of 5 min without circulation to the brain, which confirms that the absence of circulation to the brain is permanent. Finally, the Statement highlights the value of perfusion repair for increasing the success of cDCDD organ transplantation. cDCDD protocols may utilize either in situ or ex situ perfusion consistent with the practice of each country. Methods to accomplish the in situ normothermic reperfusion of organs must preclude the restoration of brain perfusion to not invalidate the determination of death.

Keywords: Determination of death, Donation after the circulatory determination of death, Normothermic regional perfusion, Organ perfusion, Organ repair, Organ transplantation, Tissue and organ procurement, Withdrawal of life-sustaining therapy

Background

The World Health Organization (WHO) and The Transplantation Society (TTS), a non-governmental organization in official relations with the WHO, seek to implement the WHO Guiding Principles on the Transplantation of Human Cells, Tissues and Organs [1] throughout the world in all countries where deceased

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organ donation is, or reasonably could be, a component of their transplantation programs.

Kidney and liver transplantation are the most frequent organ transplants performed (65% and 23% of the annual total, respectively) [2]. The WHO has estimated that the approximately 147,000 organ transplants performed annually meet just 10% of the identified global need [2]. Studies of the global burden of disease reveal that this need is probably several fold greater, based on the toll of disability and of premature loss of life that could be prevented by organ transplantation. In many countries, transplantation is not offered as a treatment modality and access to other treatments for organ failure is limited. Even in countries with robust transplant programs, thousands of patients die or endure a poor quality of life while awaiting an organ. This shortage is also the proximate cause of organ trafficking and transplant tourism, practices that violate fundamental human values and pose risks to individual and public health [3].

The WHO and TTS have called on countries to pursue self-sufficiency in transplantation by decreasing the burden of diseases treatable with transplantation and by increasing the availability of organs. But organ transplantation ought not be limited to living donation; indeed, as the WHO has stated, priority should be given to deceased donation, which should be developed to its maximum therapeutic potential [4]. As noted by the WHO, TTS, and other stakeholders, such as the International Society for Organ Donation and Procurement (ISODP), expanding deceased donation increases opportunity to help patients in need by donating organs after death when this is consistent with their intention and values.

While in some countries the number of organs transplanted from deceased donors far exceeds the number contributed by living donors, as of 2018, 10 WHO Member States (of more than 80 with transplantation services) still relied solely on living donors in liver and kidney transplants [2]. In countries where deceased donation is practiced, most cases involve donation after the neurological determination of death (DNDD) by physicians caring for the donor. This Statement focuses on an alternative source of organs from deceased donors, namely, donation after the circulatory determination of death (DCDD). We note that the terms "donation after cardiac death", "donation after circulatory death" or "non heart beating donation" have become obsolete and imprecise. Controlled DCDD (cDCDD) refers to organ donation from a patient who has died in the hospital following the withdrawal of life-sustaining treatment (WLST). We recognize that cDCDD has also been proposed following euthanasia; however, this paper will not address this approach because euthanasia is illegal in most countries. Uncontrolled DCDD refers to organ donation following failed efforts to resuscitate an individual experiencing out-of-hospital or unexpected in-hospital cardiopulmonary arrest.

A decision to WLST is derived by a conclusion that further treatment will not enable a patient to survive or will not produce a functional outcome with acceptable quality of life that the patient (or their legal surrogate) and the treating team regard as beneficial. Although many hospitalized patients die under such circumstances around the world [5], cDCDD programs have been developed only in seventeen countries: Australia, Austria, Belgium, Canada, China, Czech Republic, France, Ireland, Italy, the Netherlands, New Zealand, Norway, Spain, Sweden, Switzerland, the United Kingdom, and the United States [6, 7]. cDCDD programs are absent in jurisdictions where the legislature has not enacted a law providing relevant criteria for determining death or professional societies have not developed end-of-life care guidelines that support a pathway to cDCDD [7]. In addition to clinical criteria, such guidelines need to specify how decisions to withdraw treatment will be separated from the decision that the patient will become an organ donor after death.

Another factor holding back cDCDD is a concern that organs recovered from such donors produce inferior results for recipients. The number of organs obtained from this source has, however, expanded substantially during the last decade [2, 7], as the specific injury patterns linking aging and prolonged ischemia of DCDD organs are better understood and novel preservation and assessment techniques are being implemented. Success with cDCDD has now been shown not only with kidneys but also with heart, lung, liver, and pancreas transplantation. Moreover, one of the rationales for advancing the science of organ preservation is to improve the function and outcome of organs transplanted from cDCDD donors [8]. Increasing the skills of surgeons and ensuring their availability both to retrieve deceased donor organs and to perform the implantations will also promote transplantation in more countries.

A further obstacle to cDCDD in some countries arises with deceased donation generally and DNDD. The identification of potential deceased donors and their referral and support until they are declared dead require the use of ventilators and other equipment in an intensive care unit (ICU), resources that in many countries are not sufficient to care for patients with devastating brain injury (DBI). The inadequacy of intensive care, particularly in developing countries, may then preclude the development of cDCDD—as well as DNDD. This is made evident by the association between human development index with deceased donation [2].

Doubts about deceased donation among the general public also impede the development of cDCDD programs. Education is essential if the patients and their families are going to understand how death is determined and not have concerns when a potential donor is declared dead. Having a trained organ donation coordinator available in the ICU provides a means of answering any questions from members of a potential donor's family and obtaining permission for organ donation. Although religious leaders occasionally voice concerns about deceased donation, family members can be assured that the practice is supported by most major religions.

The Algorithm in Fig. 1 displays the pathways by which either a DBI that results in a comatose condition or other medical events that cause an arrest of cerebral circulation can progress to deceased organ donation and transplantation following death determined either by neurologic criteria (DNDD) or by the permanent absence of circulation (DCDD) under controlled circumstances. The Algorithm highlights three important points along these pathways:

- The process of determining a prognosis that justifies the withdrawal of life-sustaining treatment (WLST).
- Determining death after the permanent cessation of circulation to the brain.
- Perfusion repair for increasing organ transplantation success in cDCDD.

The process of determining a prognosis that justifies the withdrawal of life-sustaining treatment

The process described in the Algorithm (Fig. 1) reveals the transition from a care decision that ongoing life-supporting treatments can no longer achieve a satisfactory outcome/quality of life for the patient and should be withdrawn, to the subsequent presentation of the opportunity for organ donation after WLST and death. The conditions and testing that are detailed in the Statement

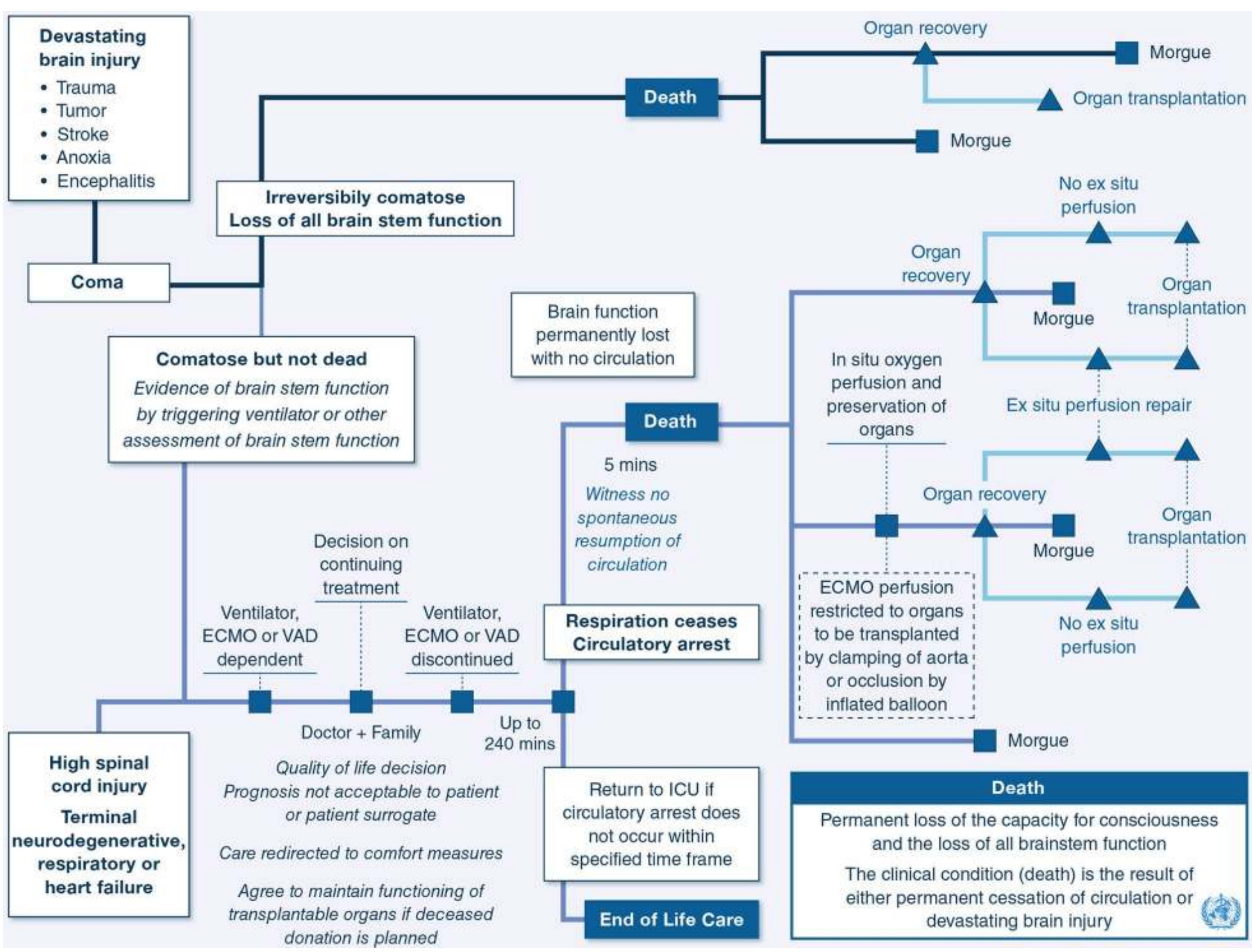

Fig. 1 Algorithm showing the pathways to death and to organ transplantation. *ECMO* extracorporeal membrane oxygenation, *ICU* intensive care unit, *VAD* ventricular assist device

are elaborated to reveal the sophistication that has evolved to objectively assess prognosis before a decision to WLST is made. The decision for WLST is reached when continued treatments are not anticipated to enable the patient's survival or an acceptable quality of life [9].

The prognosis leading to a WLST decision should only be made by the treating physician in concert with a wider multidisciplinary team, subspecialty consults and in discussion with the patient (if conscious) or the patient's family [10]. The decision for WLST may be informed by the presence of an advanced directive refusing extraordinary/invasive measures of treatment. Organ transplant and recovery physicians have no role or responsibility in the WLST decision.

Conditions in which the WLST is undertaken

The clinical conditions in which WLST may be undertaken include (see Algorithm in Fig. 1):

- Devastating brain injury (DBI).
- High spinal cord injury.
- Terminal neurodegenerative disease.
- Respiratory or heart failure.

These patients may be receiving mechanical ventilation and cardiovascular support with vasoactive agents or extracorporeal membrane oxygenation (ECMO) or may be supported by a ventricular assist device (VAD), as well as other support such as renal replacement therapy.

In the Algorithm, the term DBI encompasses patients with a neurological condition that is perceived as an immediate threat to life or incompatible with satisfactory functional recovery and a decision to WLST is being considered [11]. Souter et al. have made recommendations for the critical care management of patients with DBI who have [11]:

- An acute severe neurological condition, such as penetrating and/or blunt trauma to the brain or ischemic stroke, intracranial hemorrhage or anoxic brain injury;
- Been evaluated by a multidisciplinary team including neurosurgery and/or neurology expertise;
- A clinical condition considered to be incompatible with survival or an acceptable functional outcome not amenable to neurosurgical or other appropriate interventions;
- An ongoing requirement for critical care management.

Determining the clinical condition with poor prognosis

In the ICU, WLST becomes an appropriate course for patients suffering an unresponsive shock with multiple organ failure, with end-stage cardiovascular or respiratory failure, and disseminated malignancy. For patients with a DBI, clinical experience and repeated neurological examination to assess level of consciousness and brain stem reflexes are combined with ancillary investigations which include brain imaging by computed tomography (CT) or magnetic resonance imaging (MRI), neurophysiology assessments by electroencephalogram (EEG) and evoked potentials, and biomarkers such as neuron-specific enolase, to identify patients anticipated to die or who have a poor neurological outcome.

The decision to proceed with WLST is made by a medical team with relevant clinical experience utilizing the available scientific evidence (such as, the current prognostic models/scales of severity [12–19]), and based on the preferences of the patient, expressed personally or by representation. The models pertaining to the development of a prognosis should always be used with caution [12–19]; they are not designed to be used, and should not solely be used to prognosticate on an individual patient, but assist in informing the prognosis. The models have been designed to allow benchmarking of units (scales or scores) in outcome studies or to allow assessment of new treatments on outcome. The models have flaws evident by outcome studies where the event prior to death was the WLST that can result in a self-fulfilling prophesy, because they introduce bias toward a poor prognosis. The historical models may also not take into account recent advances in treatment. However, the prognostic models (scales of severity) are useful in discussions with the patient's family in deciding what course of action best respects the preferences and values of that patient. Predicting long-term improvement in consciousness and/or cognitive function at the time of hospitalization based on statistical modelling may be imprecise in individual cases by current diagnostic capabilities. It achieves precision only several months or years after the brain injury—having waited long enough to determine if the prognosis was correct.

Thus, prognostic error may occur either by predicting a good prognosis for patients who have a poor outcome (e.g. chronically vegetative or minimally conscious state) or by predicting a poor prognosis that leads to WLST for a patient who could have recovered with a satisfactory outcome. Predicting a poor outcome when there could have been a recovery is not ascertainable when WLST is conducted—because WLST precludes the opportunity of recovery.

Finally, biases can cloud the judgment of a physician or a healthcare team member, providing a prognostic assessment [20]. For example:

- looking for evidence to support the presumed prognosis rather than contradictory elements;
- overestimating the likelihood of a prognosis based on a recent experience with a similar case;
- focusing on salient features in the patient's presentation too early in the prognosis process and failing to adjust this initial impression in light of new information.

The decision to WLST generally should be delayed to administer appropriate treatment in the ICU for a period of up to 72 h [20–22]. This observation period in the ICU improves the reliability of establishing a prognosis: in determining whether the patient may be declared dead by neurological criteria or whose condition is progressing to brain death or whether the neurological condition is deteriorating (or not improving) and a decision to WLST is appropriate. This delay also facilitates the involvement of families in decision-making and/or end-of-life care planning. In patients who remain comatose after resuscitation from an out-of- hospital cardiac arrest, a period of up to 72 h for observation and physiological stabilisation is also recommended to more precisely identify patients who will die or have a poor neurological outcome [21].

Surrogates who may participate in decisions regarding life-sustaining treatment

When a patient is incapable of participating directly in treatment decisions, the medical team must turn to a surrogate decision-maker who is authorized to make the decision on the patient's behalf. Depending on the jurisdiction, the persons who may serve as a surrogate are determined by statute, regulation, judicial decision, or custom and typically include:

- The individual to whom the patient has given a durable power of attorney to make healthcare decisions;
- The patient's spouse or registered domestic partner;
- The patient's children who are at least 18 years of age;
- The patient's parents;
- The patient's siblings;
- Others with an established relationship to the patient;
- The appointed guardian of any patient.

The hierarchy of surrogates in decision-making varies among countries and jurisdictions.

WLST is justified when certain conditions are met

Decision-making at the end-of-life should be based not only on patients' medical prognosis but also on social, moral, and welfare considerations [23]. While the circumstances under which life-sustaining treatment may be withdrawn can vary based on local medical, cultural, religious traditions, and legal regulations, in many countries WLST is viewed today as appropriate, based on the patient's prognosis, preferences and values when:

- Further treatment has become physiologically futile because the patient's hemodynamic, respiratory, renal function and their metabolic indices (lactate, base excess, pH, renal function) are deteriorating despite increasing levels of support;

or

- The patient could survive with treatment but the healthcare team and surrogate decision-maker(s) (or patients themselves with certain underlying conditions, e.g., ALS) have concluded that the patient's expected functional outcome and quality of life will not be what the patient would want or will not provide a benefit to the patient that is sufficient to warrant the burden of continued treatment;

or

- When the treating team is made aware of an advance directive by the patient that rejects burdensome life-sustaining treatments.

The location of WLST may have an impact on the duration of warm ischemia and eventually on post-transplant outcomes [24]. However, location and procedures of WLST should be developed according to local protocols that stress the need to ensure quality in end-of-life care and to avoid both over- and under-treatment of pain and suffering [25].

Evolving change of end-of-life care in the intensive care units

Wide variation in end-of-life care practices exists in the ICUs throughout the world. This variation was initially highlighted by the Ethicus study performed in Europe at the beginning of the century [26]. The study revealed that WLST was undertaken nearly three times more frequently in northern compared to southern European countries (47.4% vs 17.9%), while the incidence of brain death was nearly four times more frequent in southern European countries compared to northern ones (12.4% vs 3.4%). The ACCORD study, focused on patients who had died as a result of a DBI, also made evident differences in the frequency of WLST across European countries [27]. These differences probably reflected variable professional practices that in turn are influenced by cultural, religious and social factors in each country.

The Ethicus study has been recently reproduced. Interestingly, while these variations across countries still persist, they are less pronounced than previously, with more limitations in life-prolonging therapies and fewer deaths without treatment limitations, suggesting a shift in end-of-life care practices toward WLST in Europe [5].

Separating end-of-life decisions from an individual's choice to be an organ donor

The opportunity to participate in deceased donation should be a routine component in end-of-life care. Indeed, those who provide intensive medical care to patients near death—including cases where treatment withdrawal is being considered—have a responsibility to refer such patients to the donation services whenever the criteria to do so are met. This principle has been endorsed by a number of professional societies concerned with ethical and humane care for patients in the ICU [28–30]. Nonetheless, for ethical as well as legal reasons, the transition from deciding about the WLST to deciding about organ donation needs to be carefully managed. The following principles should guide this process:

1. The shared decision of the ICU team and the patient or surrogate to withdraw treatment should not be influenced by the prospect that other persons could benefit if the patient's death made organs available for transplantation.
2. The treating team should not raise the possibility of cDCDD with the patients or surrogates during the discussion of WLST. If the patient or surrogates introduce the topic, however, organ donation may be addressed during conversations leading to a WLST decision. The team should also ascertain that the decision of WLST is supported regardless of the possibility of cDCDD.
3. Once a WLST decision has been reached, the treating physicians may work with the organ donation team to raise the possibility of donation with the patient or surrogate and to facilitate donation when that is appropriate given the patient's medical condition and is consistent with the patient´s wishes and values. In some countries, people are able to record a legally recognized decision to donate through a donor registry. Registries and the other legal and regulatory mechanisms provide the ethical benefit of allowing donors to make donation decisions themselves while they are still able to do so [31]. During the donation conversation with family, information should be conveyed that the donation may not proceed finally because of medical unsuitability (e.g. malignancy, infection, death not occurring within a timeframe that permits organ transplantation).
4. To avoid creating a conflict of interest or the perception of such a conflict, the physicians involved in caring for the patient, in deciding to withdraw treatment, in managing the withdrawal, and in declaring death must not currently be involved in caring for the potential recipients of the donated organs as they await the transplant or in transplanting those organs.
5. As discussed previously, the limits to prognostic certainty must be candidly discussed with all decision-makers, including the healthcare team and the patient or surrogate. These limits apply whether decision for WLST is accompanied by a decision for cDCDD—or not and do not become more grave or problematic when a WLST decision is followed by cDCDD.

Every day in ICUs around the world patients die following the WLST. Yet in the many countries that lack cDCDD programs, the autonomy of such patients and their families regarding final bodily disposition after death is diminished, because they are not offered an opportunity to donate organs. In addition, by precluding treating physicians from raising the opportunity for cDCDD once a decision to withdraw life-support has been made, these countries reduce the number of organs available for transplantation and thus undermine national efforts to achieve self-sufficiency in organ donation and transplantation.

Recommendations pertaining to the process of determining a prognosis that justifies the withdrawal of life-sustaining treatment
Health authorities, professionals and professional associations should **evaluate the circumstances of patients dying in ICUs**. In countries where WLST is an accepted practice in the consideration of treatment futility and end-of-life care, the possibility of **developing a cDCDD program as a routine component of end-of-life care** should be explored
The cDCDD program must be developed with a **comprehensive regulatory framework** that emphasizes the independence of decisions related to the WLST from the consideration of organ donation
Transplant healthcare professionals must not be involved in reaching the decision to WLST nor in the actions involved in the WLST

Determining death after the permanent cessation of circulation to the brain

Unifying concept of death

The principal consequences of the loss of brain functions—namely, that the person loses both consciousness and all brainstem reflexes including the capacity to breathe—explain why the permanent cessation of brain function provides the unifying concept of human death [32, 33]. Whether the primary pathophysiology is cerebral circulatory arrest or direct DBI, and whether the loss of brain function is measured through neurological examination or by ascertaining the permanent cessation of circulation to the brain, loss of brain functions is the ultimate criterion for determining death.

Determining death

Permanent cessation of the capacity for consciousness and of the capacity to breathe and all other brainstem functions can arise directly from an injury to the brain or indirectly when circulation to the brain has been interrupted. Determining death by the permanent cessation of brain function is consistent with the medical standards for determining death outside the context of organ donation [34, 35]. Death can be confirmed by circulatory criteria when there is:

- No forward circulatory flow to the brain;
- No perfusion of brain cells; and
- Loss of capacity for consciousness, of capacity to breathe, and of all other brainstem functions.

In those countries and jurisdictions where the determination of death by neurologic criteria is not currently accepted, then death determined by a permanent absence of circulation after a decision for WLST should be considered.

The relationship between WLST, circulatory arrest and brain function

The relationship between WLST, circulatory arrest and death determined by the permanent cessation of brain function is diagrammed in Fig. 2.

When life-sustaining therapies are withdrawn (see the Algorithm in Fig. 1) following a decision that ongoing life-supporting treatments are no longer in the patient's best interest (see Sect. 1), death may be determined after the cessation of circulation. With cessation of systemic circulation, all blood flow to the brain ceases followed quickly by cessation of all brain electrical activity. The EEG (a surrogate of brain activity) becomes isoelectric within 30 s of abrupt arrest of circulation or flow to the brain [36]. Nevertheless, the existing evidence is insufficient to:

- Resolve how long the circulation to the brain must be arrested before brain function is irreversibly lost (cannot resume under any circumstance), i.e. the time after circulatory arrest by which brain function cannot resume if brain flow and perfusion are restored;
- Understand what amount of circulation (pressure, flow) is sufficient to generate brain perfusion and how much brain perfusion is required to generate a restoration of brain function.

In the circumstance of WLST, when hypoxia/hypotension precedes cardiac arrest, isoelectric EEG may occur prior to the arrest of circulation [36, 37].

If there is no attempt to restart systemic circulation, the permanent cessation of circulation to the brain leads inevitably to permanent cessation of brain function. If circulation is restored, brain function might be restored. In animal studies, the longest documented time for complete restoration of neurologic activity in a canine model following sudden cardiac arrest is 11 min [38]. In experiments using a cytoprotective perfusate, cellular activity has been restored in pig brains up to 4 h after decapitation [39]. Despite the cellular activity, the pig brains exhibited no function as demonstrated by EEG or electrocorticogram nor recovery of the integrated brain functions necessary for consciousness. This study highlights

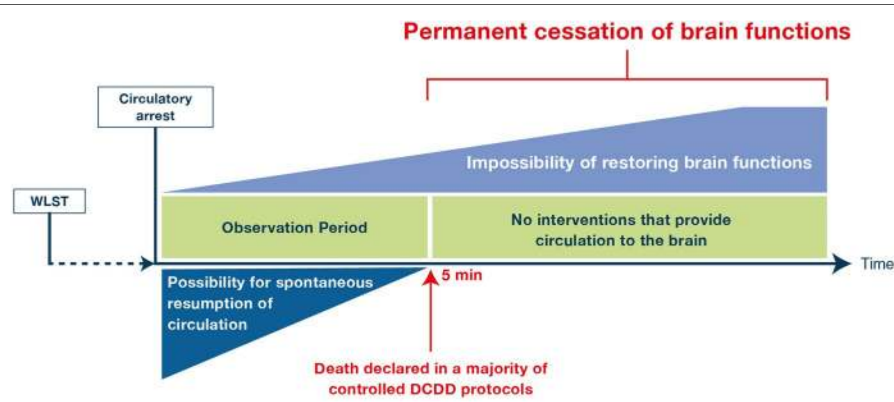

Fig. 2 Death determined by the permanent cessation of brain function. The *x* axis in time is not linear. The time that elapses from 5 min when death is declared by the permanent absence of circulation to an assured irreversibility of brain functions is in hours. *DCDD* donation after the circulatory determination of death, *WLST* withdrawal of life-sustaining therapy

the distinction between brain cellular activity and brain function relevant to determining death in human beings [40].

Irreversible versus permanent cessation

An irreversible cessation of circulation (cannot be reversed) necessarily means that the cessation is permanent, that is, lasting or intended to last or remain unchanged indefinitely. A cessation of circulation that is not irreversible is permanent if it occurs under circumstances, such as WLST, when no effort will be made to restore circulation to the brain and the point in time has passed when circulation could resume spontaneously [41–43].

When measurement of brain functions is used to determine death, the cessation of neurological functions must be irreversible but, as just noted, the circulatory standard requires the cessation to be permanent but not necessarily irreversible. This difference exists, because so-called "brain death" was developed as a retrospective determination attesting to functional loss in the brain that occurred earlier (whether from an injury or in the clinical course of care). By the time death is determined on this basis, the cessation of brain functions is clearly irreversible due to the time that has elapsed since the insult. In contrast, in the context of WLST, circulatory death determinations are made in real time, with death declared at the point of permanent cessation which may be before the loss of brain functions has become irreversible [34, 44].

Following systemic circulatory cessation, when there is no intent to attempt resuscitation (such as in patients who have a do not attempt resuscitation order or as occurs in cDCDD), and the possibility of auto-resuscitation has been excluded, death is defined as the permanent loss of capacity for consciousness and loss of all brainstem functions, determined by the permanent cessation of circulation to the brain [44].

Requisites to determine death after life-sustaining treatment is withdrawn in a cDCDD protocol

1. *Verify that the decision not to attempt resuscitation after circulatory arrest is documented in the medical record*
2. *Verify that circulatory cessation has occurred*
   The absence of systemic circulation must be reliably established by a validated test such as:

   - Absence of arterial pulsations observed by an indwelling arterial line or absence of continuous flow generated by a ventricular assist device or extracorporeal circuit;
   - Absence of opening of the aortic valve by echocardiography.
   - Absence of circulation by arterial Doppler studies;
   - Absence of electrical activity on an electrocardiogram;

   All these tests are appropriate to verify the cessation of circulation, though preference should be given to non-pulsatile arterial line monitoring. In the absence of a functioning arterial line, secondary options would be echocardiogram, Doppler, or electrocardiography. The use of an electrocardiogram to assess the cessation of circulation may unnecessarily prolong warm ischemia, since electrical activity can persist with no effective circulation.

3. *Verify that the time for possible auto-resuscitation has elapsed*

   An international collaborative prospective study has been recently conducted in Canada, United Kingdom, and Czech Republic to describe outcomes following the decision to WLST and not to provide cardiopulmonary resuscitation: 69 of 480 patients (14%) were observed to have an unassisted return of circulation (as defined by a single pulse pressure ≥ 5 mmHg) up to 4 min and 20 s after the observation of asystole [45]. None was observed to have circulation beyond 5 min and all patients died.

   The presence of one heartbeat within 60 s that results in a pulse pressure of > 5 mmHg is a proposed criterion of determining a resumption of circulation that can be used to define auto-resuscitation after circulatory arrest in cDCDD; however, this criterion is a surrogate of circulation which does not truly measure whether circulation or brain perfusion are occurring. If circulation does return in accordance with this definition during the observation period, the observation period must be recommenced.

Since the cessation of brain function results from the permanent cessation of blood flow to the brain, neurological examinations, of the sort used in DNDD, are not performed in cDCDD [46].

It also follows that the decision to withdraw treatment and permit death to occur entails prohibiting any intervention, such as cardiopulmonary resuscitation, that could restore brain circulation after death has been declared. Methods to accomplish in situ normothermic reperfusion of organs must, therefore, be targeted to preserving the organs intended for transplantation, while precluding the restoration of brain perfusion [47, 48].

Lung reinflation performed during cDCDD lung recovery could be associated with the resumption of cardiac activity and after the 5-min period of asystole that enabled a declaration of death. Therefore, lung reinflation intended to minimize warm ischemic time (WIT) of the lungs should be performed only when there is certainty that a spontaneous resumption of cardiac activity will not occur. The protocol for lung cDCDD in the United Kingdom addresses this issue by delaying this maneuver until a minimum of 10 min after loss of the circulation has elapsed, allowing only a single vital capacity inflation of the lung, followed by the application of continuous positive airway pressure or clamping of the endotracheal tube [49]. Cyclical ventilation is avoided until the surgical team has started to flush the lungs and has vented the left atrium. Alternatively, lung reinflation can be delayed until the administration of cardioplegia (in combined heart and lung cDCDD recovery) or until the pulmonary artery is cannulated and the preservation effluent is being drained through an opened left atrium. Both maneuvers render the heart incapable of coordinated contraction.

The observation period

A period of time must be established for observation of the patient after treatment is withdrawn and circulation has ceased to witness that auto-resuscitation of circulation has not occurred, and to ensure that the intention not to attempt resuscitation has been honored. Because auto-resuscitation can occur within the first 5 min following circulatory arrest, this observation period should not be < 5 min [45]. Once this period has passed, a physician (or more than one, when legally required) who is independent of the organ recovery team and of any clinical duties to potential recipients of the organs may declare death based on the permanent absence of circulation in the patient.

Recommendation pertaining to determining death after the permanent cessation of circulation to the brain
In cDCDD, **death may be declared after** an elapsed observation period of **5 min without circulation** which confirms that the absence of circulation is permanent. The permanent absence of circulation to the brain results in the permanent absence of brain functions
Transplant professionals caring for potential transplant recipients **should not be involved** in the determination of death

Perfusion repair for increasing organ transplantation success in cDCDD

The period of donor warm ischemia inherent to the cDCDD process, related to progressing hypoxemia and hypotension after WLST, can damage organs intended for transplantation and the liver and heart in particular, since the biliary and myocardial cells are highly susceptible to warm ischemia [50]. Initial experiences with DCDD liver transplantation described high rates of graft dysfunction and non-function and of ischemic type biliary lesions (ITBL). Although complication rates have decreased in frequency with experience, the rate of post-transplant ITBL remains higher among recipients of DCDD grafts vs those obtained from DNDD donors [51, 52]. Development of ITBL leads to repeat biliary procedures and hospitalizations; up to 70% of patients with ITBL either require re-transplantation or die [53]. Kidney transplants from cDCDD donors exhibit a higher incidence of delayed graft function (DGF), with similar graft survival and function in the short and mid-term [54].

Innovative approaches for the perfusion of organs recovered for transplantation are underway by ex situ (outside the body) machine perfusion of individual deceased donor organs and in situ (inside the body) regional perfusion of thoracic and abdominal organs in the deceased donor (see the Algorithm Fig. 1). Appropriate post-transplant outcomes have been accomplished with cDCDD kidneys and lungs without the necessity of dynamic perfusion strategies. Hence, developing countries need not presume that sophisticated preservation technology is a requirement for successful cDCDD kidney transplantation. Nevertheless, strategies of perfusion and repair are essential for cDCDD liver transplantation because of the complications that occur following cold storage of the liver, and to make cDCDD heart transplantation possible.

This section summarizes these recent advancements without preferentially recommending the approaches that are described.

Ex situ organ preservation and repair

Ex situ liver perfusion and repair

Most promising and actively explored methods of ex situ machine perfusion of livers include hypothermic oxygenated machine perfusion (HMP) and normothermic machine perfusion (NMP). Both modalities can be applied either to replace static cold storage or after static cold storage at the center (post-ischemic) performing the transplant [55]. While HMP reduces ischemia–reperfusion injury of DCDD grafts and may reduce the incidence of (biliary) complications after transplantation, NMP enables ex situ assessment of hepatobiliary viability of cDCDD livers prior to transplantation. In contrast to HMP, end-ischemic NMP has not yet been proven to reduce biliary complications [56, 57]. However, this technique may increase the number of transplanted organs through ex situ assessment and improve the condition of injured or marginal liver allografts [58, 59].

Ex situ heart perfusion and repair

Beginning with the first heart transplant performed by Christiaan Barnard in 1967, early transplants utilized DCDD hearts from donors who were in the same hospital as their recipients. Within several years, however, transplantation came to rely solely on DNDD hearts. Then, in 2014, a group in Sydney began a series of transplants using extracorporeal perfusion to maintain the viability of distantly procured cDCDD hearts [60], a practice now used for some transplants by a number of hospitals not only in Australia but also in the United Kingdom, and the United States (eTable 1). Recently, teams at other hospitals have begun transplanting cDCDD hearts from donors co-located with recipients, using thoraco-abdominal normothermic regional perfusion (TA-NRP), without extracorporeal perfusion (eTable 1). In total, more than 150 transplants have been performed in the past 6 years with cDCDD hearts.

Accepting that the heart is very sensitive to ischemia [61], both cold and warm—so that it is generally required that DNDD hearts be re-perfused for under 4 h of cold ischemia—several factors pertinent to the cDCDD process should be addressed before embarking upon a program of cDCDD heart transplantation:

- The administration of heparin. The ability to give heparin prior to death remains variable across countries. Few jurisdictions permit ante mortem cannulation (only Belgium and Spain in Europe). Some permit ante mortem identification of the femoral vessels to facilitate cannulation post-circulatory death determination (e.g. France, Italy and Norway) [7].
- The no-touch period between asystole to the declaration of death varies in time amongst the countries that practice cDCDD.
- WIT is marked by hypoxia, ischemia, hypoperfusion and cardiac distension culminating in warm ischemic injury that has been the major obstacle in limiting the uptake of cDCDD heart transplantation. The degree of ischemic injury and the ensuing ischemia–reperfusion injury correlates with DGF following transplantation. The Australian data suggest that limiting the time from asystole to cardioplegia delivery would limit the need for post-transplant mechanical circulatory support [62].

The original Sydney protocol describes a rapid retrieval process with subsequent instrumentation of the donor heart on to a perfusion device for ex situ reanimation. The only device that currently permits continuous perfusion and assessment of myocardial viability is the Organ Care System (OCS™-Heart, TransMedics Inc, USA). It allows the beating donor heart to be transported in a normothermic blood-based perfusion with physiological measurements of aortic pressure, coronary flow, cardiac rhythm, haematocrit and additionally by measuring the arterio-venous lactate level as a metabolic marker of myocardial health. A down-trending lactate level with evidence of lactate absorption is indicative of satisfactory myocardial reserve if the other physiological parameters are also normal [60]. In Australia, the Sydney protocol is the only permissible cDCDD heart retrieval process because the country's definition of death does not permit in situ restarting of the circulation. It has also become the preferred method for the majority of cDCDD heart transplant programs. The Papworth group has described an alternative approach of normothermic regional perfusion (NRP) that involves cannulation for extracorporeal driven circulation and in situ reanimation of the heart [63]. This approach permits the in situ assessment of the heart before cardioplegic arrest. Nevertheless, the Papworth group also performs heart recovery directly without NRP.

Devices for continuous cold perfusion which lessen the logistical burden during transportation are likely to be in clinical trials soon and these will require an additional working modality device for functional assessment prior to transplantation [64].

The outcomes from cDCDD heart transplantation out to the medium term have been excellent. The Sydney experience at five and a half years consists of 43 cDCDD heart transplants of which 10 recipients required post-implant ECMO for DGF. This requirement for mechanical circulatory support was over 30% during the earlier phase but is currently running at < 15%. The all-cause survival is 98% at 1-year and 95% at 5-years (personal communication). Similar outcomes have been reported from the higher volume program at Papworth Hospital, which reported on its first 79 cDCDD heart transplants with a 30-day survival of 97% vs 99% for the matched DNDD cohort. In the cDCDD heart transplant group, no significant differences in survival were found between 22 recipients included in the NRP protocol and 57 in the rapid recovery protocol [65].

cDCDD heart transplantation has become part of standard practice of care in the few pioneering centers in Australia and the UK. Their excellent results at medium term [62, 65] and the recent commencement of similar programs in North America and continental Europe should broaden and accelerate the uptake of cDCDD heart transplantation.

Coordination of heart and liver recovery in cDCDD

Heart recovery requires ~ 1500 mL of donor blood to prime the ex situ preservation pump (OCS™-Heart device). The collection of this donor blood from the right atrium requires attention to the differences in WIT that are computed for the heart versus the liver. WIT for the liver commences at the time of extubation. The donor heart's functional WIT starts when the SpO_2 falls below 70% or the systolic blood pressure goes below 50 mmHg. This calculated difference may enable a cDCDD heart recovery more than 30 min after extubation (but not the liver). For cDCDD liver recovery, cold perfusion of the abdominal organs with a cross-clamp of the aorta at the diaphragm should be initiated before 30 min following extubation. Thus, if the patient is declared dead between 20 and 25 min following extubation, the maneuvers to enable extraction of right atrial blood for the heart and installation of cardioplegia to the coronary arteries and perfusion of the liver must be coordinated carefully—not to exceed 30 min following extubation for successful liver recovery.

Ex situ lung perfusion and repair

Amongst all solid organs, the lung is unique in the capacity of ex situ perfusion to repair or improve the function of a deceased donor lung, as pulmonary cells can survive for hours after the absence of oxygenated blood circulation. Continued aerobic metabolism is based on parenchymal oxygen reserve delivered via a mechanism of passive diffusion through the alveoli. This tolerance to warm ischemic injury makes the lung a privileged organ in the setting of DCDD.

Normothermic ex situ lung perfusion was clinically introduced as a platform to preserve, assess and recondition lungs after recovery from the donor prior to transplantation [66, 67]. This technique was originally pioneered by Stig Steen (Lund, Sweden) [68] and further developed by the Toronto group as a clinical tool to (re) evaluate the function of the pulmonary allograft that may have suffered considerable injury during the process of organ donation [69, 70]. Several commercial devices for machine lung perfusion are currently available [71].

Several series from individual institutions and national organizations have now reported comparable early- and medium-term recipient outcomes after lung transplantation from cDCDD versus standard DNDD donors [72]. The largest experience with cDCDD comes from the DCDD Registry by the International Society for Heart and Lung Transplantation (ISHLT) with 22 participating institutions worldwide. Lung transplantation from cDCDD donors yielded excellent 5-year survival identical to DNDD donors [73].

In the ISHLT DCDD Registry Statement, only 15% of DCDD allografts underwent pre-transplant assessment by normothermic ex situ lung perfusion with the majority of such cases done at one institution [73]. This low percentage likely reflects the perception of each participating center of the real need or benefit of ex situ lung perfusion in assessing lungs from cDCDD donors. Excellent outcomes after transplantation of lungs from cDCDD donors have been reported without ex situ lung perfusion [73]. The majority of the DCDD donors in the ISHLT Registry (84.5%) suffered an agonal phase ≤ 30 min from WLST to cardiac arrest and 90% of DCDD lungs had a functional warm ischemic time (WIT) ≤ 30 min from arterial blood pressure < 50 mmHg until cold pulmonary flush [74], indicating that the risk for injury prior to cold preservation was limited in time. Therefore, the utility of ex situ lung perfusion for cDCDD lung transplantation may be selectively indicated in donors with an extended agonal period or WIT of > 30 min.

The ability to perfuse lungs for a period of time to assess function of questionable donor lungs has already significantly increased donor utilization [70]. Various technologies and techniques for ex situ lung perfusion (as well as the mode of application in the various categories of DCDD donors) continue to evolve as this concept has achieved increasing traction in clinical programs around the world. The application of ex situ lung perfusion for DCDD lungs has facilitated the use of this growing source of organ donors. The promise of ex situ lung perfusion lies in the ability to assess, treat and precondition organs prior to transplant to achieve improved donor utilization with superior short and long-term post-transplant outcomes.

Ex situ kidney perfusion and repair

The first Statement of NMP in kidney transplantation began in Leicester, UK with a series of 28 extended-criteria donors and 8 cDCDD kidneys. Circulating a red cell-based solution through the kidney allograft at near normal temperature for a brief 1-h period prior to transplantation reduced the rate of DGF from 36 to 11% in this cohort of patients. A standard cardiac pulmonary bypass technology was adapted to perfuse an isolated kidney [75].

A randomized controlled trial (Trial number: ISRCTN15821205) to assess the effects of 1 h NMP compared to static cold storage in DCDD kidney transplantation has completed recruitment and will be reported in 2021. The primary end point is the rate of DGF in the first 7 days after transplantation. Four UK transplant centres have participated in the trial (Cambridge, London, Newcastle and Edinburgh).

NMP can also be used as a device to test the quality of a kidney prior to transplantation. A particular advantage is the assessment of the microvasculature in DCDD kidneys that have been inadequately flushed at retrieval. The Leicester group is running a programme using NMP to retrieve and assess kidneys that have been discarded on this basis. A total of 21 kidneys have been assessed, 11 of these were successfully transplanted [75].

The results of the randomized trial will inform clinical practice for DCDD kidney transplants in the future. It is also likely that the technology will be used as an assessment device and as a platform for the delivery of therapeutic agents.

In situ organ preservation and repair

NRP has emerged as a strategy to reperfuse and reoxygenate organs in situ using an ECMO device, following the determination of death by circulatory criteria and before organ recovery. NRP is now routinely applied in cDCDD in France, Italy, Spain and the UK, and is being piloted in Belgium, the Netherlands, Norway, and Switzerland [7].

Abdominal NRP with ante mortem vessel cannulation

If the national legal framework allows ante mortem interventions in the body of a prospective cDCDD donor, specific informed consent should be obtained. Ante mortem cannulation of femoral vessels can be performed open or percutaneously. In some countries, the process of identifying the femoral vessels occurs prior to the WLST, but cannulation is completed after the determination of death [7]. A deflated aortic occlusion balloon is placed through the contralateral femoral artery and is advanced into the supraceliac aorta under radiographic control [76, 77].

Once death is declared (see the Algorithm in Fig. 1), the thoracic aortic balloon is inflated and abdominal NRP (A-NRP) is started, directing oxygenated blood to those organs to be recovered for transplantation and isolating brain circulation [74–78]. Two arterial lines, one from the femoral arterial cannula and the second from the left radial artery should be monitored during A-NRP to ensure blocking of the aorta [48, 76]. With occlusion of the aorta technically assured, the arterial pressure from the left radial artery will be absent, while the pressure from the femoral arterial cannula is maintained as a continuous, non-pulsatile pressure, as it is provided by the ECMO device.

Blood samples from the ECMO device are obtained just after starting A-NRP and at least every 30 min to monitor biochemical, haematological and acid–base parameters. Hepatic transaminases should remain stable throughout A-NRP. Transaminases more than three times the upper normal value at baseline and/or more than four times the upper normal limit at the end of A-NRP are considered a relative contraindication for liver transplantation [77–80]. A decrease of the initial lactate levels (following 30 and 60 min of A-NRP) may also be a good biomarker of an adequate perfusion of organs [78, 81]. A-NRP is run for 90–120 min to allow the adequate reconditioning of abdominal organs.

Abdominal NRP with post-mortem vessel cannulation

Once death is declared, the surgical team cannulates the abdominal aorta and the infrarenal vena cava. The supra-coeliac aorta is clamped and then A-NRP is initiated and managed as previously described [79].

Thoraco-abdominal NRP

Thoraco-abdominal NRP (TA-NRP) was first used in the UK to allow the successful recovery and transplantation of cDCDD donor hearts [63]. Following the declaration of death, a sternotomy is performed and the supra-aortic vessels are clamped to direct preservation fluid to organs to be recovered for transplantation (and isolate brain circulation). Recently, a refinement to current protocols has been proposed to ensure that circulation to the brain through collateral circulation does not occur during TA-NRP [47]. TA-NRP is then commenced and mechanical ventilation is also restarted. The heart is inspected after return of sinus rhythm within the cDCDD donor after weaning off TA-NRP, relying on the heart to perfuse the thoracic and abdominal organs. The donor heart is assessed clinically and by pulmonary artery catheter (cardiac output and atrial filling pressures), transoesophageal echocardiography and visual inspection. Heart is then recovered using a similar approach to the one in the DNDD setting.

In the Papworth technique, TA-NRP is followed by instrumentation on the OCS™-Heart device for transportation [82]. Successes with the TA-NRP technique followed by cold preservation and storage for transport have recently been reported by two teams in Belgium (Liège, Leuven) [83, 84] and three centers in Spain [85, 86].

Results of transplants from cDCDD donors subject to NRP

Based on data from preclinical and clinical studies, NRP seems to reverse the metabolic derangements caused by warm ischemia, re-establishing cellular physiology after energetic depletion and clearing metabolites [87]. This preconditioning effect of NRP may attenuate ischemia–reperfusion injury. NRP allows to transform an urgent into an elective recovery procedure, similar to the one in the context of DNDD [79, 80]. During NRP, an evaluation of organ viability can take place based on the behavior of certain biochemical parameters, as already mentioned.

Two recently published multicenter retrospective experiences have shown the benefits of NRP in liver transplantation from cDCDD donors [77, 79]. Both studies reveal that, compared with the standard rapid recovery technique, NRP is associated with a decreased rate of overall biliary complications, ITBL, and graft loss. The experiences also show that donor age of cDCDD liver donors could be expanded safely with NRP, as suggested by other authors [78]. The superior outcomes of NRP suggested by these reports need to be confirmed in randomized controlled trials [88].

Information on the impact of NRP on cDCDD kidney transplantation is scarce. Spanish data suggest that NRP is associated with a significantly lower incidence of DGF, but with no significant benefits in terms of primary non-function and graft survival in the short-term [89]. Some preliminary favorable results have also been published regarding pancreas transplantation in cDCDD with the use of NRP, but the experience is still limited [75, 90].

TA-NRP is being used in the UK, Belgium, and more recently in Spain as a strategy to allow the validation and preservation of hearts of cDCDD donors [63, 83–86]. In the British experience, most hearts recovered by using TA-NRP have been followed by ex situ machine perfusion. Eight heart transplant procedures have taken place in the world with the use of TA-NRP without ex situ machine perfusion. Given the high cost of ex situ machine perfusion, unaffordable in many settings, TA-NRP may become a way of making heart transplantation from cDCDD donors economically feasible in some countries.

The impact of TA-NRP on cDCDD lung transplantation is currently unknown. It is important to understand that with the technique of TA-NRP, the lungs will not receive antegrade perfusion through the pulmonary arteries until the arrested heart starts beating again. However, the lungs will receive limited flow of oxygenated blood via the bronchial circulation originating from the descending aorta. Therefore, in the setting of A-NRP using a clamp on the descending aorta, or in cases where the heart does not generate sufficient cardiac output during TA-NRP, lungs will not be perfused while remaining normothermic.

Re-establishment of regional circulation after determining death in cDCDD

NRP poses not only technical, but also ethical challenges. The most critical one is the possibility that circulation to the brain is inadvertently restored during NRP—which would retroactively negate the diagnosis of death by circulatory criteria. According to the unifying concept of death in the cDCDD context, when systemic circulation ceases, the relevant loss is the permanent cessation of circulation to the brain. The consequence of this lack of circulation is that the brain undergoes ischemic infarction, with the inevitable loss of brain function (Fig. 2). Thus, restoration of oxygenated blood flow to the thorax and abdomen when using NRP must exclude all circulation to the brain since the resumption of systemic circulation would otherwise be inconsistent with a declaration of death. Restoring brain circulation would invalidate the death determination because the unifying concept of death requires brain circulation to have ceased indefinitely, resulting in the permanent cessation of brain function [91]

Techniques used for isolating the brain in A-NRP include a balloon occlusion or surgical clamping of the thoracic aorta, which can be monitored by the absence of constant pressure at the radial artery [48] or by the lack of flow from a cannula inserted in the ascending aorta and open to the atmosphere [47]. When TA-NRP is used, isolation of brain circulation may be achieved by the clamping of the aortic arch vessels. Importantly, the free drainage of the aortic arch vessels to atmospheric or negative pressure diverts collateral blood flow away from the brain [47]. To exclude arterial anatomical variants, ante mortem tests to visualize cerebral circulation (e.g. angiography) may also be considered. Given the complexity of techniques to ensure absence of circulation to the brain during TA-NRP, this should only be performed in the context of specific research protocols by teams with sufficient training and expertise. Monitoring absence of brain circulation (perfusion or function) during TA-NRP is an essential component of such protocols.

Occluding the thoracic aorta or the aortic arch vessels to deliberately exclude brain circulation raises two concerns: (i) the involvement of the recovery surgeon in the patient´s death, and (ii) the use of an invasive intervention solely to satisfy the permanence of the cessation of brain functions.

As to the first concern, the intentional exclusion of brain circulation by use of isolation techniques is not the cause of death. The cause of death is the DBI or the underlying disease that led to the decision to WLST. Moreover, the surgeon who occludes the thoracic aorta or the aortic arch vessels in order to perfuse the transplantable organs no more causes the death of the donor than does the surgeon who recovers a heart for transplantation after a donor has been declared dead. As to the second concern, the use of techniques to prevent brain perfusion respect two decisions made by the donor or their surrogate: first, the decision not to be resuscitated after the declaration of death which entails the intention that circulation not be restored to the brain, and second, the decision to benefit patients in need of donated organs, which entails the taking of steps to maximize the functioning of the transplanted organs.

Recommendation pertaining to perfusion repair for increasing organ transplantation success in cDCDD

The value of perfusion repair for increasing the success of organ transplantation is established by this Conference Statement to **recommend that a protocol of cDCDD utilize either in situ or ex situ perfusion** consistent with the practice of each country conducting cDCDD

Overall recommendations as a result of these consensus deliberations

- The Conference Statement and Algorithm should be published in the medical literature as a reference guide for either the initiation or expansion of cDCDD.
- A review of the Conference Statement by the WHO Task Force on Organ Donation and Transplantation is requested to subsequently seek the endorsement of the WHO in promoting cDCDD to all Member States.
- A common terminology should be used for all types of donors and perfusion techniques to avoid confusion amongst professionals and the public.
- The expansion of cDCDD should be a component of the proposed WHO Global Consultation on the science of organ donation and transplantation.
- The International Professional Societies should be engaged to disseminate the Conference Statement and aligned Algorithm to provide education for members.
- The Algorithm should be submitted to professional society meetings for presentation.
- A cDCDD Committee should be developed inclusive of the professional expertise that has developed the Conference Statement and Algorithm to accomplish these tasks.

Supplementary Information

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Author contributions

NA, JLB, AMC, FLD, BD-G, DG, GVH, ARM, SD and ST conceived, designed and organized the Collaborative. Topics were distributed by the first and senior authors based on each individual expertise, as follows: Neuroscience (JLB, GVH, ARM), Intensivist expertise (DG, EM, SDS, JMS), Legal scholars (AMC, AKG), Ethicist (AM, JD), Transplant physicians (NA, SGT), Recovery investigators (Heart: KD, DL; Lung: SK, DVR; Liver: CF, JFM, RJP; Kidney: SH). All authors contributed to the writing of the paper, participated in deliberations to reach consensus and approved the final version of the manuscript.

An international conference on controlled donation after the circulatory determination of death (cDCDD) was to have been convened on April 3–4, 2020, in Montreal, Canada, with the objective of clarifying the clinical, ethical, and legal aspects of the practice of organ transplantation following cDCDD. Due to the COVID-19 pandemic, the deliberations that produced this Statement were instead carried out through remote consultations. Through a process involving multiple iterations to which the authors contributed—by drafting passages, by providing commentary, critiques, and editorial suggestions, and by review of the final document—the group achieved a consensus, which is embodied in this Statement.

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Compliance with ethical standards

Conflicts of interest

SK is a co-founder of Perfusix Canada (PXCA). This company provides ex situ lung perfusion (EVLP) services and training to University Health Network. Due to conflict of interest relative to EVLP activities as lung transplant surgeons in the institution, SK does not receive any payments from PXCA. Furthermore, with respect to the provision of EVLP services, PXCA is a non-profit company that does not generate profit from EVLP activities provided for UHN patients. SK is a co- founders of XOR Labs Toronto (XOR), a company dedicated to development of EVLP machines. The XOR EVLP machine is in development phase and has not been used in any patients reported on in this manuscript. Lung Bioengineering (LBI), a subsidiary of United Therapeutics, acquired Perfusix USA in 2015, a company that was co-founded by SK. Currently SK is a paid consultant for LBI. He provides strategic advice to LBI lung perfusion center as a member of its Scientific Advisory Board. DVR was a principal investigator in the Inspire and Expand trial sponsored by Transmedics, Inc (Andover, MA, USA). He received travel reimbursement to attend scientific advisory board meetings organized by Transmedics. The rest of the authors declare no conflicts of interest.

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References

1. WHO Guiding Principles on human cell, tissue and organ transplantation. Available at: https://www.who.int/transplantation/Guiding_PrinciplesTransplantation_WHA63.22en.pdf?ua=1. Accessed Sep 2020
2. Global Observatory on Organ Donation and Transplantation. Available at: http://www.transplant-observatory.org. Accessed Sep 2020
3. The Declaration of Istanbul on Organ Trafficking and Transplant Tourism. Available at: https://declarationofistanbul.org. Accessed Sep 2020
4. Organización Nacional de Trasplantes, The Transplantation Society, World Health Organization (2011) The Madrid resolution on organ donation and transplantation: national responsibility in meeting the needs of patients, guided by the WHO principles. Transplantation 91(Suppl 11):S29-31. https://doi.org/10.1097/01.tp.0000399131.74618.a5
5. Sprung CL, Ricou B, Hartog CS et al (2019) Changes in end-of-life practices in European Intensive Care Units from 1999 to 2016. JAMA 322(17):1–12. https://doi.org/10.1001/jama.2019.14608
6. Newsletter Transplant 2019. International figures on donation and transplantation 2018. Available at: http://www.ont.es/publicaciones/Paginas/Publicaciones.aspx. Accessed Sep 2020
7. Lomero M, Gardiner D, Coll E et al (2020) Donation after circulatory death today: an updated overview of the European landscape. Transpl Int 33(1):76–88. https://doi.org/10.1111/tri.13506
8. Smith M, Dominguez-Gil B, Greer DM et al (2019) Organ donation after circulatory death: current status and future potential. Intensive Care Med 45:310–321. https://doi.org/10.1007/s00134-019-05533-0
9. Kon AA, Shepard EK, Sederstrom NO et al (2016) Defining futile and potentially inappropriate interventions: a policy statement from the society of critical care medicine ethics committee. Crit Care Med 44(9):1769–1774. https://doi.org/10.1097/CCM.0000000000001965
10. Manara A (2015) Bespoke end-of-life decision making in ICU: has the tailor got the right measurements? Crit Care Med 43:909–910. https://doi.org/10.1097/CCM.0000000000000837
11. Souter MJ, Blissitt PA, Blosser S et al (2015) Recommendations for the critical care management of devastating brain injury: prognostication, psychosocial, and ethical management: a position statement for healthcare professionals from the neurocritical care society. Neurocrit Care 23(1):4–13. https://doi.org/10.1007/s12028-015-0137-6
12. Moseby-Knappe M, Westhall E, Backman S et al (2020) Performance of a guideline-recommended algorithm for prognostication of poor neurological outcome after cardiac arrest. Intensive Care Med 46(10):1852–1862. https://doi.org/10.1007/s00134-020-06080-9
13. Sandroni C, D'Arrigo S, Cacciola S et al (2020) Prediction of poor neurological outcome in comatose survivors of cardiac arrest: a systematic review. Intensive Care Med 46(10):1803–1851. https://doi.org/10.1007/s00134-020-06198-w
14. Crash Trial Collaborators MRC, Perel P, Arango M, Clayton T et al (2008) Predicting outcome after traumatic brain injury: practical prognostic models based on large cohort of international patients. BMJ 336(7641):425–429. https://doi.org/10.1136/bmj.39461.643438.25
15. CRASH web-based calculator for predicting outcome in TBI. Available at: http://www.crash.lshtm.ac.uk/Risk%20calculator/index.html. Accessed Sep 2020
16. Hemphill JC, Bonovich DC, Besmertis L, Manley GT, Johnston SC (2001) The ICH score: a simple, reliable grading scale for intracerebral hemorrhage. Stroke 32(4):891–897. https://doi.org/10.1161/01.str.32.4.891
17. NIH Stroke Scale. Available at: https://www.stroke.nih.gov/documents/NIH_Stroke_Scale_508C.pdf. Accessed Sept 2020
18. Roberts TT, Leonard GR, Cepela DJ (2017) Classifications in brief: American Spinal Injury Association (ASIA) impairment scale. Clin Orthop Relat Res 475(5):1499–1504. https://doi.org/10.1007/s11999-016-5133-4
19. Mourand I, Machi P, Nogué E et al (2014) Diffusion-weighted imaging score of the brain stem: a predictor of outcome in acute basilar artery occlusion treated with the Solitaire FR device. Am J Neuroradiol 35(6):1117–1123. https://doi.org/10.3174/ajnr.A3870
20. Rohaut B, Claassen J (2018) Decision making in perceived devastating brain injury: a call to explore the impact of cognitive biases. Br J Anaesth 120:5–9. https://doi.org/10.1016/j.bja.2017.11.007
21. Harvey D, Butler J, Groves J et al (2018) Management of perceived devastating brain injury after hospital admission—a consensus statement from stakeholder professional organisations. Br J Anaesth 120(1):138–145. https://doi.org/10.1016/j.bja.2017.10.002
22. Manara AR, Thomas I, Harding R (2016) A case for stopping the early withdrawal of life sustaining therapies in patients with devastating brain injuries. J Intensive Care Soc 17(4):295–301. https://doi.org/10.1177/1751143716647980
23. Committee on Bioethics (DH-BIO) of the Council of Europe. Guide on the decision-making process regarding medical treatment in end-of-life situations. Available at: http://www.coe.int/en/web/bioethics/guide-on-the-decision-making-process-regarding-medical-treatment-in-end-of-life-situations. Accessed Sep 2020
24. Cao Y, Shahrestani S, Chew HC et al (2016) Donation after circulatory death for liver transplantation: a meta-analysis of the location of life support withdrawal affecting outcomes. Transplantation 100(7):1513–1524. https://doi.org/10.1097/TP.0000000000001175
25. Healey A, Hartwick M, Downar J et al (2020) Improving quality of withdrawal of life-sustaining measures in organ donation: a framework and

implementation toolkit. Can J Anaesth 67(11):1549–1556. https://doi.org/10.1007/s12630-020-01774-6
26. Sprung CL, Cohen SL, Sjokvist P et al (2003) End-of-life practices in European intensive care units: the Ethicus Study. JAMA 290:790–797. https://doi.org/10.1001/jama.290.6.790
27. Manara A, Procaccio F, Domínguez-Gil B (2019) Expanding the pool of deceased organ donors: the ICU and beyond. Intensive Care Med 45(3):357–360. https://doi.org/10.1007/s00134-019-05546-9
28. Truog RD, Campbell ML, Curtis JR et al (2008) Recommendations for end-of-life care in the intensive care unit: a consensus statement by the American College of Critical Care Medicine. Crit Care Med 36(3):953–963. https://doi.org/10.1097/CCM.0B013E3181659096
29. Bossaert LL, Perkins GD, Askitopoulou H et al (2015) European Resuscitation Council Guidelines for Resuscitation 2015: Section 11. The ethics of resuscitation and end-of-life decisions. Resuscitation 95:302–311. https://doi.org/10.1016/j.resuscitation.2015.07.033
30. Hernández-Tejedor A, Peñuelas O, Sirgo-Rodríguez G et al (2017) Recommendations of the working groups from the Spanish Society of Intensive and critical care medicine and coronary units (SEMICYUC) for the management of adult critically ill patients. Med Intensiva 41(5):285–305. https://doi.org/10.1016/j.medin.2017.03.004
31. Glazier A (2017) Transplant law and ethics. Chapter 19. In: Danovitch G (ed) Handbook of kidney transplantation. 6th edn
32. Shemie SD, Hornby L, Baker A et al (2014) International guideline development for the determination of death. Intensive Care Med 40(6):788–797. https://doi.org/10.1007/s00134-014-3242-7
33. Gardiner D, McGee A, Bernat JL (2020) Permanent brain arrest as the sole criterion of death in systemic circulatory arrest. Anaesthesia 75(9):1223–1228. https://doi.org/10.1111/anae.15050
34. Shemie S, Gardiner D (2018) Circulatory arrest, brain arrest and death determination. Front Cardiovasc Med 5:15. https://doi.org/10.3389/fcvm.2018.00015
35. McGee A, Gardiner D, Murphy P (2018) Determination of death in donation after circulatory death: an ethical propriety. Curr Opin Organ Transplant 23(1):114–119. https://doi.org/10.1097/MOT.0000000000000478
36. Pana R, Hornby L, Shemie SD, Dhanani S, Teitelbaum J (2016) Time to loss of brain function and activity during circulatory arrest. J Crit Care 34:77–83. https://doi.org/10.1016/j.jcrc.2016.04.001
37. Norton L, Gibson RM, Gofton T et al (2017) Electroencephalographic recordings during withdrawal of life-sustaining therapy until 30 minutes after declaration of death. Can J Neurol Sci 44(2):139–145. https://doi.org/10.1017/cjn.2016.309
38. Safar P, Xiao F, Radovsky A et al (1996) Improved cerebral resuscitation from cardiac arrest in dogs with mild hypothermia plus blood flow promotion. Stroke 27(1):105–113. https://doi.org/10.1161/01.str.27.1.105
39. Vrselja Z, Daniele SG, Silbereis J et al (2019) Restoration of brain circulation and cellular functions hours post-mortem. Nature 568(7752):336–343. https://doi.org/10.1038/s41586-019-1099-1
40. Bernat JL, Delmonico FL (2019) Restoring activity of pig brain cells after death does not invalidate the determination of death by neurological criteria or undermine the propriety of organ donation after death. Transplantation 103(7):1295–1297. https://doi.org/10.1097/TP.0000000000002782
41. Bernat JL, Capron AM, Bleck TP et al (2010) The circulatory-respiratory determination of death in organ donation. Crit Care Med 38(3):963–970. https://doi.org/10.1097/CCM.0b013e3181c58916
42. Bernat JL (2010) How the distinction between "irreversible" and "permanent" illuminates circulatory-respiratory death determination. J Med Philos 35(3):242–255. https://doi.org/10.1093/jmp/jhq018
43. McGee A, Gardiner D (2017) Permanence can be defended. Bioethics 31(3):220–230. https://doi.org/10.1111/bioe.12317
44. Lizza JP (2020) Why DCD donors are dead. J Med Philos 45(1):42–60. https://doi.org/10.1093/jmp/jhz030
45. Dhanani S, Hornby L, Van Beinum A, Scales NB et al. (2020) Transient resumption of cardiac activity following withdrawal of life-sustaining measures. N Engl J Med (in press)
46. Academy of Medical Royal Colleges. A code of practice for the diagnosis and confirmation of death. Available at: https://www.aomrc.org.uk/reports-guidance/ukdec-reports-and-guidance/code-practice-diagnosis-confirmation-death. Accessed Aug 2020
47. Manara A, Shemie SD, Large S et al (2020) Maintaining the permanence principle for death during in situ normothermic regional perfusion for donation after circulatory death organ recovery: a United Kingdom and Canadian proposal. Am J Transplant 20(8):2017–2025. https://doi.org/10.1111/ajt.15775
48. Pérez-Villares JM, Rubio JJ, Del Río F, Miñambres E (2017) Validation of a new proposal to avoid donor resuscitation in controlled donation after circulatory death with normothermic regional perfusion. Resuscitation 117:46–49. https://doi.org/10.1016/j.resuscitation.2017.05.030
49. Organ donation and transplantation safety alert. Care of potential lung DCD donors. Available at: http://odt.nhs.uk/pdf/Lung_DCD_Safety_Briefing_Dec_2015.pdf. Accessed Sep 2020
50. Hessheimer AJ, Cárdenas A, García-Valdecasas JC, Fondevila C (2016) Can we prevent ischemic-type biliary lesions in donation after circulatory determination of death liver transplantation? Liver Transpl 22(7):1025–1033. https://doi.org/10.1002/lt.24460
51. Jay CL, Lyuksemburg V, Ladner DP et al (2011) Ischemic cholangiopathy after controlled donation after cardiac death liver transplantation: a meta-analysis. Ann Surg 253(2):259–264. https://doi.org/10.1097/SLA.0b013e318204e658
52. O'Neill S, Roebuck A, Khoo E, Wigmore SJ, Harrison EM (2014) A meta-analysis and meta-regression of outcomes including biliary complications in donation after cardiac death liver transplantation. Transpl Int 27(11):1159–1174. https://doi.org/10.1111/tri.12403
53. Foley DP, Fernández LA, Leverson G et al (2011) Biliary complications after liver transplantation from donation after cardiac death donors: an analysis of risk factors and long-term outcomes from a single center. Ann Surg 253(4):817–825. https://doi.org/10.1097/SLA.0b013e3182104784
54. Summers DM, Watson CJ, Pettigrew GJ et al (2015) Kidney donation after circulatory death (DCD): state of the art. Kidney Int 88(2):241–249. https://doi.org/10.1038/ki.2015.88
55. Karangwa SA, Dutkowski P, Fontes P et al (2016) Machine perfusion of donor livers for transplantation: a proposal for standardized nomenclature and reporting guidelines. Am J Transplant 16(10):2932–2942. https://doi.org/10.1111/ajt.13843
56. Dutkowski P, Guarrera JV, de Jonge J et al (2019) Evolving trends in machine perfusion for liver transplantation. Gastroenterology 156(6):1542–1547. https://doi.org/10.1053/j.gastro.2018.12.037
57. Nasralla D, Coussios CC, Mergental H et al (2018) A randomized trial of normothermic preservation in liver transplantation. Nature 557(7703):50–56. https://doi.org/10.1038/s41586-018-0047-9
58. Van Leeuwen OB, de Vries Y, Fujiyoshi M et al (2019) Transplantation of high-risk donor livers after ex situ resuscitation and assessment using combined hypo- and normothermic machine perfusion: a prospective clinical trial. Ann Surg 270(5):906–914. https://doi.org/10.1097/SLA.0000000000003540
59. Mergental H, Laing RW, Kirkham AJ et al (2020) Transplantation of discarded livers following viability testing with normothermic machine perfusion. Nat Commun 11(1):2939. https://doi.org/10.1038/s41467-020-16251-3
60. Dhital KK, Iyer A, Connellan M et al (2015) Adult heart transplantation with distant procurement and ex-vivo preservation of donor hearts after circulatory death: a case series. Lancet 385(9987):2585–2591. https://doi.org/10.1016/S0140-6736(15)60038-1
61. Iyer A, Gao L, Doyle A et al (2014) Increasing the tolerance of DCD hearts to warm ischemia by pharmacological postconditioning. Am J Transplant 14(8):1744–1752. https://doi.org/10.1111/ajt.12782
62. Chew HC, Iyer A, Connellan M et al (2019) Outcomes of donation after circulatory death heart transplantation in Australia. J Am Coll Cardiol 73(12):1447–1459. https://doi.org/10.1016/j.jacc.2018.12.067
63. Messer SJ, Axell RG, Colah S et al (2016) Functional assessment and transplantation of the donor heart after circulatory death. J Heart Lung Transplant 35(12):1443–1452. https://doi.org/10.1016/j.healun.2016.07.004
64. Steen S, Paskevicius A, Liao Q, Sjoberg T (2016) Safe orthotopic transplantation of hearts harvested 24 hours after brain death and preserved for 24 hours. Scand Cardiovasc J 50(3):193–200. https://doi.org/10.3109/14017431.2016.1154598
65. Messer S, Cernic S, Page A et al (2020) A 5-year single-center early experience of heart transplantation from donation after circulatory-determined

death donors. J Heart Lung Transplant 39(12):1463–1475. https://doi.org/10.1016/j.healun.2020.10.001
66. Cypel M, Neyrinck A, Machuca TN (2019) Ex vivo perfusion techniques: state of the art and potential applications. Intensive Care Med 45(3):354–356. https://doi.org/10.1007/s00134-019-05568-3
67. Van Raemdonck D, Rega F, Rex S, Neyrinck A (2018) Machine perfusion of thoracic organs. J Thorac Dis 10(Suppl 8):S910–S923. https://doi.org/10.21037/jtd.2018.02.85
68. Steen S, Sjöberg T, Pierre L, Liao Q, Eriksson L, Algotsson L (2001) Transplantation of lungs from a non-heart-beating donor. Lancet 357(9259):825–829. https://doi.org/10.1016/S0140-6736(00)04195-7
69. Cypel M, Yeung JC, Liu M et al (2011) Normothermic ex vivo lung perfusion in clinical lung transplantation. N Engl J Med 364(15):1431–1440. https://doi.org/10.1056/NEJMoa1014597
70. Cypel M, Yeung JC, Donahoe L et al (2019) Normothermic ex vivo lung perfusion: does the indication impact organ utilization and patient outcomes after transplantation? J Thorac Cardiovasc Surg S0022–5223(19):31732–31735. https://doi.org/10.1016/j.jtcvs.2019.06.123
71. Possoz J, Neyrinck A, Van Raemdonck D (2019) Ex vivo lung perfusion prior to transplantation: an overview of current clinical practice worldwide. J Thorac Dis 11(4):1635–1650. https://doi.org/10.21037/jtd.2019.04.33
72. Ceulemans LJ, Inci I, Van Raemdonck D (2019) Lung donation after circulatory death. Curr Opin Organ Transplant 24(3):288–296. https://doi.org/10.1097/MOT.0000000000000627
73. Van Raemdonck D, Keshavjee S, Levvey B et al (2019) Donation after circulatory death in lung transplantation-five-year follow-up from ISHLT registry. J Heart Lung Transplant 38(12):1235–1245. https://doi.org/10.1016/j.healun.2019.09.007
74. Levvey B, Keshavjee S, Cypel M et al (2019) Influence of lung donor agonal and warm ischemic times on early mortality: analyses from the ISHLT DCD lung transplant registry. J Heart Lung Transplant 38(1):26–34. https://doi.org/10.1016/j.healun.2018.08.006
75. Hosgood SA, Barlow AD, Hunter JP, Nicholson ML (2015) Ex vivo normothermic perfusion for quality assessment of marginal donor kidney transplants. Br J Surg 102(11):1433–1440. https://doi.org/10.1002/bjs.9894
76. Miñambres E, Suberviola B, Domínguez-Gil B et al (2017) Improving the outcomes of organs obtained from controlled donation after circulatory death donors using abdominal normothermic regional perfusion. Am J Transplant 17(8):2165–2172. https://doi.org/10.1111/ajt.14214
77. Hessheimer AJ, Coll E, Torres F et al (2019) Normothermic regional perfusion versus super rapid recovery in controlled donation after circulatory death liver transplantation. J Hepatol 70(4):658–665. https://doi.org/10.1016/j.jhep.2018.12.013
78. Ruiz P, Gastaca M, Bustamante FJ et al (2019) Favorable outcomes after liver transplantation with normothermic regional perfusion from donors after circulatory death: a single-center experience. Transplantation 103(5):938–943. https://doi.org/10.1097/TP.0000000000002391
79. Watson CJE, Hunt F, Messer S et al (2019) In situ normothermic perfusion of livers in controlled circulatory death donation may prevent ischemic cholangiopathy and improve graft survival. Am J Transplant 19(6):1745–1758. https://doi.org/10.1111/ajt.15241
80. Miñambres E, Rubio JJ, Coll E, Domínguez-Gil B (2018) Donation after circulatory death and its expansion in Spain. Curr Opin Organ Transplant 23(1):120–129. https://doi.org/10.1097/MOT.0000000000000480
81. Miñambres E, Ruiz P, Ballesteros MA et al (2020) Combined lung and liver procurement in controlled donation after circulatory death using normothermic abdominal perfusion. Initial experience in two Spanish centers. Am J Transplant 20(1):231–240. https://doi.org/10.1111/ajt.15520
82. Messer S, Large S (2016) Resuscitating heart transplantation: the donation after circulatory determined death donor. Eur J Cardiothorac Surg 49(1):1–4. https://doi.org/10.1093/ejcts/ezv357
83. Tchana-Sato V, Ledoux D, Detry O et al (2019) Successful clinical transplantation of hearts donated after circulatory death using normothermic regional perfusion. J Heart Lung Transplant 38(6):593–598. https://doi.org/10.1016/j.healun.2019.02.015
84. Tchana-Sato V, Ledoux D, Vandendriessche K et al (2019) First report of a successful pediatric heart transplantation from donation after circulatory death with distant procurement using normothermic regional perfusion and cold storage. J Heart Lung Transplant 38(10):1112–1115. https://doi.org/10.1016/j.healun.2019.08.009
85. Pérez-Redondo M, Alcántara S, Villar S et al (2020) Transplantation of a heart donated after circulatory death via thoraco-abdominal normothermic regional perfusion and results from the first Spanish case. J Cardiothorac Surg 15(1):333. https://doi.org/10.1186/s13019-020-01372-z
86. Miñambres E, Royo-Villanova M, Pérez-Redondo M et al (2020) Spanish experience with heart transplants from controlled donation after the circulatory determination of death using thoraco-abdominal normothermic regional perfusion and cold storage. Am J Transplant. https://doi.org/10.1111/ajt.16446
87. Net M, Valero R, Almenara R et al (2005) The effect of normothermic recirculation is mediated by ischemic preconditioning in NHBD liver transplantation. Am J Transplant 5(10):2385–2392. https://doi.org/10.1111/j.1600-6143.2005.01052.x
88. van de Leemkolk FEM, Schurink IJ, Dekkers OM et al (2020) Abdominal normothermic regional perfusion in donation after circulatory death: a systematic review and critical appraisal. Transplantation 104(9):1776–1791. https://doi.org/10.1097/TP.0000000000003345
89. Spanish Annual National Report on Controlled Donation after the Circulatory Determination of Death. Available at: http://www.ont.es/infesp/Memorias/Actividad%20Donaci%C3%B3n%20y%20Trasplante%20Donaci%C3%B3n%20en%20Asistolia%20Controlada.pdf. Accessed Sep 2020
90. Oniscu GC, Randle LV, Muiesan P et al (2014) In situ normothermic regional perfusion for controlled donation after circulatory death—The United Kingdom experience. Am J Transplant 14:2846–2854. https://doi.org/10.1111/ajt.12927
91. Dalle Ave AL, Bernat JL (2017) Donation after brain circulation determination of death. BMC Med Ethics 18(1):15. https://doi.org/10.1186/s12910-017-0173-1