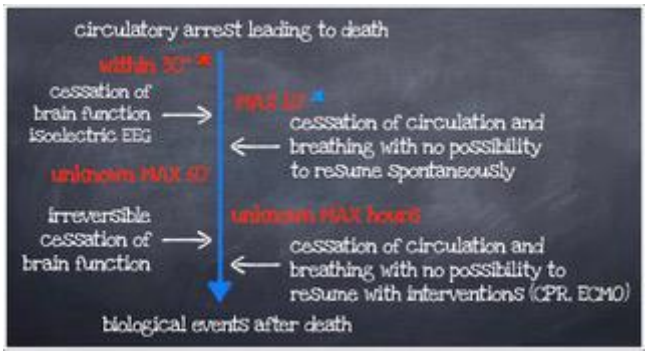
DCD & EISOR

Donation after **circulatory death determination, DCD**, defines the retrieval of organs for the purposes of transplantation In the context of diagnosis and confirmation of death based on circulatory criteria. Many countries have reconsidered these donors, introducing and actively promoting DCD programs as a strategy to increase the availability of organs for transplant, addressing the growing mismatch between potential donors and recipients on waiting list. Previously named **non-heart-beating organ donation**, **NHBOD** or **NHBD**, DCD has been also referred to as donation after cardio-circulatory determination of death or (improper) donation after cardiac death.
According to **dead donor rule**, **DDR**, an ethical standard stating that organs retrieval must not kill the patient, donors must be declared dead before donation. To fulfil DDR, all DCD protocols describe a **mandatory** observation period after cardio-circulatory arrest, named **no-touch time** or **no-touch period**: during this interval it's not allowed for the retrieval team to touch the body to perform any intervention on the potential donor. The rationale behind this hands-off period is to guarantee that the **possibility** of **autoresuscitation**, **AR**, spontaneous, unassisted resumption of heart function after cardiac arrest generating circulation, specifically within the time period where the brain might be responsive to re-perfusion, has **elapsed**, and a condition of **permanent arrest** of **cerebral circulation**too is occurred in the potential donor (picture 1).



picture 1. Physiological sequences in the dying process from circulatory arrest to permanent and irreversible cessation of brain (on the left) and cardio/respiratory function (on the right) if no reanimation provided, modified from Shemie and Gardiner, Front Cardiovasc Med. 2018. Red asterisk, in normothermic critically ills suffering prolonged hypoxia/hypotension or preexisting brain injury, cerebral activity could be loss before asystole may induce neuronal dysfunction or injury before cardiac arrest; blue asterisk, modified according to Hornby et al. Crit Care Med. 2018. CPR, cardio-pulmonary resuscutation; ECMO, extracorporeal membrane oxygenation.

There is no consensus about how long circulation and respiration must cease in order to determine death with circulatory criteria, and consistency about no-touch is lacking. No-touch time is a **no-flow**time: the organs are not perfused but still normothermic or quite normothermic, so completely unprotected; shortening of the no-touch time could reduce ischemic period improving graft condition and transplantation outcome while its extension could eventually make organs unsuitable for Tx. With this premise, the waiting period is variably defined according to different legislations; although a 2 to 5 minutes period is considered safe, regarding the potential for AR (most countries recommending a 5'), some states have cut no-touch to 75'', while other have extended to 10'; in Italy 20 minutes of hands-off are requested. In studies reporting timing and proper monitoring, AR has not been recorded to occur beyond 10 mins after failed CPR in adults.

Warm ischemia time, **WIT**, is defined as the amount of **time without oxygenated blood supply** elapsed from circulatory arrest to organs topical cooling/cold perfusion during removal procedure: WIT is a main determinant of graft damage before retrieval. In the context of diagnosis and confirmation of **death** based on **neurological criteria**, **WIT** is **minimal** because organs are cooled at the same time as circulatory arrest occurs in the OR during removal. By contrast, in **DCD** warm ischemic periods can be **long** enough to induce a significant ischemic injury in the graft, potentially complicating transplantation from these donors, with increased rates of primary graft dysfunction or chronic ischemic lesions. To be precise, warm ischemia could arise (well)

before the circulatory arrest, with a period of hypoxia and/or hypoperfusion, named agonal or agonic period, outlining a condition of **functional warm ischaemia** (**fWIT** or true WIT). fWIT is the (variously) defined interval beginning as arterial oxygen saturation decreases below **70%** or systolic arterial blood pressure decreases below **50/60 mmHg** (irrespective of SaO_2) or both; organs seem suffering more from desaturation than from hypothension. With the conventional donor management, warm ischemia ends at the time of organ removal, with topic cooling and cold perfusion prior to cold static storage or ex-vivo reperfusion.

Maastricht classification (and modification to...)
DCD donors are traditionally categorized according to a classification proposed at an international meeting on Non Heart Beating Organ donation in Maastricht in 1995. This 4 categories classification, in table 1, divides potential donors into **uncontrolled**, **uDCD** (categories I and II) and **controlled** DCD donors, **cDCD** (categories III and IV). Maastricht classification underwent repeated **revisions**over the last 20 years in order to further differentiate between distinct logistic and clinical conditions (potentially impacting on organs function and Tx outcomes), to embracing new evolving strategies of resuscitation and life support. Herein the Modified Maastricht classification of DCD (Paris DCD Conference, 2013, table 1):
• category **I: found dead;** sudden, unexpected, **unwitnessed cardiac arrest**, **CA**, without any attempt of resuscitation by a medical team.
• category **II: witnessed cardiac arrest;** sudden, unexpected and irreversible CA with unsuccessful resuscitation by a medical team (no Return Of Spontaneous Circulation, ROSC) and without indications to persist in resuscitation attempts.
A distinction is made between **out-of-hospital** CA (subcategories **IA** and **IIA**) and **in-hospital** cardiac arrest (**IB** and **IIB**); all these donors are uncontrolled.
• category **III: awaiting cardiac death**; this category includes patients for whom CA follows the **planned** withdrawal of life sustaining treatments, **WLST** (as mechanical ventilation and vasopressors or inotropic medications), performed either in the ICU, in the ED or in the OR (depending on the country). A typical example belonging to this category is the patient suffering from irreversible brain injury with catastrophic prognosis but not fulfilling the neurological criteria for death. Further life-saving treatments are no longer In the patient's best interest. Decision of withdrawing life support needs to be shared within the ICU team and to be undertaken in full compliance with the recommendations of Intensive Care Societies, in consensus with patient relatives; over the whole procedure comfort therapy need to be provided to avoid any suffering in the potential donor. In WLST, AR has been recorded to occur between 2-5 minutes. Donors are controlled.
• category **IV: cardiac arrest while BD**; refers to CA during or after the **determination of death** with neurological criteria (during donor life-management prior to organ recovery). Donors can be uncontrolled or controlled.

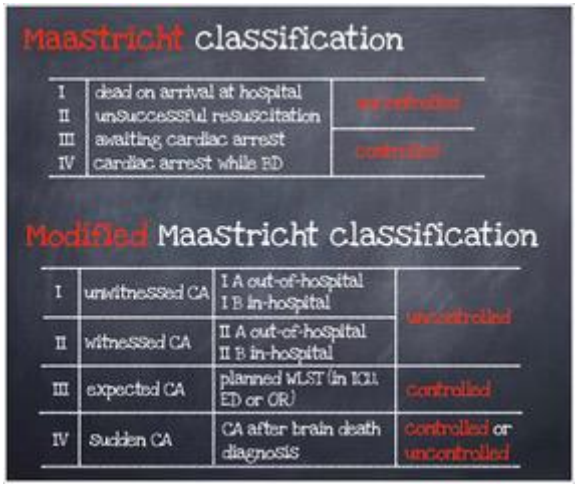
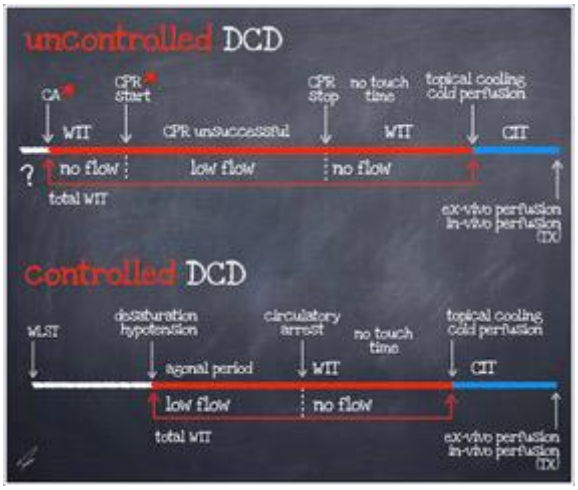


table 1. The Maastricht categories of Non Heart Beating Organ donors (Kootstra et al. 1995) and Modified Maastricht classification of DCD donors (Paris DCD Conference, 2013). BD, Brain Death; CA, Cardiac Arrest; WLST, withdrawal of life sustaining treatments ICU, intensive care unit; OR, operating room; ED, emergency department.

[In a (even more) modified classification category IV has been divided in some sub-categories: cardiac arrest in BD donor (subcategory **IV A**), and donors on **ECMO support prior to death**(subcategory **IV B**), with a distinction between two scenarios:
- **IV Ba: ineffective ECLS**; WLST in a decompensated patient despite extracorporeal support, if no expected recovery of native cardiac function and no indications for Tx or for long time Mechanical Circulatory Support as ventricular assist device or total artificial heart.
- **IV Bb: BD on ECMO/ECLS**; evidence of devastating cerebral injury leading to **determination of death by neurological criteria** while **on extracorporeal support**, most commonly secondary to hemorrhagic stroke due to anticoagulation or to anoxic brain injury as a result of cardiac arrest before ECLS or ECPR.]
It's important to discriminate between controlled and uncontrolled donors: the total length of warm Ischemia time can be extremely variable according to the donor category. In uDCD WIT, starting at the time of CA or before CA if desaturation and hypotension preexist, is usually longer; details and timing of the events are unknown or only partially known, and sometimes inaccurate (e.g. indirectly reported in OHCA). In controlled DCD WIT is minimized: organs procurement process may start within few minutes after the determination of death and patient's vital signs/timing are closely monitored and recorded, but fWIT duration depends on how much the patient is rely upon supports before WLST. In picture 2, a schematic (not to scale) of total WIT in uncontrolled and controlled DCD (respectively).



picture 2. warm (red line) and cold (blue line) ischemia times in uncontrolled and controlled DCD (timing are not to scale). Red asterisk, CPR start may coincide with CA if witnessed; question mark, events (eventual hypotension /desaturation) preceding CA are unknown. CA, Cardiac Arrest; WIT, Warm Ischemia Time; CPR, Cardio-Pulmonary Resuscitation; CIT, Cold Ischemia Time; TX, Transplant; WLST, Withdrawal of Life Sustaining treatment.

Abdominal organs have different tolerance to warm ischemia: pankreas and liver can tolerate about 15-30 minutes on average, kidney 120/150 minutes. A period of postischemic reperfusion could fully restore aerobic cellular metabolism and actively revert, thanks to the warm oxygenated environment, damages eventually incurred during WIT or previously established, increasing the number of organs suitable for transplantation.
Different **(re)perfusion techniques** have been proposed to promote **active reconditioning** of the grafts, the two main options: normothermic oxygenated **ex-vivo** or ex-situ **perfusion** of the organs following recovery (described and increasingly performed for lungs, heart, kidney and liver) and **selective in situ perfusion**. According to the ELSO nomenclature, extracorporeal interval support for organ retrieval, **EISOR**, is defined as the **temporary** use of veno-arterial extracorporeal membrane oxygenation to provide splanchnic vascular
bed **reperfusion** with **warm oxygenated blood** in non-heart-beating organ donors in the interval between circulatory death determination and organ removal, in order to restore/improve abdominal organs function.
This strategy is alternatively known as:
• normothermic regional perfusion, **NRP**;
• abdominal normothermic oxygenated recirculation, **ANOR**;

• normothermic ECMO, **NECMO**; by avoiding to recall ECMO in the name of the technique, a clear distinction is made between extracorporeal support in a patient requiring critical care and extracorporeal selective reperfusion of abdominal organs in a deceased potential donor for the purpose of transplantation.

EISOR - the technique

To perform EISOR vessels are cannulated as for femoro-femoral veno-arterial ECMO support, with a **venous drainage catheter** inserted through the femoral vein and advanced to Inferior Vena Cava and an **arterial reperfusion catheter** inserted through the femoral artery and advanced to the common iliac artery or aortic carrefour. Before starting perfusion, to avoid any possibility of resumption of cerebral circulation, invalidating the determination of death, is mandatory to prevent heart and brain reperfusion with warm oxygenated blood impeding any arterial flow above diaphragm. Complete exclusion can be achieved inserting a **balloon catheter** large enough to **completely occlude aortic lumen** once inflated (as an aortic stent graft balloon catheter, a large angioplasty balloon, a Fogarty or REBOA catheter; if on site, an intra aortic balloon pump catheter manually and steadily inflated could also be used for the purpose). The balloon catheter is inserted (usually percutaneously, over the wire) through the contralateral femoral artery and advanced to the descending thoracic aorta; positioning immediately above the diaphragm need to be confirmed e.g. by fluoroscopy (inflating the balloon with a mixture of normal saline and radio-opaque dye); **proper occlusion** should be **evaluated** before and during EISOR. Blood pressure monitoring through an arterial line placed in the lower limb (e.g. femoral) looking for the disappearance of pressure waveform tracing with a baseline value, as the balloon is inflated, while the left radial pulse is maintained, has been proposed to confirm proper location and volume requested for the balloon to be occlusive. Some legislations do not accept the aortic balloon as a strategy to reliably exclude the cerebral circulation and request an aortic **cross clamping** before perfusion is commenced. In picture 3, a schematic of EISOR.

picture 3. schematics of EISOR. A: venous femoral drainage cannula; B: arterial femoral reinfusion cannula and inflated aortic balloon, C: aortic cross clamping. SCV, superior vena cava; RA, right atrium; IVC inferior vena cava.

Some **antemortem interventions** in the dying patient, to maintain donating potential and optimise/accelerate normothermic reperfusion implementation following determination of death, are **controversial** and erratically allowed/regulated; notably:

- **cannulation**;
- percutaneous **guidewire insertion** and/or **surgical exposure** of the vessels to fasten post-mortem cannulation;
- insertion of the **aortic balloon (deflated)**;
- administration of **unfractioned heparin** to promote systemic anticoagulation during no-touch time (unless there is a concern that may contribute to death e.g. high bleeding risk patient);
- patient **transfer** to the OR/ICU;
- **checking** the **donor register** and/or **approaching the relatives** about donation;
- checking the patient's **anamnestic** and **clinical data** relevant to donation;
- testing blood or serum samples to obtain **clinical data** relevant to donation.

Involvement of transplant coordinator, retrieval team and recipient's clinical team in the care of the potential donor while still alive is considered as unacceptable.

The first EISOR circuits were CPB derived; actually, standard **ECMO circuits** are employed; dedicated organ donor low cost extracorporeal circuits are also available, with no integrated pressure monitoring systems and polypropylene (PP) membrane lung, intended for short time use. About the perfusion settings and monitoring during the run, some suggestions (no univocal consensus):

- extracorporeal **blood flow** at about 1.7/2.4 lt/min for a target MAP ≥ 60–65 mmHg, checking repeatedly arterial blood gas, with the target of a pH in the normal physiological range, 7.35–7.45 (eventually correcting with bicarbonate), looking for a (consistent) drop in the lactates level.
- **oxygen fraction** to the membrane lung at about 30% at start (higher fractions if severe hypoxia in the peri-arrest phase) adjusted for a target PaO_2 of 100-150mmHg; fresh gas flow is arranged to reach normocapnia.
- **heater unit** set to maintain a **temperature** of 37° C in the arterialized blood;
- **hematocrit** ≥ 25%;
- **ACT** monitoring and eventual administration of UFH;
- evaluation of **biomarkers** of **liver injury** and **renal function** every 30-60';
- if balloon on site, continuous monitoring of **upper limb arterial pressure**, showing baseline post CA value, could be used to early detect displacement/leakage (increasing radial pressure).

The reperfusion period can also be used to **evaluate** the **donor**, in particolar in uDCD, (anamnestic data defining risk categorization, blood typing, immunogenetic profiling,...) and for organs allocation.

Extracorporeal support is maintained until laparotomy in the OR and subsequent topical cooling and cold perfusion with preservation solution or ex-vivo organ reperfusion could be performed.

Implementing DCD protocols could substantially **expand** the **donor pool**, **increasing the availability** of deceased donor **organs** and positively impacting on transplant programs, enhancing grafts condition and recipients outcome; the willingness to be an organ donor of patients who traditionally will be considered out of procurement procedure could be respected.

In this scenario, temporary abdominal extracorporeal reperfusion with normothermic oxygenated blood is a feasible, promising technique for both controlled and uncontrolled donors; in uDCD EISOR can be critical for successful donors enrolment.

References

Shemie SD, Hornby L, Baker A, Teitelbaum J, Torrance S et al. International guideline development for the determination of death. Intensive Care Med. 2014 Jun;40(6):788-97. open access link

Thuong M, Ruiz A, Evrard P, Kuiper M, Boffa C et al. New classification of donation after circulatory death donors definitions and terminology. Transpl Int. 2016 Jul;29(7):749-59. open access link

Shemie SD, Gardiner D. Circulatory Arrest, Brain Arrest and Death Determination. Front Cardiovasc Med. 2018; 5: 15. open access link

Pana R, Hornby L, Shemie SD, Dhanani S, Teitelbaum J. Time to loss of brain function and activity during circulatory arrest. J Crit Care. 2016 Aug;34:77-83. link

Hornby L, Dhanani S, Shemie SD. A systematic review of autoresuscitation after cardiac arrest. Crit Care Med. 2010 May;38(5):1246-53. link

Hornby L, Dhanani S, Shemie SD. Update of a Systematic Review of Autoresuscitation After Cardiac Arrest. Crit Care Med. 2018 Mar;46(3):e268-e272. link

McGee A, Gardiner D, Murphy P. Determination of death in donation after circulatory death: an ethical propriety. Curr Opin Organ Transplant. 2018 Feb;23(1):114-119. link

Kuiper MA, Hollenberg S, Crippen D, Whetstine LM. The Potential to Increase Organ Donation After Death by Circulatory Criteria. Crit Care Med 2017; 45:e111 link

Kootstra G, Daemen JH, Oomen AP. Categories of non-heart-beating donors. Transplant Proc. 1995 Oct;27(5):2893-4.

Conrad SA, Broman LM, Taccone FS, Lorusso R, Malfertheiner MV et al. The Extracorporeal Life Support Organization Maastricht Treaty for Nomenclature in Extracorporeal Life Support. A Position Paper of the Extracorporeal Life Support Organization. Am J Respir Crit Care Med. 2018 Apr 3. link

Dejohn C, Zwischenberger JB. Ethical implications of extracorporeal interval support for organ retrieval (EISOR). ASAIO J. 2006 Mar-Apr;52(2):119-22. open access link

Ortega-Deballon I, Hornby L, Shemie SD. Protocols for uncontrolled donation after circulatory death: a systematic review of international guidelines, practices and transplant outcomes. Crit Care. 2015 Jun 24;19:268. open access link

Manara AR, Murphy PG, O'Callaghan G. Donation after circulatory death. Br J Anaesth. 2012 Jan;108 Suppl 1:i108-21. open access link

Giannini A, Abelli M, Azzoni G, Biancofiore G, Citterio F, et al. "Why can't I give you my organs after my heart has stopped beating?" An overview of the main clinical, organisational, ethical and legal issues concerning organ donation after circulatory death in Italy. Minerva Anestesiol. 2016 Mar;82(3):359-68. open access link

Peris A, Lazzeri C, Cianchi G, Bonizzoli M, Batacchi S et al. Implementing a donation after circulatory death program in a setting of donation after brain death activity. Minerva Anestesiol. 2018 May 28.[Epub ahead of print] link

Miñambres E, Rubio JJ, Coll E, Domínguez-Gil B. Donation after circulatory death and its expansion in Spain. Curr Opin Organ Transplant. 2018 Feb;23(1):120-129. link

Perez-Villares JM, Rubio JJ, Del Río F, Miñambres E. Validation of a new proposal to avoid donor resuscitation in controlled donation after circulatory death with normothermic regional perfusion. Resuscitation. 2017 Aug;117:46-49. link

Extracted from EuroELSO: http://www.euroelso.net/education-and-simulation/68-dcd-eisor.html