

**Coordination:** 

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### Members of the steering committee 2013-2018

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- 2 AFU :
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- 4 CMS : Comité médical et scientifique de l'Agence de la biomédecine
- 5 ACHBT : Association de chirurgie hépato-biliaire et de transplantation hépatique 6
- Coordination hospitalière CH :
- 7 SRLF : Société de Réanimation de Langue Française
- 8 SPLF : Société de pneumologie de langue française 9
- Association française pour l'étude du foie Société Française de Médecine d'Urgence AFEF : 10
- SFMU : 11
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# agence de la biomédecine Part I: A NATIONAL PROTOCOL

# A. The regulatory context

Article R.1232-4-1 and its implementing decrees (Orders dated August 1 2014 and April 13 2018) provide that kidneys, liver, lungs, and pancreas can be recovered from deceased persons with persistent cardiac and respiratory arrest, referred to as recovery of donations from deceased donors after circulatory death (DCD) (1). These processes take place according to protocols promulgated by the *Agence de la biomédecine*. All persons involved in this activity must therefore adhere to the national guidelines.

A meeting in Maastricht in 1995 (2) established four categories of donation after circulatory death, which were revised in February 2013. This classification clearly identified two different situations:

- those involving so-called uncontrolled donors (categories 1, 2, and 4), for which there exists a degree of uncertainty about the exact duration of warm ischemia, including:

- Sudden unexpected irreversible cardiac arrest (CA), without attempted resuscitation (uncontrolled and unwitnessed CA);
- Sudden unexpected irreversible cardiac arrest with unsuccessful resuscitation (uncontrolled and witnessed CA);
- o Individuals with brain death who go into irreversible circulatory arrest during resuscitation.

- those so-called controlled donors (category 3), for whom circulatory arrest is planned and expected after withdrawal of life-sustaining treatment (WLST), euthanasia excluded. In this situation, the donor's hemodynamic status and the T0 of circulatory arrest are often shorter and known to the medical team.

This classification describes various clinical situations, each raising different ethical and logistic questions (4). Uncontrolled DCD donors present the difficulty of an urgent search to ascertain any patient refusal reported by family to organ donation and the issue of acceptable warm ischemia time (WIT). In terms of recovery, these categories raise issues of organization because of the short time available, in situations impossible to anticipate (uncontrolled) that depend largely on the management by the prehospital medical team.

The situation of a controlled DCD donor implies there was a collegial decision to limit or withdraw life support treatment. This subject remains both complex and delicate in France, despite the enactment in 2005 of a law defining patients' rights at the end of life: the so-called Léonetti Law (5), completed by the so-called Claeys-Leonetti Law in February 2016 (6).

Articles R1232-4-1 and R1232-4-2 of the Public Health Code authorized the recovery from a deceased person who presented a persistent cardiorespiratory arrest. The list of organs that can be retrieved is determined by the Minister of Health, based on a proposal by the *Agence de la biomédecine*.

Recovery of kidneys has been authorized since 2005 and that of the liver (7, 8) since 2008, initially in the context of an uncontrolled DCD program.



Recovery of lungs has been authorized since August 1, 2014 (9), and that of the pancreas since April 13, 2018 (10).

# B. The principles underlying the national protocol (11)

- Nationwide adherence to all applicable ethical and organizational guidelines
- Decisional processes for the WLST must comply with the law on patients' rights at the end of life.
   The relatives will not be approached about organ donation until the decision for WLST has been made and independently agreed to.
- "the dead donor rule and organ transplantation" must be strictly respected. This states that patients must be declared dead before any organs are removed and that intervention after WLST does not accelerate death.
- The objective is to obtain posttransplantation results similar to those obtained from so-called "optimal" donations after brain death (DBD), even though the data from the literature and prognostic score models clearly identify grafts from donations after circulatory death (DCD) as "expanded criteria" organs, that is, with posttransplantation results poorer than those obtained from "optimal" DBD.

To reach this objective, this protocol was designed to exclude or limit as much as possible the factors that aggravate the injuries induced by warm ischemia (12–16).

# 1) Stricter donor and recipient selection criteria

- ✓ Donors:
  - By age (< 61 years until May 2017, then < 66 years until June 2018, and now < 71 years);</li>
  - By the absence of organ failure, by not accepting for transplantation any organ with acute or chronic failure.
- ✓ Recipients, by excluding:
  - Patients awaiting retransplantation (because their posttransplantation results are significantly poorer than with grafts from DBD for kidney, pancreas, and liver transplantations);
  - Patients with hemodynamic failure (which signifies an additional period of hypoperfusion for the transplanted organ);
  - HLA-incompatible grafts; virtual crossmatch allows these to be avoided while minimizing WIT.

# 2) Adherence to ischemia limits with:

- ✓ An agonal phase < 3 hours;
- ✓ Controlled functional WIT and asystole phase;



✓ The shortest possible cold ischemia time (CIT) for all organs.

#### Definitions

The agonal phase extends from the start of treatment withdrawal to circulatory arrest.

<u>The circulatory arrest phase</u> corresponds to the period of asystole (the no-flow period), that is, to the absence of blood flow in the organs. It begins at the moment that circulatory arrest is determined by the disappearance of arterial pulsatility, recorded with the invasive arterial line, and is completed at the moment of pneumoplegia for the lungs and at the start of normothermic regional perfusion (NRP) for the intraabdominal organs.

<u>Functional WIT</u> corresponds to the time period during which the organs are hypoperfused and then not at all perfused because of circulatory arrest. It starts when organ perfusion reaches a critical point (MAP  $\leq$  45 mmHg) and is completed at pneumoplegia for the lungs and at the start of NRP for the intraabdominal organs.

<u>Cold ischemia time</u> covers the period during which the organs are preserved in a hypothermic state, or in static storage, or under hypothermic machine perfusion.

Organs	Agonal phase	Functional warm ischemia time	Circulatory arrest	Cold ischemia time
Kidneys	< 3 h	≤ 120 min		≤ 18 h
Liver	< 3 h	≤ 30 min		≤ 8 h
Pancreas	< 3 h	≤ 30 min		≤ 12 h for a whole-organ pancreas transplantation
Lungs	< 3 h	≤ 90 min	≤ 60 min	As rapidly as possible

Duration of ischemia authorized for the first version of the protocol (2015-2018):

# 3) Starting postmortem normothermic regional perfusion (NRP)

- ✓ Enables the recovery of cell damage induced by prolonged warm ischemia (17–19).
- ✓ The arterial and venous cannulae are placed after the patient is declared dead, and an endoaortic balloon clamp is placed into the descending thoracic aorta, thus preventing reperfusion of the brain and the heart.
- ✓ It is mandatory for the recovery and transplantation of the liver and pancreas and strongly recommended for kidney transplantation.

Organs	In situ normothermic perfusion	Minimum	Maximum	
Organs	in situ normothermic pertusion	duration	duration	
Kidneys	Recommended+++	> 60 min	≤ 4 h	



	Mandatory if included in the local protocol		
Liver	mandatory	> 60 min	≤ 4 h
Pancreas	mandatory	> 60 min	≤ 4 h
Lungs	NA		

# 4) Ex vivo perfusion

After the kidneys and lungs have been recovered, to optimize the conditions of their preservation and enable both rehabilitation of the organ and assessment of its viability (20, 21):

Organs	Ex vivo perfusion	Minimum duration	Maximum duration
Kidneys	Mandatory hypothermia	> 2 h	CIT ≤ 18 h
liver	Not mandatory		
Pancreas	NA		
Lungs	Normothermic oxygenation is mandatory	According to th	e local protocol

### In the framework of the national protocol, all organ transplant teams agree to:

- Adhere to each condition of the national protocol and those added to the local protocol, in particular, the recipient selection criteria, and make every effort to use ex vivo perfusion for kidney and lung transplants.
- Report serious events: graft loss, death of the recipient, their causes and possible associations with the type of recovery (association with prolonged circulatory arrest).
- Update the CRISTAL Recipients database: collect data about the performance of the transplant, its immediate or delayed function, the onset of possible posttransplantation complications, graft loss, recipient's death, and outcome at every year.

# C. Training

Because of the complexity of the procedure, particularly the potential pitfalls of the NRP technique, the national protocol is supported by robust training programs. The *Agence de la biomédecine* offers training by its online education platform. Teams are encouraged to contact the Agence's office to schedule regional training sessions.

Two types of programs are planned:

- An initial information course (level 1) reviewing the protocol fundamentals (legislative framework, implementation strategy, stages of the procedure and management, bibliography). This course is open to all.



 A second course (level 2) is reserved to teams that want to set up the protocol in their hospital and have formalized this intention by a letter to the *Agence de la biomédecine*. It takes up in detail the particularities of the interview/maintenance, implementation and management of NRP, the practical aspects of the recovery of different organs, the CRISTAL DCD donor database, examples of clinical situations, etc.).

Moreover, together with the level 2 course, the *Agence* offers, through regional pairing, a session (1-2 days, according to the center) of simulation training in approved centers. This session is open to staff from medico-surgical teams that have adequately advanced in the drafting of procedures for their own hospital.

The different stages of the procedure are developed there, which enables teams to test their local procedures, adjust them if necessary, and optimize the interactions of the professionals on the team.

Creation of a specific register of potential controlled donation after circulatory death that includes all patients:

- in an intensive care unit in an authorized hospital
- for whom WLST is decided, based on a collegial decision,
- without evident contraindication of organ donation,
- after contact with the hospital organ procurement organization (OPO) team, managing donation services and coordination as well as providing relevant expertise

A controlled donation after circulatory death donor is a patient who has not reached brain death, for whom the decision has been made to withdraw life-sustaining therapy and with no medical contraindications to organ donation.

#### **Objectives:**

- Identify all procedures of any type involving the OPO team and any steps it takes related to organ donation, regardless of the response to these steps or of the patient's outcome after WLST
- Collect information about the criteria that led to an indication for WLST, in accordance with the relevant regulations in force
- Collect the methods used for implementing the WLST (withdrawal of ventilator support, analgesia, etc.)
- Know the outcome of all procedures related to treatment withdrawal in which organ donation was considered, regardless of the reason the procedure failed: patient's refusal reported by family, discovery of a contraindication, agonal phase or circulatory arrest that lasted too long.

OPO teams are asked to enter all of this information and to specify the reasons for stopping the organ donation (quality process).

Data entry about the follow-up of the recipients is mandatory and takes place according to the same procedures as grafts from DBD in the CRISTAL Recipient database.



# D. Results of the controlled DCD program between 2015 and 2018

Between 2015 and 2018, 566 potential donors were identified at 26 authorized sites, and organs were recovered from 287.

Year	2015	2016	2017	2018	2019
Number of active centers	4	9	20	26	35

The analysis of data from the CRISTAL controlled DCD donor register confirms the adherence to the ethical and organizational guidelines established by the SFAR, SRLF, and SFMU intensive care societies:

- Results of all clinical investigations performed (to confirm irreversible brain injury and catastrophic prognosis); 95% of donors with organs recovered had at least 1 examination, 63% 2 or more, 31% 3 or more, including EEG, CT, MRI, evoked potentials, and biomarkers).
- Systematic opinion of an external consultant
- Collective decision to withdraw life-sustaining treatment
- Mean time of 10 days between ICU admission and the decision about withdrawing life support treatment, with this time used to confirm irreversible brain injury and catastrophic prognosis.

The profile of donors differs from that described in series from other European countries, with in particular:

- An interval between admission and the decision to withdraw life-sustaining treatments> 8 days (mean: 10.6 days, median 6.5 days);
- 55% of the donors whose organs were procured showed postanoxia cerebral lesions related to the initial cardiac arrest (versus 25% of this type of donor in the United Kingdom), and there are few donors identified after hemorrhagic strokes (contrary to 45% in English-speaking countries);
- A progressive increase over time of admissions for hypoxic brain damage (successful resuscitation after cardiac arrest)

The mean age of the donors with organs recovered rose from 49 to 52.1 years over 4 years (increase in maximum age authorized from 60 to 65 years inclusive in May 2016).

The identified/procured conversion rate is 50% with:

- The procedure halted due to opposition to donation in 30% of cases, a rate similar to that observed for brain-dead donors (30.5%);
- 7-8% for medical contraindications;
- 5% of procedures that failed for logistic reasons or hemodynamic instability;



- 18 technical incidents during cannulation or establishment of the NRP circuit;
- Circulatory arrest failing to occur within 3 hours after withdrawal of life support treatment in around 20 potential donors.

Analysis of the CRISTAL DCD data shows the presence of diabetes (insulin-dependent or not) and of hypertension in respectively 18% and 47% of DCD donors aged 60 to 65 years; 35% of this age group had neither diabetes nor hypertension.

All of the WITs mandated by the national protocol were met:

- Agonal phase time: mean 23 minutes, median 15 minutes, Q1-Q3 11-21 minutes.
- Functional WIT: mean 27 minutes, median 26 minutes, Q1-Q3 20-31 minutes.
- The asystole phase, which includes the 5-minute "no touch" period before death is declared and the time needed to place the NRP cannulae and start it, which is a mean of 22 min (median 19 min).

	N	mean	minimum	maximum
Agonal phase time (min)	282	23	1	180
Asystole time abdominal organs (min)	281	22	6	68
Asystole time lungs (min)	26	52	17	115
Functional WIT abdominal organs (min)	281	28	7	83
Functional WIT - lungs (min)	26	58	28	127
NRP duration - abdominal organs (min)	279	165	50	268
NRP duration - lungs (min)	25	37	10	101

Time required for the procedure of organ recovery (at least one organ) for DCD after the limitation or withdrawal of life support treatment (controlled DCD) (2014-2018)

In conclusion, 649 organ transplants were offered with this program during the first four years: 504 kidney transplants (93% of recovered kidneys were transplanted), 123 liver transplants (87.3% of recovered livers), and 22 lung transplants (5 lungs were finally not transplanted, due to the assessment by ex vivo perfusion). These results are detailed in the sections devoted to each of these three organs: kidneys, liver, and lungs.

The program was extended to the recovery and transplantation of the whole-organ pancreas or of islets of Langerhans in November 2018. Three centers are currently approved for procurement and two transplant teams for pancreas-kidney transplantation, but none was performed in 2018 and 2019.



# E. Medical-economic aspects

### Preamble

As part of activity-based healthcare facility funding (T2A), the identification of donors, surgical organ recovery, and transplantation in the strict sense of the term receive either specific annual funding (CPO, FAG) or gradual progressive funding (PO).

To fund the procurement activity of the OPO teams: the annual lump sum appropriation, the CPO, is paid at the start of the year on the basis of the previous year's activity.

Multiorgan procurement is funded as it occurs, by an appropriation called PO, which varies according to the organ or organs recovered.

Hospitalizations for transplantation are funded, like all other hospitalizations, by a *groupe homogène de séjour* (homogenous hospitalization group, GHS, similar to diagnosis-related groups), which vary by organ and severity. In addition, the annual transplantation appropriation (FAG) is intended to cover the activities related to transplants (OPO, HLA typing, organ transport, clinical studies, etc).

# 1) Funding of the procurement activity of the organ procurement organization team: CPO appropriation, basic fees, and supplements

The basic CPO depends on the hospital's **authorization** and the number of donors identified, whether or not organs were recovered; supplemental payments are added to this basic fee and are cumulative:

- According to the number of donors from whom tissues or organs are procured;
- According to the activities performed by the organ procurement organization team: number of procurements under the uncontrolled DCD protocol, the procurement network (differentiating by the number of satellite facilities); implementation of the CRISTAL Action program

These appropriations can be modified each year, on the joint decision of the Ministry of Health and the National Health Insurance Fund.

a) Basic fee: based on the number of donors identified.

All types of donors are taken into account: brain death (DBD) or circulatory death, controlled or not (DCD), with no difference in the amount according to mode of death.



The different levels of basic fees are described in the Table below:

Basic fee	Type of authorization of the organ procurement organization team	Activity considered	Number of donors identified (DBD, DCD)	Amount of basic fee
D	Authorization for tissue procurement only	Recovery from tissue donors	starting at 5	€ 25,000
F1			from 1 to 4	€55,000
F2	_		from 5 to 9	€110,000
F3			from 10 to 14	€165,000
F4			from 15 to 19	€215,000
F5		Identification	from 20 to 29	€265,000
F6		of organ	from 30 to 39	€315,000
F7	Authorization for organ and tissue procurement	donors and	from 40 to 49	€365,000
F8		tissue	from 50 to 59	€415,000
F9		procurement	from 60 to 74	€465,000
F10			from 75 to 89	€515,000
F11			from 90 to 104	€565,000
F12			from 105 to 119	€615,000
F13			from 120 to 134	€665,000

Above 135 donors, the basic fee increases by  $\in$  50,000 per increment of 20 donors

b) <u>Tissue supplement</u>: when tissue is recovered, it opens the right to a tissue supplement. Here, it is the donor who is counted (1 donor for 2 corneas, + counted as many times as the number of types of tissues recovered). Note that there is a minimum threshold of 10 donors for cornea procurement.

Category	Number of deceased donors with corneas recovered (in the mortuary or during a multiorgan recovery)	Fee
CO1	from 10 to 19 donors with corneas recovered	€21,910
CO2	from 20 to 39	€30,710
CO3	from 40 to 69	€39,510
CO4	from 70 to 109	€48,310
CO5	110 and +	€57,110



Category	Number of deceased donors with bone and soft tissue recovered from the musculoskeletal system + number of donors from whom blood vessels were recovered (veins and arteries) + number of donors from whom cardiac valves were recovered + number of donors from whom skin was recovered	Fee
AT1	from 5 to 9 donors with other tissues recovered	€12,520
AT2	from 10 to 14	€21,320
AT3	from 15 to 24	€30,120
AT4	from 25 to 44	€38,920
AT5	45 or more	€47,720

# c) Since 2016, **other supplements** have been created to take the following activities into account more qualitatively:

Category	Criteria	Amount
DCD	Organ procurement organization team identifies at least 6 deceased donors after circulatory death <b>(uncontrolled DCD)</b> per year	€40,000
ROP1	<b>Operational local network</b> composed of 1 or 2 healthcare facilities (not authorized to recover organs)	€10,000
ROP2	Operational local network composed of 3 or more healthcare facilities (not authorized to recover organs)	€20,000
СА	Organ procurement organization team implements the entire <b>CRISTAL</b> <b>ACTION</b> program (equivalent to the Donor Action program in Spain)	€15,000

<u>Comment concerning the uncontrolled DCD supplement in the table above</u>: this supplement was created to support uncontrolled DCD activity and encourage facilities to participate in it at the minimum level that would justify additional paramedical donor coordination duty.

At the end of 2018, the Agence de la biomédecine obtained an exceptional additional appropriation of almost €300,000 intended for the procurement activity of organ procurement organization teams related to controlled DCD donors (7 facilities in 2019, based on their activity in 2018).

In 2019, the DGOS (directorate general of healthcare provision), at the request of the *Agence*, validated the creation of a permanent supplement that considers uncontrolled DCD and controlled DCD. Nonetheless, to sustain the efficiency of organ recovery, this financial incentive will be attributed to establishments authorized for controlled DCD for *several* organs, and the indicator will be the number of controlled DCD donors identified from whom *at least one organ other than kidneys* was proposed for distribution (reference: T2A funding pamphlet).



# 2) Funding of organ recovery: Organ procurement appropriations (PO)

This appropriation is intended to cover the costs associated with multiorgan procurement (occupation of operating rooms, donor assessment and HLA typing, return and transportation of donors' bodies, organ preservation); they are paid to the hospital where the organ is recovered and to the hospital to which the surgical team is attached These fees are paid as they occur (their billing is associated with the donor's PMSI hospitalization).

a) Fees intended for the hospital that is headquarters of the multiorgan recovery

When the uncontrolled DCD program was established in 2006, a specific fee was established, categorized as **PO4**.

Since 2016, the amount of the PO4 payment has been set at €13,600 (note: PO4 is the highest of the PO payments; it should be compared with the PO3 payment of €8500 for multiorgan recovery for DBD).

It was decided to apply the same payment level for controlled DCD as for uncontrolled DCD, that is, PO4.

Table of PO payments intended for the hospital where the organs were recovered:

PO PAYMENTS FOR ORGAN RECOVERY (for the hospitals where organs were recovered)		Fees 2019	
	(Ior the hospitals where organs were recovered)		Private
PO 1	Procurement of one or both kidneys and/or of the liver for DBD	€7344.59	€ 5653.87
PO 2	Procurement of one or both kidneys, the liver, heart, pancreas, one or both lungs and/or the intestines, or of at least 7 organs from one person with brain death	€10,337.36	€ 8588.62
PO 3	Other organs recovered from a person with brain death	€8499.95	€ 6799.83
PO 4	Recovery of organ or organs for DCD	€13,621.76	€ 7915.43

Note that any **recovery** from a DCD donor, either **uncontrolled or controlled**, regardless of the organ or organs recovered, results in the billing of a PO4 allocation by the hospital where the recovery took place.



#### b) Payments intended for the hospitals to which the surgeons are attached

These are based on the organ or organs recovered, as indicated in the following table:

PO PAYMENTS FOR RECOVERY (for the <u>establishment to which the surgeons are attached</u> )		Fees 2019	
			Private
PO 5	Recovery of one or both kidneys for DCD or DBD	€ 405.39	€ 405.39
PO 6	Recovery of a liver for DCD or DBD	€ 405.39	€ 405.39
PO 7	Recovery of one or two lungs for DCD or DBD	€ 516.87	€ 516.87
PO 8	Recovery of a heart or "heart-lung block" for DBD	€ 486.47	€ 486.47
PO 9	Recovery of a pancreas for DCD or DBD	€ 608.08	€ 608.08
PO A	Recovery of both kidneys for DBD with use of hypothermic machine perfusion	€ 809.29	€ 809.29

NB: The POA fee for recovery of kidneys with use of machine perfusion is reserved for BD donors; that is, for DCD, the NRP and the attachment of the kidneys to the perfusion machines were included in the PO4 fee described above.

It should also be noted that for kidneys and lungs, organ perfusion is funded by the **annual transplantation allocation** (FAG<sup>14</sup>); that is, this funding covers the purchase and maintenance of the perfusion material (machines and supplies): this involves the transplant team, most of the time for the kidneys and always for the lungs.

For further information about funding, see the information pamphlet revised annually by the *Agence de la biomédecine*.

<sup>&</sup>lt;sup>14</sup> For the kidneys: € 8814 per 3 uses of the perfusion machines (perfusion of 2 kidneys); For the lungs: € 31,340 per transplant after use of ex vivo machine-perfusion ventilation.



# Part II: MANDATORY STAGES OF THE DONOR MANAGEMENT PROCESS

### PRELIMINARY REMARK

Each of the stages described below must be the subject of detailed written local procedures that are consistent with the guidelines of this protocol.

# A. Decision to limit or withdraw life support treatment. Information to families about the withdrawal of active treatment.

Act 2005-370 dated 22 April 2005 (5) *about the rights of patients including at the end of life* authorizes the withdrawal of life support treatment according to a transparent, regulated procedure.

The provisions in this statute about patients' rights and the end of life indicate that medical procedures "*must not be implemented or continued when they result from unreasonable obstinacy. When they appear futile, disproportionate or when their only effect* is the *artificial maintenance of life, they can be suspended or not undertaken,* in accordance with the patient's wishes or, should the patient be unable to express these wishes, after a collective procedure defined by regulations."

Law n. 2016-87 dated 2 February 2016, known as the Claeys-Léonetti Act (6), reaffirmed these principles and created new rights for persons at the end-of-life. In particular, it introduced the possibility of using deep, continuous sedation that allows the patient to be unconscious until death. This right is also applicable when the patient is unable to express his/her wishes and is in a situation of unreasonable obstinacy, as defined by the law. The first phase of the procedure to limit or withdraw life support treatment is serious consideration of this decision; during this time, life-sustaining treatments continue and may even be intensified if necessary.

The aim of this stage is to recognize that treatment for a given patient appears to be at an impasse, that the phase of unreasonable and futile obstinacy has been reached, and that withdrawal of life support treatment appears legitimate and appropriate. The medical decision to withdraw life support treatment of a person unable to express his or her wishes cannot be reached until after the collective procedure required by law and defined by the Code of Medical Ethics, and the consultation of the patient's advance directives, or if there are none, of the health proxy, or if none, the family or close friends.

The collective procedure involves cooperation with the care teams and, on the other hand, the opinion of at least one physician called in for consultation, or even a second consultant at the request of the either the physician responsible for the patient's care or the first consultant; the bases of their opinions must be stated. The decision to withdraw life support treatment "takes into account the wishes previously expressed by the patient in advance directives. In the absence of these directives, testimony about the patient's wishes is collected from the health proxy, or failing that, from the family or close friends. The collective procedure is initiated by the physician managing the patient or at the



request of the health proxy, or failing that, by the family or a close friend. The Claeys-Léonetti Act, moreover, specifies that advance directives are now binding on physicians.

Finally, the decision to stop life support treatment must be justified: "the opinions collected, the nature and the sense of cooperation that occurred within the treatment team as well as the reasons for the decision are recorded in the patient's file."

At the conclusion of every collective procedure, the final decision about withdrawing treatment is a medical decision, which is the responsibility of the physician managing the patient. The reasons for the decision must be stated: the opinions collected, the nature and the sense of cooperation that occurred within the treatment teams as well as the reasons for the decision are recorded in the patient's file. On the other hand, "the health proxy or, failing that, the family or a close friend are informed of the nature and reasons for the decision". At this stage, no referral for organ donation is envisioned, and the organ procurement organization team does not — must not — intervene. The information concerns only the decision about stopping life-sustaining treatment and the ways it can be carried out.

# The underlying principle is that all treatment withdrawal decisions must be made and implemented similarly, independently of any consideration of organ donation; the discussion of donation can only be envisioned afterwards.

The prognosis of a given disease must be based on the most advanced techniques, particularly in the area of imaging (e.g., MRI). These examinations must be available and performed before any decision about withdrawing life support treatment that requires them.

The tasks of the *Agence de la biomédecine* do not include intervention in the development of good practices in intensive care. Strict adherence to national, international, ethical, and technical guidelines issued by professional societies is a prerequisite (22–25).

- The possibility of organ donation must not influence the decision to stop life-sustaining treatment.
- Hermetic separation of processes: Resuscitation/intensive care team (decision to withdraw treatment and its implementation), OPO and transplant teams (organ donation procedure).
- Chronology: decoupled procedures differentiating, on the one hand, the time between the discussion and decision about treatment withdrawal, and on the other hand, an approach to the family to inform them about the possibility of donation.



### B. Identification of a potential donor. Initial evaluation.

This phase, which follows the decision to withdraw life support treatment, corresponds to the period during which the patient is "declared to be dying", during which life support treatments continue. The organ procurement organization team is alerted by the ICU and works to verify that the patient has no obvious contraindication to donation on the basis of medical history (history of cancer, progressive infectious disease, etc.) or clinical condition (no multiorgan failure, etc.), possibly by requesting an opinion from the regulation/coordination staff at the *Agence de la biomédecine*.

In no case can an opinion about procurability be made, either by the organ procurement organization team or the *Agence de la biomédecine* unless and until a decision to withdraw treatment has been made and the family has agreed with it.

This donor qualification procedure at the Agence de la biomédecine will involve consultation of the medical file and can require the performance of noninvasive laboratory or radiologic tests and some minimal assessment; it should not require moving the patient.

This first search for contraindications makes it possible to stop the organ donation process in cases of an absolute contraindication to organ recovery and thereby avoid a futile approach to the family. The latter are not informed of this first assessment.

Current regulations make it impossible to query the national refusal register until after the determination of death, as the death report must be attached to the query request.

The following examinations can be performed after the decision to withdraw treatment and before the family is approached:

- all mandatory serology and PCR results that could be disqualifying for health security reasons
- functional organ tests: creatinine levels, proteinuria, complete liver function tests; blood gases
- AP chest radiography
- bedside abdominal pelvic ultrasound.

The absolute contraindications to organ donation by controlled DCD donors are:

- The standard contraindications to organ donation:
  - o Unidentified patient
  - o Uncontrolled sepsis
  - o Lack of diagnosis of initial disease
  - o Multiorgan failure
  - Some cancers (according to the guidelines in effect)
  - Positive serology or viremia results that require disqualification of the donation (health security decree): HCV, HIV, HTLV
  - Active tuberculosis
  - Rabies, viral encephalitis
  - o Suspected Creutzfeldt-Jakob disease or situations at risk for it
- Specific contraindications for controlled DCD:
  - Age  $\geq$  71 years;

#### • Patients whose progression towards brain death is anticipated

The situations of patients under guardianship or with medicolegal problems do not present specific problems and are treated as they are in situations of brain death.

The recovery of organs from minors is authorized under the controlled DCD program. The conditions for its performance must be identical to those for adults in the types of resuscitation authorized and must comply with the specific guidelines (under development) of the Pediatric Intensive Care society.

The conditions for obtaining authorization from parents or guardians before any tissue or organ is recovered from a minor or from an incapacitated adult under guardianship are specified in Article L. 1232-2 of the Public Health Code (26):

"If the deceased was a minor or an adult under guardianship, recovery for one or more of the purposes mentioned in article L. 1232-1 can take place only on condition that each of the holders of parental authority or the guardian consent in writing. Nonetheless, should it be impossible to consult one of the holders of parental authority, the recovery can take place on condition that the other consents in writing."

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# C. Search for opposition and contraindications to organ and tissue donation.

1. Opposition to organ and tissue donation)

Article R.1232-4-4 of the Public Health Code applies, regardless of the type of death (advance approach, DCD...) (27).

Decree 2016-1118 dated 11 August 2016 specifies the ways that refusal of recovery after death can be expressed (28).

In accordance with the decree dated 16 August 2016 approving the good practice guidelines for interviews with family and close friends concerning the recovery of organs and tissues (29), if there is no contraindication to organ recovery, the hospital OPO team will conduct an interview with family and close friends to inform them of the possibility of organ and/or tissue donation. Depending on local organization, an OPO staff member will be paired with a critical-care specialist for this interview. The donor coordination team will collect their statements reporting the expression of possible opposition to organ donation (written by the patient, or oral refusal reported by family and close friends, etc.). It should be noted that in some cases, after agreeing to the suggestion to withdraw treatment, some families spontaneously mention their loved one's known wish to donate organs after death and want to know if this remains possible despite his or her health status.

Some physicians participating in the organ procurement organization team are also hospital staff ICU or resuscitation physicians. This scenario already occurs in cases of brain death but is much more sensitive in cases of donors for whom life support treatment is being withdrawn. The work of the OPO team is not urgent and is most often performed on work days. It is thus essential to ask these professionals not to participate in procurement work when they are currently the intensivist responsible for the patient awaiting a decision about treatment withdrawal.

The organ procurement organization team is asked to draft and make available to families a specific information booklet which reviews point by point the information transmitted during the conversation and the different stages of the donation procedure, with contact information so family can contact the team. This booklet will be attached to the file of the authorization request.

Procedure sheet n°2 describes this interview process.

Procedure sheet n°3 describes the tasks of the organ procurement organization teams in relation to the recovery of controlled DCD organs and tissues, that is, of persons who die after circulatory arrest.

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# D. Implementation of the withdrawal of life support treatment and the beginning of the agonal phase

It appears clear and consistent with both international guidelines and French law (the Léonetti Act and the Claeys-Léonetti Act) concerning the end of life that the withdrawal of life support treatment must be implemented and performed only by the Intensive Care medical team, although the donor coordination team is present to collect the necessary data. It cannot intervene until after circulation has stopped, death has been declared, and the death certificate signed.

The entire procedure (see procedure sheet n°6) must be transcribed in the patient's file so that every stage (treatment withdrawal decision, synthesis of different expert opinions reported in the file, and the course of the withdrawal) is traceable.

The withdrawal procedure must be set up by the same ICU team that decided to withdraw life support treatment, and it must adhere to statute, regulations, and professional society guidelines.

# 1) Treatments

The protocols for sedation/analgesia used during the withdrawal of life support treatment are thus part of the procedures drafted locally and must comply with the Claeys-Léonetti Act as well as with the guidelines of the relevant intensive care societies (30,31). Curariform substances must not be used.

To preserve the quality of the organs, some treatments that have become futile for the patient may nonetheless be continued, initiated, or intensified, such as antibiotic therapy.

In the absence of contraindication, an intravenous bolus administration of heparin (300 IU/ kg) is recommended and administered at the withdrawal of life support treatment, to reduce the negative impact of the microcirculation hypoperfusion that precedes circulatory arrest. It must not be injected if there is a known hemorrhagic risk (e.g. intracranial hemorrhage).

# 2) Conditions before withdrawal of ventilatory support

The withdrawal of ventilator support modalities is described in the department's procedures for the WLST.

The choice to withdraw ventilatory support and the steps to accomplish it are the responsibility of the intensive care team and depend on the ICU's regular practices.

# 3) Location of withdrawal of life support treatment

Treatment withdrawn in the operating room (OR):

In this option:

• The intensive care team, physicians and nurses currently responsible for both the patient and for the withdrawal of treatment, remain in the OR until the declaration of death;



- The OR is occupied (together with one or more surgical teams) for at least 3 hours;
- The patient is transferred to the OR before the withdrawal phase, which is uncomfortable and inconvenient for the family, if they are present, with a risk of death during the transfer and the impossibility of organ recovery if the distance between the ICU and the OR is too long (excessively long circulatory arrest);
- Surgical preparation (asepsis of the skin and surgical draping) occurs at arrival at the OR, before death;
- The OR must be reorganized to allow family members to be present until the patient is declared dead, a point that must be stipulated in the information booklet they receive,
- The patient is transferred back to the ICU (occupying a part of it until death is declared) if death does not occur in the time planned.

#### Treatment is withdrawn in the ICU without using NRP:

#### This option is not recommended because it involves:

- Very urgent transfer to the OR once death is declared and the refusal register has been queried
- an OR located very close to the ICU
- Significant prolongation of warm ischemia, possibly harmful for kidney grafts, so that the expected results will not match those recorded and reported to the potential recipients
- Contraindication to liver and pancreas recovery, due to absence of NRP.

### Treatment is withdrawn in the ICU and uses NRP:

In this option:

- The occupation of the OR is shorter;
- The OR transfer occurs with functional NRP underway;
- The kidney and liver recovery teams have more time to remove the organs and cold ischemia is delayed for a duration equivalent to that of the NRP duration, for at least 1 hour to a maximum of 4 hours (measured from the start of NRP at vessel clamping and organ washout);
- Rapid transfer to the OR as soon as the NRP is running, if lung recovery is planned.

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# 4) Ischemia times: definition and limits

The definition of these phases is very important (see the definitions in section I.B.2) because the length of the phases of hypo- and no organ perfusion are a major prognostic factor for organ viability after transplantation.

#### Incidents during NRP

It is imperative to take into account, in the calculation of the duration of asystole, any NRP incident leading to an added period of hypoperfusion (e.g., accidental decannulation, poorly placed cannulae or balloon, inadequate NRP flow). The incident must be immediately reported to the *Agence de la biomédecine* and to the transplant teams and must be reported in CRISTAL Green (*Agence de la biomédecine* tool for reporting incidents). The total nonfunction or dysfunction time of the normothermic perfusion must be subtracted from the normothermic perfusion time (NRP) and added to the asystole time. Asystole delay that is too long can make the liver, the pancreas, and/or the kidneys unusable by exceeding total warm ischemia time.

# <u>Table summarizing the charges in donor age and ischemia time according to organ (as of 18/06/2019).</u>

	LIVER KIDNEYS		KIDNEYS		PANCREAS
Agonal phase	≤ 3 hours				
Donor age	< 71 years	< 66 years	≥ 66 years < 71 years	< 71 years	< 66 years (< 49 years for the vascularized pancreas)
Functional warm ischemia	≤ 45 minutes				≤ 30 minutes
Asystole (circulatory arrest)	≤ 30 minutes	≤ 45 minutes	≤ 30 minutes	≤ 90 minutes	

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#### In conclusion:

The procedure fails if circulatory arrest does not occur in the 3 hours after treatment withdrawal.

If circulatory arrest occurs in the 3 hours after WLST, total asystole time must not exceed:

	Donor age			
Organs	< 66 years	≥ 66 years and < 71 years		
Kidneys	45 minutes	30 minutes		
Liver	30 minutes provided that the functional WIT $\leq$ 45 minutes			
Lungs	90 minutes			

For pancreas recovery, the functional WIT must not exceed 30 minutes.

The decision to stop the donation procedure if circulatory arrest does not occur in the time allowed and the decision to not recover one or more organs after death in cases exceeding critical WIT are the responsibility of the organ procurement organization team. The OPO team and the ICU team jointly inform the family.

The OPO team is in charge of monitoring hemodynamic and oximetric indicators during the agonal phase. Procedure sheet n°4 describes the various times and indicators for this monitoring.

Any operating incident/malfunction during NRP must be reported to Agence de la biomédecine, the surgical recovery teams, and the transplant teams.



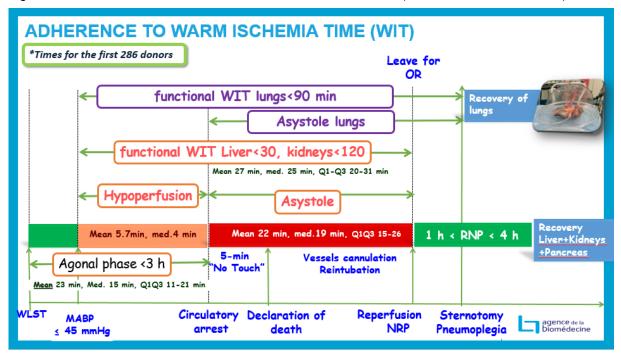


Figure 1: Warm ischemia times observed between 2015 and 2018 (mean, median, Q1 and Q3).

#### E. Declaration of death

The occurrence of circulatory arrest is monitored by invasive measurement of arterial blood pressure. The diagnosis of death by circulatory arrest involves:

- the observation for 5 minutes, without any medical intervention at all (the so-called "no-touch period"), of the absence of spontaneous hemodynamic activity or cardiac efficacy by the disappearance of arterial pulsatility, recorded with an arterial line or echocardiography;
- clinical signs of brain death must also be sought.

This information must be included in the patient's file.

The death report is signed by the ICU team physician in accordance with decrees 1232-1 and 1232-3. The death report is that mandated by the decree of 2 December 1996 (32).

No resuscitation maneuver, even intended to limit the consequences of organ ischemia, shall be undertaken.

This 5-minute "no-touch" period was selected because no cases of self-resuscitation have been described in these conditions more than 65 seconds after the circulatory arrest.

Use of continuous ECG recording has been abandoned, because electrocardiographic activity can persist for several minutes after the start of mechanical asystole (complete absence of efficacious ventricular contraction) and can needlessly prolong the WIT.

# After the declaration of death, it is mandatory to query the national refusal register, which the donor coordinating team does by contacting the *Agence de la biomédecine*.

Procedure sheet n°5 describes the declaration of death and the national refusal register query.

# Part III: IN SITU NORMOTHERMIC REGIONAL PERFUSION, ORGAN RECOVERY, AND METHODS OF PRESERVATION

# A. Methods for preserving organs after the declaration of death and before recovery

After receipt by the donor coordination team of confirmation that national refusal registry does not record any opposition by the patient.

# 1) Preservation of the airways if lung recovery is planned

If the qualification assessment and WIT allow, lung recovery is envisioned and requires, after the declaration of death and the national refusal register query, re-intubation (when applicable) and the resumption of assisted ventilation to ensure the re-expansion and oxygenation of the lungs before transfer to the OR, as rapidly as possible.

Procedure sheet n°7 describes the reventilation procedure.

# 2) No use of NRP

The non-use of NRP means only lung recovery is possible.

In the absence of NRP, recovery is not authorized of either the liver or the pancreas. Kidney recovery without use of NRP is not authorized unless it is planned in the local protocol, and it is, in any case, not recommended. The recovery and transplantation of kidneys, after a super rapid recovery without NRP, presents two problems: the prolongation of WIT, and the fairness of the information provided to recipients about transplantation results; these results are based on data from the first four years of this French program, with 100% of procedures performed with NRP.

This procedure is possible only if the withdrawal of life support treatment takes place near or in the OR and complies with the WITs recommended by this protocol.

# 3) Setting up NRP

NRP applies the principle on which ECMO (extracorporeal membrane oxygenation) is based. Its objective is to extract and oxygenate the blood while maintaining its temperature and then reinject it. Oxygenation takes place through a membrane oxygenator where the exchange of  $CO_2/O_2$ ) occurs, like the alveolar exchange of these gases. The FiO<sub>2</sub> (inspired oxygen) of the oxygenator ventilation gas is then selected and monitored. Blood circulation is ensured by the vortex effect of a centrifugal pump with non-pulsatile flow. The blood temperature is chosen and managed by a thermal regulator. Optimal flow is obtained by using large femoral vessel cannulae. Blood is normally taken via a cannula introduced into the femoral vein and reinjected by a second cannula introduced into the femoral artery. Systemic anticoagulation limits thrombosis in the tubing. An intraaortic occlusion balloon makes it possible to not revascularize the supraceliac region, by limiting this circulation to the abdominal area.



NRP enables treatment to be withdrawn in the ICU, to avoid an emergency transfer to the OR when death is pronounced (unless lung recovery is planned) and to recondition the abdominal organs normothermically. Many studies, principally English, Spanish, and recently French, have demonstrated the interest of in situ oxygenated reperfusion, that is, NRP for deceased donors after circulatory arrest (17–19,33).

A detailed procedure sheet n°8 describes how to perform NRP.

In France, pre-mortem vessel cannulation is prohibited: cannulation is allowed only after death is declared.

To reduce the time between circulatory arrest and normothermic organ reperfusion and to reduce the deleterious impact of a too-long WIT, the day before WLST the intensivist places one both a venous and an arterial central catheter, percutaneously, via the femoral vessels (i.e., central lines). The venous line is used to perfuse drugs (antibiotics, analgesia, etc.) and the arterial line for the invasive monitoring of arterial pressure during the agonal phase.

After death is declared, these small central catheters are replaced by a venous and an arterial cannula, by the intensivist or the surgeon, in intensive care unit. Cannulae are larger than the catheters and more appropriate for obtaining an adequate flow of NRP.

At the same time, the descending thoracic aorta is occluded by an intra-aortic balloon before the normothermic regional perfusion is started. The intra-aortic balloon is introduced through a femoral artery, either by the arterial cannula (using the Edwards double lumen cannula), or by another new contralateral arterial cannula.

After institution of NRP and possibly a final "farewell" by the family, the donor is transferred to the operating room so that organ recovery can start.

In lung recovery, warm ischemia of the bronchi can be prevented by placing the intraaortic occlusion balloon high enough in the aorta that NRP can perfuse the bronchial artery branches of the intercostals.

The modes of monitoring NRP as well as of optimizing normothermic perfusion are described in procedure sheet n°9.

It is essential that each center participating in this activity and choosing to use NRP master this technique perfectly.

When withdrawal of life support treatment is envisioned for patients with circulatory assistance (ECMO/ECLS), the procedure remains feasible, by using the cannulae for it already in place. This technique is detailed in procedure sheet n°10.



# B. Organ and tissue donation

# 1) Process for DCD kidney procurement and hypothermic perfusion

When all the conditions for DCD kidney procurement have been met, the technique used is the same as that for kidney recovery for DBD. The different steps of the surgical management of the donor and the conditions of transplantation are explained in procedure sheets n°11–13 and 17. It is recommended but not mandatory to perform the perfusion and wash out the kidneys with an extracellular preservation solution containing colloids.

When kidney recovery takes place, it is also necessary to:

- manage any kidney biopsies, if needed,
- ensure the graft's traceability,
- complete the Kidney packing slip
- ensure that the body is returned *ad integrum* to the family.

Retrospective analysis of most cases of primary nonfunction during these first four years has confirmed that the grafts appeared purplish or badly discolored. It is therefore essential that the procurement surgeon describe in detail the macroscopic appearance of the kidneys on the Kidney shipping slip and report any anomalies to the procurement coordinator and to the *Agence de la biomédecine*.

From the pathophysiologic perspective, machine perfusion of the kidneys makes it possible to reduce the rate of delayed function, by diminishing intrarenal vasoconstriction, improving perfusion of the renal cortex and expulsion of microthrombi from both the renal cortex and the medullary microcirculation, maintaining intracellular pH, limiting tissue edema, contributing metabolic substrates, and eliminating the products of catabolism. The French experience of the perfusion of grafts from DBD, published in 2019, concluded that ex vivo hypothermic perfusion diminished the risks of delayed graft function and graft failure at one year, as well as time to first hospitalization (21).

Because countries using controlled DCD kidney grafts on a large scale consider them to be from "expanded criteria" donors, this protocol mandates the use of machine perfusion. It must take place for at least two hours. This 2-hour period was selected by the experts on the steering committee as the minimum period required to be able to hope for a benefit from the perfusion.

#### If the machine does not work or arterial cannulation is impossible:

- The donor coordination team shall immediately alert the coordination/regulation office of the Agence de la biomédecine.
- > If at least one of the 2 grafts can be put on the machine for perfusion:
  - The donor coordination team shall communicate the contralateral kidney's resistance values.



- Preserve and graft the non-perfused kidney locally
- Use the perfusion machine for the kidney graft that must travel.
- > The Agence de la biomédecine shall alert the kidney transplant teams involved.
- The kidney transplant team commits itself to the shortest possible CIT (ideally less than 12 hours), subject to a detailed and reassuring description of the graft at the moment the organs are recovered and an asystolic period ideally less than 30 minutes due to the lack of data for the resistance of the kidney on the machine.

The protocol for machine perfusion of kidneys is explained in procedure sheet n°13.

# 2) Process for DCD liver procurement

When all the conditions for DCD liver procurement have been met, the recovery technique implemented is the same as that for recovery of the liver for DBD. The different steps of the surgical management of the potential donor as well as the conditions for transplantation are explained in procedure sheets n°11, 14, and 18.

It is recommended but not mandatory to perform the perfusion and wash out the liver with an extracellular preservation solution containing a colloid. If the liver is recovered, it is also necessary to ensure:

- the performance and immediate reading of the liver graft histology (mandatory),
- the traceability of the liver graft,
- that the body is returned *ad integrum* to the family.

The procuring surgeon must pay attention to the macroscopic appearance of the graft, especially for the oldest age groups and when the asystole time has been maximal.

# 3) Process for DCD pancreas procurement

The pancreas is an organ very sensitive to warm ischemia. Moreover, prolonged cardiac arrest is often an obstacle (contraindication) to the recovery of the pancreas for DBD.

Imperatives due to the need to limit warm ischemia:

- not more than 30 minutes should elapse between the moment when the MABP is less than 45 mmHg and the start of NRP;

- if the liver graft is not recovered for transplantation because of acute or chronic liver damage, the pancreas cannot be used for transplantation of either the vascularized pancreas or the islets of Langerhans.

The recovery technique has already been the topic of collaborative work by the Pancreas Transplant Working Group and is described in detail in the *Agence de la biomédecine's* technical documents on multiorgan recovery. This document is the reference (Appendix) but some key points of the surgical technique and assessment of the graft quality must be reviewed in the framework of recovery for DCD.



Placement of arterial and venous cannulae must be particularly prudent: both the arterial and venous iliac axes can be used for preparation of the pancreatic transplant.

The procurement begins by a broad approach to the abdominal cavity.

Just as for recovery for DBD, the procedure continues by the administration of 300 IU/kg IV of heparin by a flash perfusion just before perfusion of the preservation fluid.

The extracellular organ preservation solution containing a colloid is then administered directly via the NRP arterial cannula. Concomitantly the abdominal cavity is chilled by the placement of ice.

The surgical recovery technique is described in procedure sheets n°11 and 15.

The phase of inspection and palpation of the organ during and at the end of its recovery are essential to qualify the graft before the transplantation. Their aim is to recognize ischemic areas or any pancreatic edema.

The requirements to be met to recover a pancreas-kidney graft are presented in procedure sheet n°19.

# 4) Process for DCD lung procurement and their ex vivo rehabilitation

### a. Procurement

The procurement involves the two-lung block and does not differ fundamentally from that performed for DBD; parenchymal and esophageal wounds must be avoided as much as possible. The lungs are recovered inflated if possible, with a clamp in place on the trachea. It is nonetheless appropriate to section the cervical trachea just under the cricoid cartilage and the pulmonary artery trunk immediately above the pulmonary valve. The left atrial collar is made in the same way as for in situ separation of the heart and lungs when the heart is also recovered. It can be necessary to recover a segment of the descending thoracic aorta if the pulmonary artery trunk is not long enough.

With NRP, extraction of the lungs requires:

- either that a transesophageal ultrasound with a contrast challenge has been performed to rule out any interatrial communication and enable continuation of abdominal normothermic perfusion, as described with venous cannula positioned in the inferior vena cava (IVC);
- Or, most often, in the absence of an echocardiography with bubble test or when this test shows an atrium septal defect (ASD), that double cannulation be planned of the IVC and the superior vena cava (SVC) when opening the right atrium (+ withdrawing the femoral cannula) to avoid air intake when opening the atrium in the extracorporeal recirculation device.



The pneumoplegia is then performed with the NRP in place and functioning for the intraabdominal organs.

Procedure sheets n°11, 16, and 20 explain the different steps of the surgical management of the potential donor as well as the conditions of the transplantation.

Double-lung grafts recovered in controlled DCD donors require an additional evaluation of their transplantability.

Although the lung is the organ that best supports warm ischemia, that imposed by the conditions of recovery for DCD is long and potentially harmful.

The use of machine perfusion versus static immersion improves the conditions of lung preservation, its rehabilitation, and the evaluation of its viability. Use of perfusion is justified by an accumulation of unfavorable prognostic factors such as extended stays in the ICU, exceeding a week on average, the very frequent presence of radiologic pulmonary abnormalities, and asystole that can reach 90 minutes.

# b. Assessment of lungs recovered for controlled DCD donors

<u>Ex vivo lung perfusion</u> (EVLP) comprises perfusion, ventilation, and an ex vivo evaluation of the lung grafts recovered. It can provide critical assistance in assessing lung grafts from controlled DCD donors. It enables the evaluation before transplantation of grafts from controlled DCD donors with a long agonal phase and prolonged WIT.

More than 10 years of worldwide experience with controlled DCD donors show that these are good grafts, with results similar and even superior to those of standard transplants (34). The clinical use of controlled DCD donors does not require systematic use of EVLP, and these results are obtained with or without EVLP use, depending in particular on the duration of the agonal phase.

Important research from European, Australian, and US laboratories has shown that the tolerable WIT before recovery ranges from 60 to 90 minutes and that the duration of the agonal phase is an important factor in the quality of the lung graft (35–40).

Today, there are no clear data attesting that EVLP should be systematic for all lungs recovered from DCD donors because lung function can be assessed before care is withdrawn in the ICU. On the other hand, if the agonal phase is prolonged, the reliability of that assessment diminishes strongly. The lungs can have been impaired by a state close to brain death or been damaged during the withdrawal of care by prolongation of the agonal phase and of hypotension or by aspiration after extubation. A retrospective study comparing



transplantations from DCD grafts with or without EVLP showed no difference in survival, but the durations of hospitalization, ventilation, and ICU stay were shorter for these reconditioned grafts (41).

The particularity of the French protocol is its systematic use of NRP for liver, pancreas, and kidney grafts. In these conditions, lung recovery is delayed and WIT prolonged. Consequently, the systematic use of EVPP for all of these grafts allows an intermediate stage for evaluation and thus the transplantation of these lungs in the optimal safety conditions.



# 5) Tissue procurement

Tissue procurement is of course integrated into the controlled DCD program. The specific procedure sheets must be incorporated into the local protocol, in collaboration with the professionals responsible for this activity in the hospital. More than 170 corneas have been recovered from controlled DCD donors since the program began, and almost 60 donors provided cardiac valves and vessels in 2017 and 2018.

Table TT2 - Number of procedures recovering tissue from deceased donors according to the
type of tissue and of donor in 2018

Number of deceased donors from whom tissue was recovered	DCD tissue donor	DBD tissue donor	Uncontrolled DCD donor	Controlled DCD donor	TOTAL
Corneas	4716	797	11	75	5599
Skin	€ 111	195	3	14	323
Bones	7	85	1	2	95
Vessels	8	341	8	28	385
Cardiac valves	26	180	3	40	249

# Table TT1 - Number of donors from whom tissues were recovered by donor type in 2018compared with 2017

Number of donors from whom tissues were recovered	2018	2017
DBD donors	997	1021
Uncontrolled DCD donors	12	23
Controlled DCD donors	99	70
DCD tissue donors	4762	4862
TOTAL DECEASED DONORS from whom tissues were recovered	5870	5976
TOTAL	5870	5976

# PART IV: CONDITIONS OF ORGAN TRANSPLANTATION

# A. Kidney transplantation

# 1) Results of kidney transplants from controlled DCD donors

These results are considered satisfactory and are globally similar to those from DBD expanded criteria donors (42–44). Snoeijs et al. have even showed a survival benefit for recipients of kidney grafts from DCD donors compared with patients eligible for transplantation but who remained on dialysis awaiting a standard-criteria DBD donor (45).

Well-established risk factors such as prolonged WIT or CIT, an HLA-incompatible donor, previous transplantations, and elevated doses of calcineurin inhibitors in the postoperative period compromise the results of this type of graft.

Organic kidney injuries are secondary to and correlated with functional and total WIT, that is, with the period of renal hypoperfusion once hypotension reaches a critical stage, and especially with the period of asystole. Warm ischemia is only the first assault of a more complex process called ischemia/reperfusion injury (IRI).

This WIT is ineluctable and intrinsic to organ recovery after circulatory arrest.

<u>The donor selection criteria</u> were chosen to limit the factors promoting poor tolerance of prolonged warm ischemia, such as advanced age, preexisting vascular injuries induced by diabetes or chronic hypertension, or preexisting acute or chronic kidney injury/disease.

The criteria for the <u>selection of recipients</u> are also important for the success of the graft from controlled DCD donors; HLA-compatible recipients awaiting a first kidney graft should be favored, and, if possible, the anticipated WIT should be short. Data from the UK transplant register show significantly lower graft survival after retransplantation from controlled DCD donors than from DBD donors, with a difference of almost 25% at 5 years (summers Lancet 2010).

<u>Finally, cold ischemia must be as short as possible</u>; the negative impact of this variable on graft survival has been clearly demonstrated (46). Specifically, this survival decreases from 91% to 81% at 3 years according to whether CIT is less than 12 h compared with 12 h or more.

# 2) The results of the first controlled DCD kidney grafts transplanted in France between 2015 and 2018

These results are excellent and similar to those obtained from standard DBD donor (2019 annual report Agence de la biomédecine).

The primary nonfunction rate of 2.3% is similar to that observed from standard DBD donors (3.5%), but in particular the rate of delayed graft function is only 16.5%. This rate is significantly lower than that observed for standard DBD donors (25.7%) and in the international literature (50 to 80%). It represents major savings in terms of posttransplant dialysis and shorter hospitalization. The short CIT — a mean of 10.3 hours (median 9 h) — is evidence of the strong involvement and availability of transplant teams. The mean glomerular flow rate, estimated by the MDRD formula at hospital discharge, is 48 ml/min and at 1 year, 75% of the recipients with a functional graft have an eGFR equal to or greater than 50 ml/min with a mean creatinine level of 128  $\mu$ mol/l.

Graft survival at one year is 95.1% (Cl95% 92,8% - 96,7%), similar to that observed from standard DBD donors younger 94,4% (Cl95% 94.1% - 94.7%).

# 3) The criteria chosen for the national protocol

#### **Recipient selection**

- Patients who have been fully informed and signed the information letter
- Adults (as we await the specific guidelines for the recovery and transplantation of pediatric controlled DCD kidney transplantation)
- Patient awaiting a first organ transplantation of a kidney only
- With an up-to-date CRISTAL Recipient immunological file of results for anti-HLA antibodies tested by a sensitive technique and automatic transfer of the HLA data accepted. The aim of this update is:
  - To avoid late refusal of HLA-incompatible kidney grafts
  - To avoid the transplantation of HLA-incompatible kidney grafts, which have poorer posttransplant results when WIT is prolonged.
  - To be able to perform virtual crossmatch as soon as the HLA typing of the proposed graft is available, due to regular immunological follow-up and potentially to not have to await the cytotoxic crossmatch to start the transplantation and thus reduce CIT.
- Patient has been duly informed and has consented (informed consent before the procedure: see procedure sheet n°17). Although the results of transplantations from DCD donors have very clearly improved over the years and now appear similar to those from DBD donors, informing and obtaining informed consent from the recipient remain essential.
- Prudence about recipients with predictable surgical difficulties that can markedly increase the recipient WIT (anastomosis time): patients with severe chronic vascular disease or a high BMI, when the graft has already been subjected to one or several periods of warm ischemia before its procurement.

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- Donor age: < 71 years
- Special attention to cumulative vascular comorbidities in an elderly donor (47–49).
- Normal renal function:
  - No chronic kidney disease or acute kidney failure (AKF) before withdrawal of life support treatment began (Attention: AKF = contraindication)
  - $\circ$  Clearance  $\geq$  60 ml/min; with no significant proteinuria
- Agonal phase: < 180 minutes
- Asystole phase ≤ 45 minutes for donors younger than 66 years
- Asystole phase ≤ 30 minutes for donors aged 66-70 years inclusive
- Normothermic regional perfusion
- Machine perfusion is mandatory
- Viability criteria to verify before starting transplant:
  - Macroscopic appearance of kidneys at recovery,
  - Resistance profiles during ex vivo hypothermic perfusion. The members of the steering committee considered that there is not enough evidence in the literature to impose a threshold machine resistance value that rules out kidney transplantation. On the other hand, they did recommend recording the values at connection, at 30 minutes, at 2 hours and at disconnection, and making the decision on the criteria as a whole (donor age, quality of NRP functioning, asystole time, known donor comorbidities, etc.).

## Cold ischemia

The kidney transplant team agrees to perform transplantations on an emergency basis at any hour of the day or night to obtain the shortest CIT possible,

- Ideally less than 12 hours
- In all cases less than 18 hours.

Teams that accept grafts must commit to meet this CIT, or they will be excluded from the program (major criterion clearly noted in the agreement).

## Immunosuppressant treatment:

The initial rationale, drafted in 2013, based on the literature of that period, made mandatory the use of depleting induction and the delayed introduction of nephrotoxic calcineurin inhibitors, underlined:

- its positive role in limiting IRI (lymphocyte adhesion and infiltration in response to ischemia and anoxia during the phase with no cell perfusion) and the incidence of delayed graft function,
- Decrease in the incidence of rejection (46),
- Reduction in nephrotoxicity injuries due to calcineurin inhibitors, which are introduced later and at smaller doses, in the context of delayed graft function and endothelial distress of ischemic origin (increased immunogenicity).

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<u>The use of lymphocyte-depleting induction by antithymocyte globulin (ATG)</u> is no longer required. This criterion was rediscussed at the national steering committee meeting in November 2018. The steering committee nephrologists proposed to modify its mandatory nature while recommending its use. The rationale for ATG use is based on:

- A reduction in the incidence of acute rejections.
- The possibility of delayed introduction of calcineurin inhibitors (CNI) in patients with grafts potentially more sensitive to IRI and to the nephrotoxicity of CNI.

Most French teams have continued to follow these recommendations, with more than 90% of the 504 grafts performed since the beginning of the controlled DCD program treated with depleting induction. The pertinence of this strategy is confirmed by the good results, with in particular a low incidence of delayed graft function of around 9%.

We must nonetheless underline the low level of evidence about the benefit of delayed introduction of CNIs, as the British guidelines point out (50,51).

In this context, several teams have reported their experience with transplantations from DCD grafts, some patients received induction by anti-RIL2 antibodies. An English team has thus published the results of a single-center cohort of 112 transplantations from controlled DCD grafts; 25 (22.3%) recipients underwent induction by an anti-RIL2 monoclonal antibody (basiliximab or daclizumab). This induction was reserved for patients with a history of neoplasms or hematologic abnormalities. Induction by anti-RIL2 antibodies was not significantly associated with a higher incidence of DGF. On the other hand, this type of induction and a donor age greater than 60 years were independently associated with a higher risk of graft loss at 5 years (52).

In conclusion, the immunosuppressant treatment must include:

- Induction by ATG, preferably. Induction by anti-RIL2 antibodies is possible, depending on the recipient's history and fragility.
- The introduction of CNIs, which can be delayed
- Association with an antimetabolite
- Corticosteroid therapy, according to the center's usual procedure.

<u>A preimplantation kidney biopsy</u> is strongly recommended in all cases, but it is difficult to expect it to be read immediately to decide about the graft, given the short CIT. Nonetheless, we note that these recoveries are generally performed at the end of the morning or the early afternoon, which makes this analysis possible during working hours for sites that want it. Some studies recommend it for elderly donors or those with cardiovascular comorbidities (53,54).

## 4) Kidney allocation rules

The donor's HLA must be typed from a peripheral blood sample taken after the interview with the family, should none of them have indicated opposition by the patient. The list of potential recipients can thus be established before the procurement and the virtual crossmatch performed as soon as a graft is proposed.

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If the virtual crossmatch, performed according to the procedure validated by the Scientific Committee of Agence de la biomédecine, is negative and the kidney graft is attributed by the Agence de la biomédecine the transplantation can take place without awaiting the cytotoxic crossmatch, which enables a substantial reduction in CIT. The cytotoxic crossmatch can be performed as soon as the lymph nodes and spleen segments have been recovered during the surgery, or retrospectively during working hours if the decision to graft this organ was based on the virtual crossmatch result.

Some conditions set in this protocol influence kidney allocation system:

- Choice of a pre-identified recipient who agreed to receive a graft from an controlled DCD donor,
- Choice of a recipient whose immunological record is up to date, with the automatic transfer of HLA data accepted,
- Irreducible CIT

Because of the constraints associated with CIT, it is preferable to limit graft transfers that depend on train schedules and to exclude from the selection assistance list the patients with a national priority. On the other hand, there are no exclusions for patients with a national priority for extreme urgency or hyperimmunization. If the allocation score identifies these recipients in the first ranks, the team is free to accept the graft for these patients, <u>as long as virtual crossmatch results are available and negative.</u>

Kidneys allocation system if controlled DCD donors:

- No proposal for national priority
- The teams that accept the graft (or grafts) agree to:
- Perform a virtual crossmatch that must be negative for the HLA loci A, B, DR, and DQ beta, according to the protocol validated by the Medical and Scientific Council in 2015, on the basis of regular and consistent immunological follow-up.
- To continue machine perfusion of the kidneys until transplantation, with regular evaluation of renovascular resistance at connection, at 30 min, at 1 h and at disconnection). The perfusion monitoring parameters must be entered in CRISTAL.
- To adhere to the CIT of 18 hours maximum (and ideally 12 h maximum).
- The kidneys allocation rules are based on the application of the national kidney allocation system, which takes into account waiting time on the waiting list, time since initiation of dialysis, number of HLA incompatibilities between donor and recipient, age differential between donor and recipient, and potential matched donors (Estimation of potential well matched donors (PMD) by simulation software). The <u>distance between the recovery team and the transplantation team</u> is considered more strongly than for the attribution of DBD kidney grafts to limit the transportation time for grafts over long distances, in time slots unfavorable to rail transport. Should a perfusion machine fail to work, the graft with the longest cold ischemia time should be favored, that is, the graft attributed at the national level.



- If the kidney recovery takes place in the hospital of the kidney transplant team or in a hospital belonging to the recovery network, one of the 2 kidneys recovered is considered the local graft. The kidney grafts is attributed by the *Agence de la biomédecine* according to the national kidney allocation system (NKAS), in the same ABO blood group, solely for patients meeting the selection criteria of the protocol, with the possibility of a waiver of the ranking for the recipient selected, a waiver that must be justified in writing to the *Agence de la biomédecine* within 48 hours.
- The second kidney graft is attributed according to the NKAS, to a patient meeting the protocol's selection criteria, within the same ABO blood group, and then by compatible ABO blood group.
- High anti-HLA immunization estimated by calculated panel-reactive antibodies (cPRA), is not an exclusion criterion for kidney allocation, especially if HLA compatibility between the donor and recipient is very good.
- At the moment that the graft offer is accepted, the transplant team agrees to perform the transplantation in a CIT of less than 18 hours, and if possible less than 12. If a team repeatedly exceeds this limit and fails to adhere to the protocol, the Agence de la biomédecine reserves the right to exclude this team from the protocol until it has implemented the corrective measures necessary.

Kidney grafts can be offered as a pair, according to the usual criteria.



In conclusion, for kidney grafts:

The kidney can be transplanted if

- time since circulatory arrest ≤ 30 minutes, if the donor age ≥ 66 years
- time since circulatory arrest ≤ 45 minutes if the donor age < 66 years

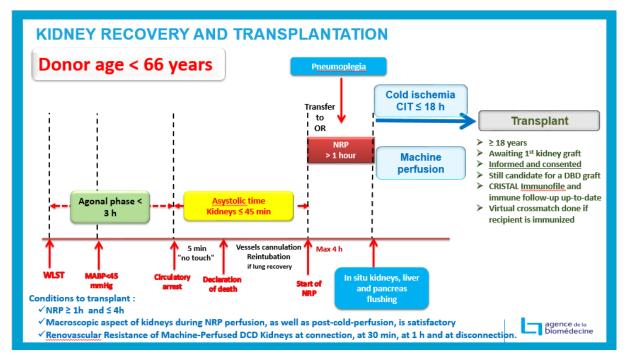
Conditions to transplant:

- NRP  $\geq$  1h and  $\leq$  4h
- Macroscopic aspect of kidneys during NRP perfusion, as well as post-cold-perfusion, is satisfactory
- Renovascular Resistance of Machine-Perfused DCD Kidneys at connection, at 30 min, at 1 h and at disconnection

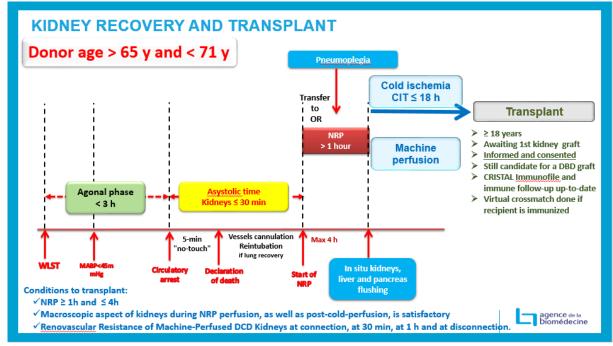
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Even if liver recovery is not planned, transaminase kinetics (≥ 3 samples) under NRP can be tested because it is very informative about the quality of the normothermic perfusion.

Diagrams summarizing the criteria permitting kidney transplantation when the graft comes from a controlled DCD donor, stratified by donor age







## B. Liver transplantation

## 1) Results of liver transplantation from controlled DCD donors

Grafts from controlled DCD donor account for more than 20% of the liver transplantations in the Netherlands, the UK, and Belgium. Results of liver transplantations from controlled DCD donors are considered satisfactory and globally similar to those of expanded criteria DBD donors and DBD donors older than 60 years (55).

The great majority of the studies published are retrospective, single-center studies, sometimes comparative. These articles report a global increase in the risk of graft failure on the order of 30%, because the liver is the most sensitive of the three organs (with kidneys and lungs) to warm ischemia. The studies show that primary nonfunction and ischemic-type biliary lesions (ITBL), rates are associated not only with donor age (threshold of 60 years in most studies), but especially with a WIT that cannot exceed 30 minutes and a cold ischemia that must not exceed 8 hours (56–62).

To give an order of magnitude for the comparison of controlled DCD versus DBD transplantations, we cite data from Abt et al. (56). The DCD transplantations have:

- Higher rate of higher primary nonfunction (11.8% versus 6.4%, *P*=0.008)
- Excess early mortality (first 60 days)
- Higher rate of liver dysfunction and gall bladder complications
- A higher retransplantation rate (13.9% versus 8.3%, P=0.04)

<u>The risk factors for graft failure</u> by univariate and then multivariate analysis according to the initial period are:



- <u>Cold ischemia time</u>: major independent risk factor with a 17% increase in risk of graft loss for each additional hour or a graft loss rate during the first 60 days of: 10.8% if CIT < 8 hours, 30.4% if CIT between 8 and 12 hours and 58% if CIT > 12 hours.
- <u>Patient's pretransplant clinical status</u> (mechanical ventilation and/or use of inotropic agents, associated organ failure). It is preferable to attribute these grafts to less hemodynamically unstable recipients to optimize resumption of graft function and avoid an added period of hypoperfusion of the liver.

## The donor's history and liver status:

- The presence of acute liver failure before the start of withdrawal of life-sustaining treatment, of chronic liver disease, and moderate or severe hepatic steatosis are contraindications.
- To better evaluate the steatosis and fibrosis: A liver biopsy read on an emergency basis is mandatory (recovery is organized in the daytime). The hepatic steatosis level must be less than 20% and the fibrosis stage < F2 in this situation involving prolonged exposure to warm ischemia. This level may be revised in a subsequent version of the protocol when the use of machine perfusion of liver grafts enables organ rehabilitation and the ability to test its viability.</li>

## Warm ischemia time and normothermic regional perfusion (NRP)

Several authors recommend NRP to attempt to limit the harmful effects of warm ischemia. In the past three years, several publications by British and Spanish teams have demonstrated significant improvement in the results of controlled DCD liver transplants when in situ NRP has been used after the declaration of death (17–19). They observed a decrease in the number of cases of primary nonfunction but especially in the number of cases of ischemic-type biliary lesions (ITBL), the principal medium-term complication of liver grafts from DCD donors.

The transaminase kinetics recorded during NRP are considered indirect markers of liver damage in the French and Spanish uncontrolled DCD programs and essential for the Maastricht 3 protocol.

## 2) The results of 123 liver transplantations performed from 2015 through 2018

They are excellent and similar to those of a cohort of adult recipients awaiting a first single graft and receiving an optimal liver graft.

There were 4 cases of primary nonfunction, 3 cases of graft loss after resumption of function (2 with vascular complications), and 10 deaths, principally by de novo or recurrent cancer. Three cases of primary nonfunction occurred after failure to adhere to the procedures for selection of the graft or recipient (accidental ABO-incompatible graft, malposition of the occlusion balloon and very high transaminase kinetics, and recipient with a high MELD score with portal vein thrombosis).

The professionals identified few or no cases of reperfusion syndrome and a low rate of early graft dysfunction (20%); its grade was moderate due to the systematic use of NRP.



As of now, there has only been one case of ITBL among the first 123 controlled DCD liver grafts, associated with exceeding the authorized asystole time (due to NRP dysfunction).

Patient survival at 1 year is 95.5% and similar to that observed with DBD donors.

## 3) The criteria chosen for the national protocol

- Ability to transplant the graft on an emergency basis at any hour of the day or night to obtain a CIT < 8 hours.</li>
- For graft selection:
  - Donor aged < 71 years
  - No acute liver disease at the withdrawal of life-sustaining treatment (acceptable levels of transaminases less than 4x the upper limit of normal) and without chronic liver disease
  - Agonal phase: < 180 minutes
  - Asystolic phase ≤ 30 minutes
  - Functional WIT ≤ 45 minutes
  - Only with NRP
  - With non-rising transaminase kinetics under NRP, tested at a minimum of 3 time points, with values less than 4 ×the upper limit of normal
  - Only if the preimplantation biopsy confirms the absence of chronic liver disease and finds steatosis ≤ 20% and a fibrosis stage < F2.</li>
- To select recipients without added risk, enabling the rapid transplantation of the liver graft and the tolerance of liver reperfusion syndrome, the following criteria are applied:
  - Recipient, aged at least 18 years and less than 66 years,
  - Awaiting a first transplantation,
  - Recipients considered not too sick to cope with post-reperfusion syndrome not ventilated, no inotropic agents ...)
  - No major surgical history and no portal vein thrombosis; To minimize cold and recipient ischemic time (anastomotic time), patients where the recipient hepatectomy was predicted to be difficult were excluded
  - With a MELD score  $\leq 25$
  - Patient has been duly informed and has consented. Although the results of transplantations after DCD have very clearly improved over the years, clear information for the recipient and the provision of informed consent both remain essential. This means making clear to the patient the risk of primary nonfunction as well as of ischemic cholangiopathy and early arterial thrombosis.



These measures can contribute to the improvement of results. The advantage is to target a population at a lower risk of early graft dysfunction and of primary nonfunction in a situation of prolonged and sometimes repeated warm ischemia.

## 4) Liver allocation rules

Some of the conditions set in this protocol influence the liver allocation system with the exclusion of too sick recipients, in particular hyper-emergencies. Controlled DCD liver allocation system takes into account:

- The donor's blood group.
- Eligibility criteria:
  - Recipient has been informed and has signed the information letter
  - <sup>D</sup> Awaiting a first single liver transplantation.
  - In an overall and hemodynamic condition able to support the initial graft dysfunction and to optimize graft function resumption, a MELD score ≤ 25 the day called for transplantation and not in the super-emergency category.
  - <sup>D</sup> Score aFP  $\leq$  2 at the last morphologic assessment, within the past 90 days.

Because the maximum CIT is very short, the liver is transplanted, if possible, at the local level (local or local network), by ABO blood group, to a recipient meeting the selection criteria described above.

□ CIT  $\leq$  8 hours.

If there is no recipient at a local level with the ABO blood group, the local team is asked to perform the procurement for another transplant team, to facilitate the logistic organization of the multiorgan recovery with NRP. The graft is proposed by ABO blood group to the teams closest by travel time that have recipients meeting the selection criteria described above and agreeing to adhere to the protocol and in particular to the CIT.

The recovery team, local or exterior if the local team is unavailable, must clearly understand the specificities of the surgical recovery:

- due to the NRP system
- in terms of onsite availability once withdrawal of life-sustaining treatment begins.

Agence de la biomédecine will be **systematically** informed of the identity of recipient before the transplant. This recipient must necessarily appear on the list of eligible candidates according to the mandatory criteria of the national protocol.



## In conclusion, for liver transplantation:

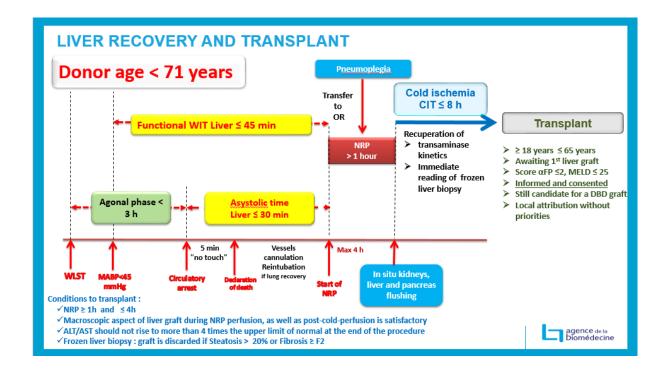
## The liver can be transplanted if — functional warm ischemia time ≤ 45 minutes

## - time to circulatory arrest ≤ 30 minutes

Conditions to transplant:

- NRP  $\geq$  1h and  $\leq$  4h
- Macroscopic aspect of liver graft during NRP perfusion, as well as post-cold-perfusion is satisfactory
- ALT/AST should not rise to more than 4 times the upper limit of normal at the end of the procedure
- Frozen liver biopsy : graft is discarded if Steatosis > 20% or Fibrosis ≥ F2

## Diagram summarizing the criteria to be met to transplant a liver graft from a controlled DCD donor



## C. Pancreas transplantation: whole-organ pancreas and islets of Langerhans

## 1) Results of pancreas transplantation from controlled DCD donors

The data from the international literature (63–68) and the recommendations of the expert advisory group on the occasion of the 6th international conference on DCD (63) concluded that the results of this type of graft are entirely satisfactory, as long as some selection criteria for donors and recipients are met (Appendix 3).



During this international consensus meeting, the principal criteria discussed were:

- > A functional WIT < 30 minutes for a whole-organ pancreas graft
- > A functional WIT < 60 minutes for grafting islets of Langerhans
- > Avoidance of donors aged 50 years and older
- Not using donors with a BMI of 30 kg/m<sup>2</sup> or more for a whole-organ graft, although they can be used for islets of Langerhans
- Use of NRP is appropriate in view of the very good results obtained in liver transplantation and those published in two series (18,66)
- ➢ Short CIT
- > Prefer local allocation to reduce CIT, and use virtual crossmatch
- For recipients: close monitoring of vessel permeability by repeated Doppler ultrasound and of pancreatic enzyme kinetics; optimization of anticoagulation.

The decree dated 1 August 2014 modifying the decree dated 2 August 2005 setting forth the list of organs authorized for recovery from DCD donors was modified on 13 April 2018 and now specifies that the organs that can be recovered are the kidneys, liver, lungs, and pancreas (10).

The CRISTAL Donor and Recipient databases have been modified to take into account the procedures specific for the recovery and transplantations of whole-organ pancreas grafts and of islets of Langerhans, and recovery of the pancreas has been authorized since November 2018, with 3 centers currently authorized.

## 2) Criteria chosen for the national protocol

After a review of the data from the international literature and the recommendation of the expert advisory group for the 6th international conferences on DCD (February 2013, Paris), the steering committee selected and the Medical and Scientific Council (CMS) of the *Agence de la biomédecine* validated the following criteria in May 2017:



## For the donor

- Aged < 66 years</p>
  - With a proposal for the whole-organ pancreas when aged ≤ 45 years and BMI < 27. Switch to proposing islet tissue if the pancreas is not taken for a vascularized graft.
  - With a proposal for islet tissue aged  $\geq$  50 years and/or BMI  $\geq$  30.
  - With the local team able to choose between the whole-organ or islet tissue if the donor is aged 45 to 49 years at most and/or if BMI ranges between 27 and 29.
- No known pancreatic disease (chronic or acute pancreatitis), no diabetes, and no chronic alcoholism before initiation of the WLST.
- Functional WIT  $\leq$  30 minutes.
- Mandatory use of NRP for at least 1 hour and no longer than 4 hours.
- No recovery of the pancreas for a graft if the liver recovery is cancelled for pre- or intraprocedure liver damage (the pancreas can be recovered if the contraindication to liver recovery is associated with a vascular anatomical anomaly).
- The lipase concentration must be less than 3 x normal in the days before the withdrawal of lifesustaining treatment and be falling.

## For the recovery and the transplantation:

- The technique for pancreas recovery in controlled DCD donors is essentially identical to that described for DBD donors. It is synthesized in procedure sheet n°18 (Appendix) with support for some important points related to the prerequisite warm ischemia and NRP use.
- Shortest cold ischemia and necessarily < 12 hours.

## For recipients:

- Awaiting a first combined pancreas-kidney transplantation or a transplantation of islets of Langerhans.
- > Aged  $\geq$  18 years, < 56 years for the combined pancreas-kidney graft.
- > Patient awaiting a first organ transplantation.
- With an up-to-date Cristal Recipient immunological file of results for anti-HLA antibodies tested by a sensitive technique and automatic transfer of HLA data. The aim of this update is:
  - To avoid late refusal of HLA-incompatible kidney grafts.
  - To avoid the transplantation of HLA-incompatible kidney grafts, which have poorer posttransplant results.



- To be able to perform virtual crossmatching as soon as the HLA typing of the proposed graft is available and potentially to not have to await the cytotoxic crossmatch to start the transplantation and thus reduce CIT.
- Patient has been duly informed and has consented.
- Prudence about recipients with predictable surgical difficulties that can markedly increase the warm ischemia time (anastomosis time): patients with chronic progressive vascular disease or a high BMI

## 3) Pancreas allocation rules

- For the vascularized pancreas: local attribution, for a patient classified as "priority", aged less than 56 years, awaiting a first organ transplantation.
- In the absence of a recipient at the local level, pancreas and kidney grafts are offered at the national level to controlled DCD eligible recipients..
- For the pancreas for islet tissue only: attribution to one of the programs authorized on a criterion of proximity and with eligible recipients on the waiting list.
- Attribution of the graft based on virtual crossmatch, signifying that the transplant teams commit to ensure that these recipients have an HLA follow-up every 3 months, with at least one Luminex Single Antigen analysis at inscription and at least two a year, if the recipient is immunized.

## SELECTION CRITERIA FOR VASCULARIZED PANCREAS TRANSPLANTATION

## Donor

#### Age < 50 years

No history of diabetes, alcoholism, or pancreatitis

No chronic liver disease or liver before withdrawal of active treatment

Lipase level should not rise to more than 3 times the upper limit of normal in the days before treatment withdrawal + kinetics descending

Functional WIT < 30 min

NRP mandatory

 AST/ALT kinetics during NRP allow assessment of ischemic damage before retrieval

Maximum CIT < 12 hours



## Recipient

> 18 years

Awaiting a first combined pancreas-kidney graft

No benefit for retransplantation

HLA file in CRISTAL up-to-day and validated • To allow Virtual crossmatch

Informed and consented

Still candidate for a DBD graft

Allocation rules: Same as for DBD grafts

Induction by ATG

agence de la biomédecine



## SELECTION CRITERIA FOR ISOLATED ISLETS OF LANGERHANS



## Donor

#### Aged < 66 years

No history of diabetes, alcoholism, or pancreatitis

No chronic liver disease or failure before withdrawal of active treatment

Lipase level should not rise to more than 3 times the upper limit of normal in the days before treatment withdrawal + kinetics descending

Functional WIT < 30 min

#### NRP mandatory

 AST/ALT kinetics during NRP allow assessment of ischemic damage before retrieval

Maximum CIT < 12 hours

## Recipient

> 18 years

Solely for patients included in authorized clinical research protocols Informed and consented Still candidate for a DBD graft

Allocation rules: Same as for DBD grafts



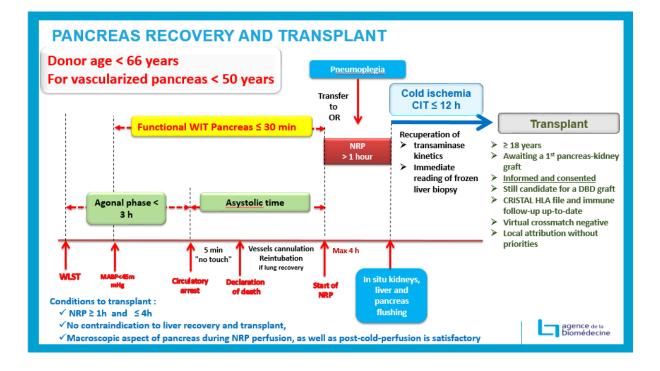


## For the pancreas graft:

The pancreas can be transplanted if the functional warm ischemia time  $\leq$  30 minutes

Conditions for transplant:

- NRP  $\geq$  1h and  $\leq$  4h
- No contraindication to liver recovery and transplant,
- Macroscopic aspect of pancreas during NRP perfusion, as well as post-cold-perfusion is satisfactory
- .





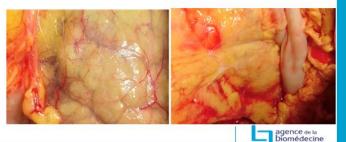
## **PROCEDURE SHEETS**

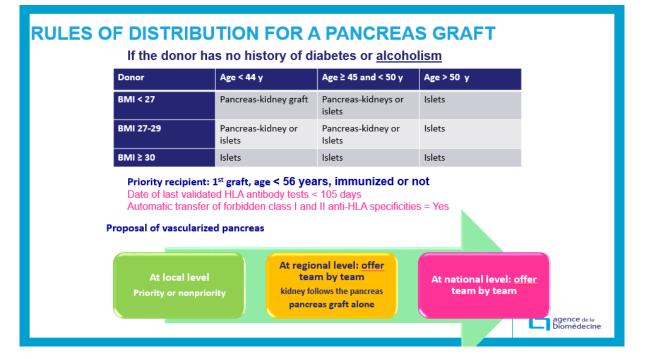
Surgical Quality Assessment Procedure

- Rapid dissection of the pancreas and the duodenum with minimum handling of the pancreas while dissecting as close as possible to the pancreas but avoiding its enveloping capsule.
- The preparation of the pancreas takes place after exposure of the IVC and the aorta, together with preparation of the liver
- Inspection and palpation: recovery stops if macroscopic signs of pancreatitis

## Heparin and preservation fluid

- Bolus of 20,000 IU when SBP ≤ 60 mmHg,
- 300 IU/kg of heparin in a flash perfusion just before perfusion of the preservation fluid.
- The extracellular organ preservation solution, which contains a colloid, is administered directly by the RNP arterial cannula.







## D. Lung transplantation

## 1) Results of lung transplantation from controlled DCD donors

The first lung transplantation using the lungs of a deceased donor after circulatory arrest dates back to 1993 in Chicago. The use of these donors developed in response to a lack of lung grafts from DBD donors. Anecdotal until 2005, transplantation from these donors has since developed in North America, Australia, and Europe (69,70).

In August 2014, lungs were added to the list of organs that can be recovered for DCD (9). Lung recovery and transplantation from controlled DCD donors were therefore authorized from the start of the controlled DCD program in France.

Evaluation of the donor is based on clinical findings, radiography, and blood gases before withdrawal of life support treatment but also on examination of the lungs after flushing. Accordingly the intervention on the recipient only begins once the lungs have been recovered and examined.

The results of lung transplantation from controlled donors have been very satisfactory. The lungs appear to tolerate warm ischemia particularly well, and better than they do the cytokine storm induced by brain death. Results of lung transplantation are similar to those observed from DBD donors according to the ISHLT registry, with an identical rate of primary graft failure, identical medium-term survival, and for the moment no difference in terms of occlusive bronchiolitis (34,71). On the other hand, the time elapsed between the withdrawal of life support treatment and the lung flush is correlated with the onset of complications. The longer the time, the higher the risk of complications (72). It has been empirically determined that a threshold of 120 minutes should not be exceeded. It rarely exceeds an hour in all of the series thus far published with these good results.

Table I: Short- and medium-term results from different lung transplantation programs using DCD (73).

Cohort	Years	Maastricht Category (MC)	n	PGD ( <i>n</i> ) ISHLT GRADE <sup>€</sup> >2	Survival % at 1 year	Survival % at 3 years	BOS (n) at 3 years
UW/Loyola [27°]	'9-'09	MC III	24	12.3%	80.4	80.4	2
St Louis [35]	'03-'11	MC III	13	4/13	84.6	47	3
Cleveland [36]	'04-' 7	MC III	31 <sup>\$</sup>	3	90	$86^{\Omega}$	4
Australia [11°]	'06-'10	MC III	32	3/32	100	NA	9
Newcastle [37 <sup>•</sup> ]	'07-'11	MC III	25	4/25	72	57.4	3
Groningen [38,39*]	'05-'09	MC III	35	24 #	95	pending	pending
Toronto [40]	'04-'11	MC III	31 $\Sigma$	3	84	່ 61 ັ	. 0
Spain [41,42]		MC I		9/17; 53%	69	58	

Information presented based on personal communication with representative physicians of each lung transplant program for updates on previously published cohorts (see references and acknowledgments). N/A, data not available; €, ISHLT criteria for primary graft dysfunction (PGD) [43]; #, data at 72 h after LTx; ∑, includes ex-vivo lung perfusion (EVLP) optimized donation after cardiac death (DCD) lungs in this cohort; Ω, survival at 24 months; \$, 2004–2007 cohort, three patients required extracorporeal membrane oxygenation (ECMO) to survive.



With this prognostic period between the start of the withdrawal of life support treatment and the lung flush set aside, lung recovery from DCD donors has been substantially less than that of kidneys and livers because of the lack of a reliable evaluation of the graft at the moment it is recovered.

Ex vivo lung perfusion enables an optimal assessment of these lung grafts before transplantation and its systematic use could increase the number of lungs recovered in this type of donor (20,41).

The team at Toronto has been heavily involved in lung transplantation from controlled DCD donors. They performed ex vivo lung rehabilitation in half their cases at the initial phase of their program and now use it nearly routinely. The number of lungs ruled out by these viability tests is not detailed. This information is important to assess the efficiency of the program for lung recovery. Finally, posttransplant survival results are similar to those obtained from DBD donors (74,75).

## 2) Results observed in lung transplantation from 2016 through 2018

These results are excellent and similar to those from DBD donors. The particularity of the French protocol is the performance of pneumoplegia and of lung recovery with NRP already underway. Functional WIT and asystole time reach, even exceed 60 minutes, but its potential impact on the graft quality is immediately attenuated as well as measured due to the routine use of ex vivo lung perfusion, a technique that enables the rehabilitation of the organ and the assessment of its viability.

Among the grafts not transplanted, 4 were rejected based on data from the ex vivo perfusion.

All patients are alive with a functional graft except for two who died after early severe graft dysfunction in December 2018, presumably unassociated with either the type of donor or the method of recovery.

## 3) Criteria chosen for the national protocol

The members of the committee proposed several modifications to the controlled DCD program in November 2019. After incorporation of these changes, <u>the protocol for lung recovery and</u> <u>transplantation from controlled DCD donors is as follows:</u>

- ✓ Donor selection criteria
  - Donor aged < 71 years (as for kidneys and liver).
  - Exclusion criteria identical to those used for DBD donors.
- ✓ Lung tests to perform after the decision to withdraw life support treatment and before the interview with family and close friends:
  - Blood gases FiO2 100%, then 40%, PEEP 5.



- ✓ Lung tests to perform after the interviews with family and observing the lack of opposition:
  - A thorax/abdomen/pelvis computed tomography scan is strongly recommended. If performed, thoracic slices are mandatory (and must be transferred from the recovery center to the transplant team).
  - **Bronchoscopy is mandatory**, with samples taken for bacteriological testing and macroscopic description of the bronchi (CRISTAL Donor items).
    - Endobronchial tumor Yes/No.
    - Apparent inflammation of the distal airways: Yes/No.
      - Purulent distal bronchial secretions after bronchoalveolar lavage: Yes/No.
- ✓ <u>Management of airway protection after the declaration of death according to the procedures for</u> withdrawal of life-sustaining treatment (withdrawal of ventilator support).

If withdrawal of ventilator support included extubation, the deceased donor is reintubated after death is declared and the national refusal register has been queried; the donor is then ventilated at FIO2 50%, with a tidal volume of 7 ml/kg PEEP 5 while maintaining a plateau pressure of 25 mmHg; this is followed by a bronchoscopy and distal samples. If the withdrawal of active treatment takes place in the ICU, the team can move to the OR by clamping the intubation catheter after insufflation (FiO2 100%) and then resume ventilation in the OR. This avoids the need to move with the ventilator.

- ✓ Elimination of the maximum functional WIT. Functional warm ischemia time is not relevant
- ✓ Increase the delay to 90 minutes of the maximum asystolic period before pneumoplegia, with transplantation of the lung grafts after rehabilitation and viability assessment during the ex vivo perfusion.
- ✓ Harmonization of the procedures for recovery of the lungs under NRP; a procedure sheet has been drafted for lung recovery under functional NRP. This sheet (procedure sheet n°12) proposes three fairly similar surgical scenarios for the recovery of the lungs under functional NRP. Centers are free to choose any one of these three procedures. The 3rd procedure is considered the simplest. With an NRP, extraction of the lungs requires:
  - Either that transesophageal ultrasound with a contrast challenge has been performed to rule out any interatrial communication and enable continuation of abdominal normothermic perfusion, as described with the venous cannula positioned in the inferior vena cava (IVC).
  - Or, most often, in the absence of an echocardiography or when this test shows an atrium septal defect (ASD), that double cannulation be planned of the IVC and the superior vena cava (SVC) when opening the right atrium (+ withdrawing the femoral cannula) to avoid air intake when opening the atrium in the extracorporeal recirculation device.

The pneumoplegia is then performed while the NRP is running for the intraabdominal organs.



- ✓ In the absence of in situ normothermic perfusion with NRP, the donor
  - is transferred rapidly to the OR after death is declared (withdrawal of life support treatment performed in the ICU)
  - is transferred to the OR before WLST and withdrawal is performed in OR only by the ICU team
- ✓ As soon as the surgical setup is completed (asepsis, exposure of the operative field), a sternotomy is immediately performed, with standard pneumoplegia..
- ✓ <u>Mandatory ex vivo rehabilitation + viability tests: lung compliance, vascular resistance, gas</u> <u>exchange</u>

The lung graft is transplanted as a function of the viability tests performed during the perfusion (lung compliance, vascular resistance, gas exchange), in a manner similar to the strategy used for non-optimal lung grafts:

- Minimum duration 2 hours.
- $PaO_2/FiO_2 > 350$  at the end of the procedure.
- ✓ <u>Maximum CIT:</u>

No maximum delay proposed, as the grafts are perfused ex vivo.

- ✓ Selection of recipients identical to those for recipients awaiting a graft from a DBD donor, with the possibility of choosing from the waiting list a patient awaiting a retransplantation or in the superemergency national priority category. A lung graft from a controlled DCD donor is first allocated to a patient on the local list. In the absence of a local recipient, the graft is proposed to a team authorized for controlled DCD recovery with recipients eligible for the relevant blood group. This team agrees to:
  - Perform the virtual crossmatch as soon as the donor's HLA type is known if the recipient is immunized and to formally validate with the Agence de la biomédecine its acceptance of the graft on the basis of the virtual crossmatch without awaiting a physical crossmatch.
  - To verify that the clinical state of a recipient either with super-emergency priority or awaiting retransplantation is compatible with transplantation at the moment of the offer.
  - To have an ABO-compatible recipient systematically in reserve in the department or to warn the Agence de la biomédecine as early as possible to identify a reserve team able to accept the graft for one of their recipients.
  - To perform the ex vivo perfusion for another team in the case of late refusal of the graft and in the absence of ABO- or HLA-compatible recipients.



## 4) Lung allocation rules

Some conditions set in this protocol influence the attribution of lung grafts, in particular by the exclusion of patients with the super-emergency priority.

The published series certainly show overall similar survival at 1 year and 3 years between DCD and DBD donors, but also a higher rate of early or primary graft dysfunction (PGD) for DCD donors. It is thus preferable to attribute these grafts to patients less seriously ill and less hemodynamically unstable to optimize the resumption of graft function.

Outside the priorities — national (super emergency) and regional (combined lungs + other organ graft), the attribution of lung grafts from DBD donors is a team allocation to the patient who team members consider most urgent of those meeting the morphologic constraints.

In the case of grafts from a DCD donor, the lung graft will be proposed first to the local team, initially by ABO blood group, and then by an ABO-compatible blood group for a patient who is informed, consents, and meets the protocol selection criteria. The idea of a local recipient will be extended in this case, to the lung transplant team, which will have signed a contract with the recovery site, if it does not have such a team, for a more effective collaboration.

If the "local" team designated by the agreement is unavailable, the graft is offered in turn to teams — only teams familiar with the technique of lung recovery under NRP and with the technique of ex vivo rehabilitation, set up for and with patients listed for this type of graft in CRISTAL and appearing in the selection assistance list (=informed and consenting) with the same ABO blood group or an ABO-compatible blood group.

## The transplant team must

- Clearly understand the specificities of surgical recovery, in particular in terms of onsite availability as soon as the withdrawal of life support treatment begins.
- Adapt to the surgical scenario of lung recovery under functional NRP, in accordance with the local controlled DCD protocol.
- > Master and have a plan for ex vivo rehabilitation and finally have eligible recipients on their list.

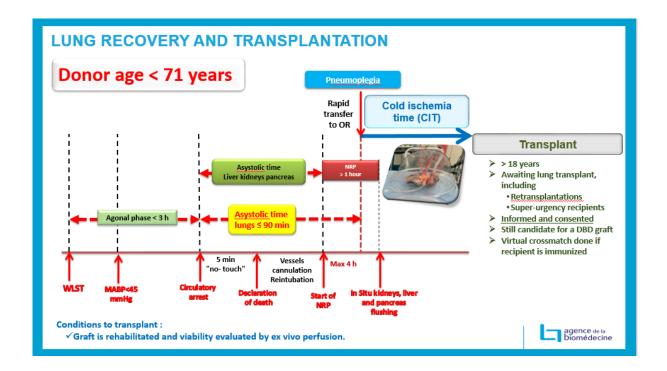
Teams that accept the grafts must agree to adhere to the warm ischemia interval, or they will be excluded from the program (major criterion signaled in the agreement between the transplant team and the Agence de la biomédecine).



## **Conditions for transplant:**

Lungs are the organs that best tolerate warm ischemia. In view of the very good results and the systematic evaluation and rehabilitation by ex vivo perfusion, the following criteria have been set:

- > Asystolic time  $\leq$  90 minutes
- > Graft to be rehabilitated and its viability evaluated by ex vivo perfusion





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