Organ Donation

TEDOR

Transeuropean Educational initiative in Organ Donation and Transplantation

THE PROJECT

The TEODOR project was a 36-month initiative funded by the European Commission's Erasmus+ programme. It was led by the Pauls Stradiņš Clinical University Hospital and Latvijas Universitate, in collaboration with prestigious institutions such as the Universitat de Barcelona and Spain's DTI Foundation, the National Transplant Office of the Ministry of Health of Lithuania, Fakultní nemocnice Královské Vinohrady of the Czech Republic, and Karolinska University Hospital of Sweden. The main goal of the TEODOR project was to create a new training programme for organ donation and transplantation. This programme was specifically designed for doctors and healthcare personnel in Latvia, the Czech Republic, and Lithuania.

This e-book contains information prepared for the TEODOR training programme, with a dedicated focus on organ donation. The content covers a wide range of relevant topics, intended to equip healthcare professionals with essential knowledge and expertise in this critical area. By disseminating this information, the e-book aims to improve organ donation practices, and ultimately enhance patient care and outcomes across the participating countries.

TEODOR
Transeuropean Educational initiative in Organ Donation and Transplantation

DTI
DONATION & TRANSPLANTATION INSTITUTE

Co-funded by the Erasmus+ Programme of the European Union

FAKULTNÍ NEMOCNICE VINOHRADY

NTB

UNIVERSITAT DE BARCELONA

LATVIJAS UNIVERSITĀTE

KAROLINSKA UNIVERSITETSSJUKHUSET

PAULA STRADIŅA KLĪNISKĀ UNIVERSITĀTES SLIMNĪCA

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The donation process

ORGAN DONATION

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Demand for organs has increased in step with the rapid increase and considerable success of transplantation, with a consequent widening of the gap between supply and demand for organs, which has resulted in a major organ shortage. The goal of this course is to improve the quantity, quality and effectiveness of organ and tissue donation. This topic discusses types of donors and how to successfully conduct the first step of the donation process.

Objectives

- Provide high-quality training adapted to current needs in the field.
- Provide knowledge and skills on how to evaluate potential donors, rule out biological risk factors, perform laboratory screening tests and medical history studies, in addition to clarifying the aetiology of death.
- Present different quality control systems for donor detection, causes of donor loss and analysis of donor detection procedures.
- Facilitate an understanding of expanded criteria donors.

INTRODUCTION

Transplant coordinators play a key role in the donation process. To do a good job they need to have adequate skills, knowledge of the donation process, and be able to solve any problems that may arise when trying to convert a potential donor into an actual one.

The objectives of this unit are to:

- understand the types of donor that exist, their characteristics and differences;
- become familiar with the steps in the donation process, the actors and foreseeable problems, and acquire the appropriate terminology used in the donation process;
- be able to perform a proper assessment of the organ donation potential of a hospital and effectively use the health care facilities available;
- identify potential problems that may hinder the donation process and acquire the tools to find and propose adequate solutions.

1. SECTION 1: TYPES OF DONOR

1.1 Introduction

There are two basic types of donor:

- **Living donor:** a living human being from whom cells, tissues or organs are removed for the purpose of transplantation.
- **Deceased donor:** a human being declared, by established medical criteria, to be dead and from whom cells, tissues or organs are recovered for the purpose of transplantation.

Both types of donor may donate organs, tissues or both. This chapter focuses on organ and tissue donors. Each type of donor requires different approaches, which are mainly related to the detection system and donor evaluation.

The transplant coordinator (TC) must be aware of all types of organ donors and the differences between them. One task of the TC is to ensure that all procedures (regardless of the kind of donor) comply with the best medical knowledge as well as the legal and ethical regulations of each country.

DID YOU KNOW...?

The type of donor from which organs and tissues may be recovered varies from country to country, depending on legal, cultural and organizational issues. At the present time most of the organs removed for transplant come from deceased donors, although in some countries or hospitals living donors represent a significant number of donation resources.

1.2 Living donors

A living donor may have one of the following three possible relationships with the recipient:

1.2.1 Related:

1.2.1.1 Genetically related:

- 1st degree genetic relative: parent, sibling, offspring.
- 2nd degree genetic relative: grandparent, grandchild, aunt, uncle, niece, and nephew.
- Other than 1st or 2nd degree genetically related, for example cousin.

1.2.1.2 Emotionally related: spouse, in-laws, adopted, friends.

1.2.2 Unrelated: not genetically or emotionally related

Living donation is currently the only source of donors in some countries such as Jordan and represents a minor source for other countries like Spain. Such differences could be explained by the different legal, cultural, political, technical or logistical conditions that exist in each country (Figures 1 and 2).

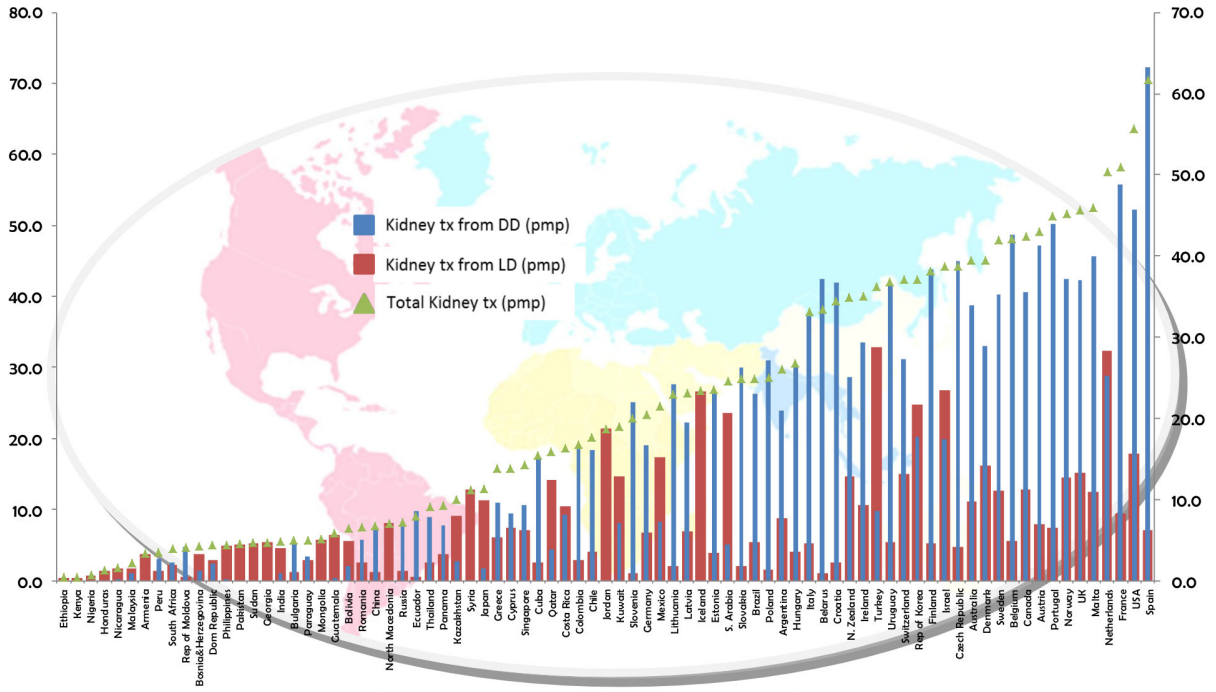

Figure 1. Kidney transplants from deceased and living donors (pmp) 2017. Source: Global Observatory on Donation and Transplantation (GODT).

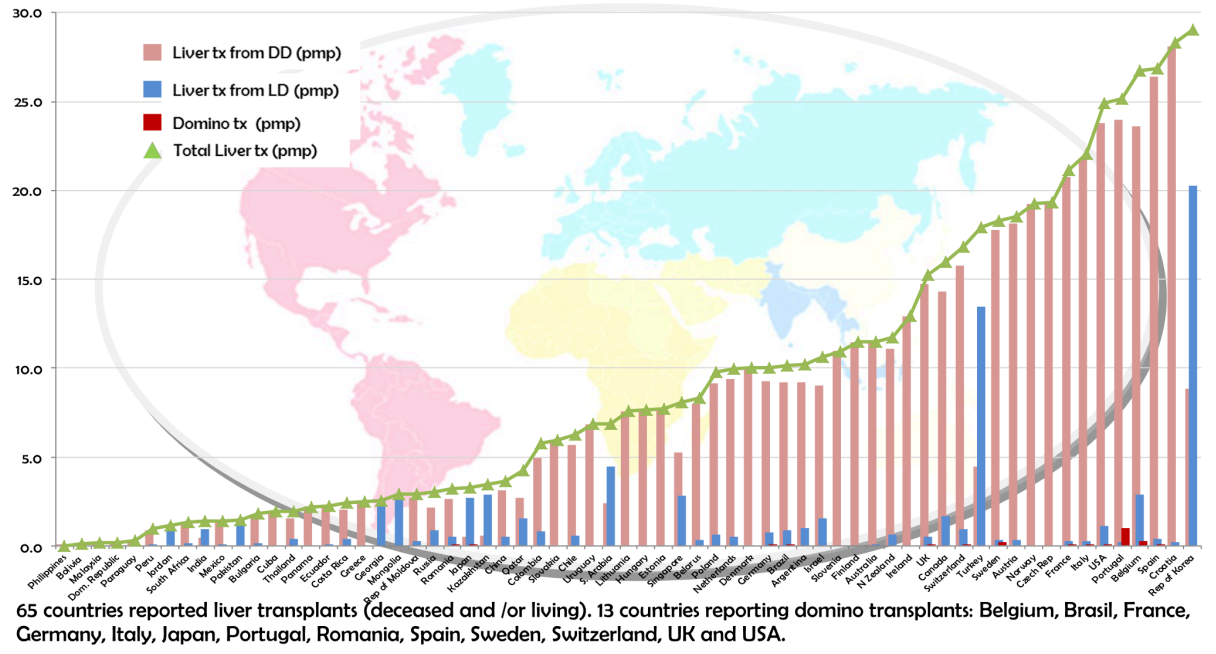

Figure 2. Liver transplants from deceased, living donors and domino (pmp) 2017. Source: Global Observatory on Donation and Transplantation (GODT).

DID YOU KNOW...?

Historically, the first organ donors were living donors (kidney). In 1965, the first organ recovery from a brainstem death donor was performed. Nowadays, the kidney is the most frequently donated organ, followed by liver segments, and occasionally lung lobes, pancreas or intestinal segments.

In all cases it is mandatory to follow all the legal and ethical requirements that exist in each country, and it is the TC's responsibility to ensure it. The global concern is to avoid the "commercialization" of living organ donation procedures.

1.3 Deceased donors

The term "deceased donor" will be used to refer to any donor that has been declared dead in accordance with established medical criteria before donation occurs. The term "deceased" needs to be correctly translated into other languages to avoid any confusion. The use of terms such as "cadaveric donors" is no longer recommended.

Deceased donors can be divided into two different categories depending on the cause of death as follows:

» **Donor after brainstem death (DBD):** is a donor who was declared dead and diagnosed by means of neurological criteria.

» **Donor after circulatory death (DCD):** is a donor who was declared dead and diagnosed by means of cardio-pulmonary criteria.

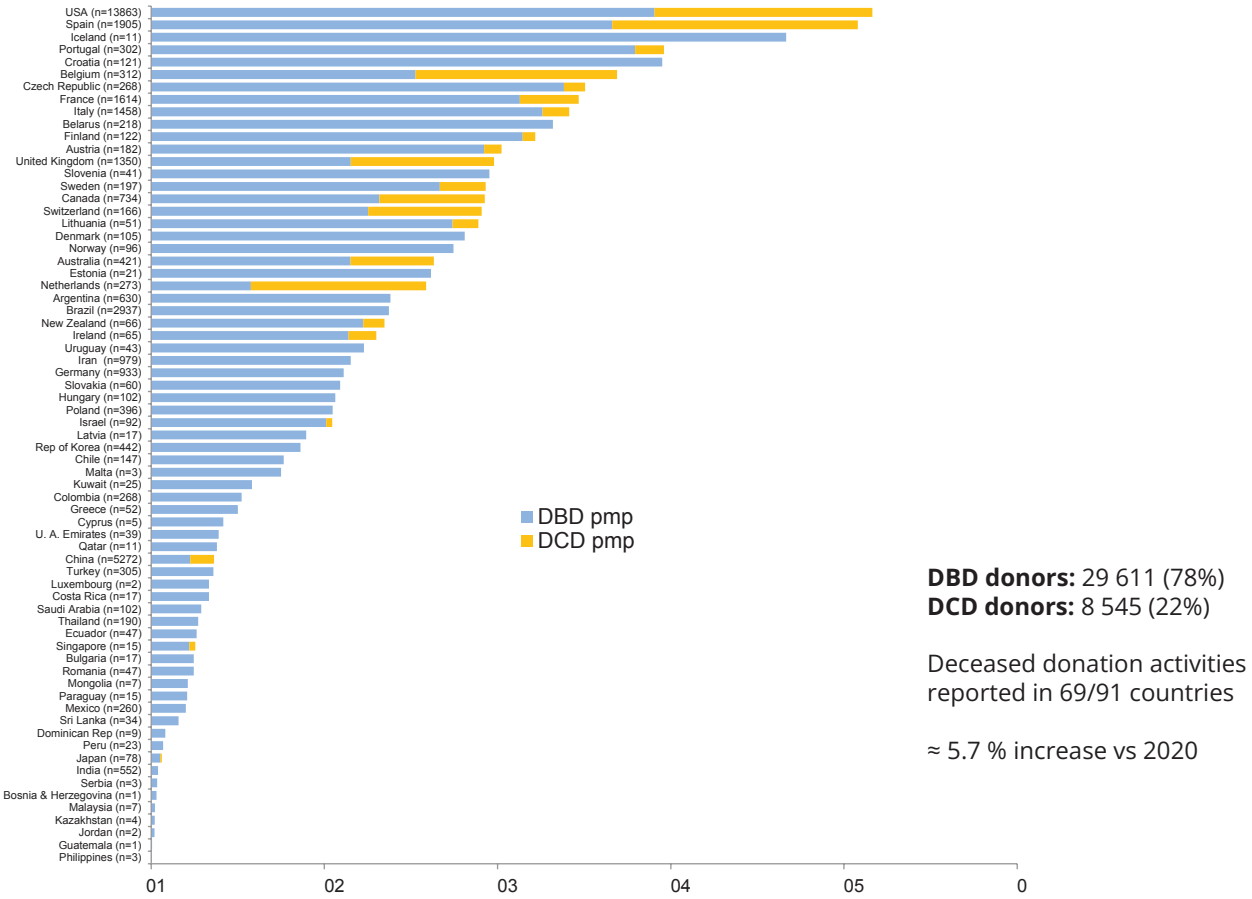

Figure 3. Actual deceased organ donors by donor type (pmp) 2021.

1.4 Donor after brainstem death (DBD)

Brainstem death is defined as the irreversible cessation of hemispheric and brainstem neurological functions. The most frequent causes of brainstem death are (Figure 4):

- cerebrovascular accident, ischaemic or haemorrhagic ;
- brain trauma;
- anoxic encephalopathy;
- primary brain tumour.

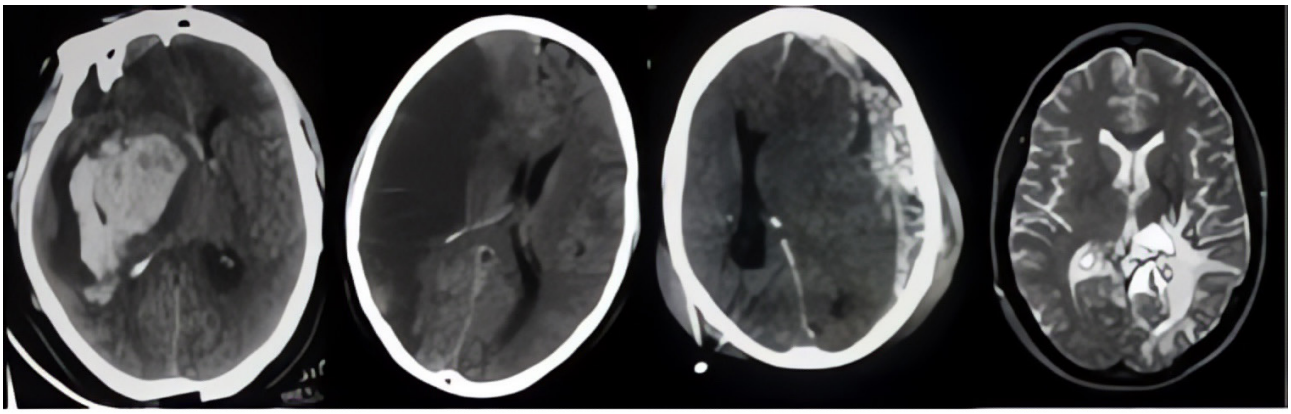

Figure 4. Most frequent causes of brain death.

The percentage of these causes leading to brainstem death may vary between countries depending mostly on demographics, the rate of traffic accidents, technological advances and health care facilities existing in every country.

EXAMPLE

Currently, around 70% of the donors are brainstem death donors.

1.5 Donors after circulatory death (DCD) (1/2)

Donors after circulatory death (DCD) were initially classified according to the Maastricht criteria established in 1995 [4]. Now, the most commonly used criteria is the Modified Maastricht Classification for Donors after Circulatory Death (Madrid 2011) (Table 1), but others exist. Transplant International 2016; 29:749–759.

Other classifications of a more practical nature categorize DCD as “uncontrolled” or “controlled” depending on whether the circulatory arrest occurs spontaneously or after medical therapy limitation.

Uncontrolled donation after circulatory death refers to donation after circulatory arrest occurred unexpectedly, outside or inside a hospital, and from which the patient cannot be resuscitated (Maastricht type 1 and 2). Patients diagnosed with brainstem death who suffer circulatory arrest before the start of organ removal (Maastricht type 4) represent a minority of DCD.

Potential candidates for "controlled" DCD include patients being considered for limitation of mechanical-sustaining support who are also likely to die shortly after its application. This group includes patients with terminal pulmonary and musculoskeletal diseases as well as end-stage irreversible brain injuries (traumatic brain injury, cerebral haemorrhage, and cerebral hypoxia) that do not meet the neurological criteria for brainstem death and may be candidates for donation after their heart has stopped following the restriction of their therapy.

Table 1. The modified Maastricht classification of DCD

Category I Uncontrolled	**Found dead** IA. Out-of-hospital IB. In-hospital	Sudden unexpected circulatory arrest without any attempt of resuscitation by medical team
Category II Uncontrolled	**Unsuccessful resuscitation** IIA. Out-of-hospital IIB. In-hospital	Sudden unexpected irreversible circulatory arrest with unsuccessful resuscitation
Category III Controlled	Withdrawal of lifesustaining therapy	Planned withdrawal of lifesupport with anticipated circulatory arrest
Category IV Uncontrolled controlled	**Cardiac arrest during brainstem death**	Sudden circulatory arrest after brain diagnosis during donor life-management but prior to organ recovery
Category V Controlled	**Euthanasia**	Organ donation after euthanasia

1.6 Donors after circulatory death (DCD) (2/2)

To date, DCD accounts for up to 20% of total deceased donors worldwide. However, the implementation of DCD programmes varies between countries. While in the USA, 10% of the deceased donors are DCD, in Japan they represent more than 90%. Spain has an increasing number of DCD with a rate of 13.5 pmp during 2018 (30% of the total deceased donors). Most DCD donors worldwide come from Maastritcht group 1 and 2. However, the USA and the Netherlands were the first countries to develop DCD type 3 protocols. Nowadays, Canada, Australia and some European countries [5-8] have also implemented controlled DCD protocols within their transplantation programmes.

The implementation of such programmes requires a well-organized structure and excellent coordination of all actors involved in the process. Once death has been certified, preservation techniques must be initiated, or rapid organ recovery must be performed to avoid warm ischaemia damage.

Besides increasing the deceased donor pool, organs removed from DCD donors have shown long-term outcomes comparable with grafts from conventional DBD if both donors and recipients are adequately selected and managed [9].

2. SECTION 2: THE ORGAN DONATION PROCESS. BASIC TERMINOLOGY

As previously mentioned, transplant patients have a higher risk of developing cancer. According to Kasiske et al. [1], kidney cancer might occur up to 15 times more frequently than in the general population. Hepatobiliary, cervical or vulvo-vaginal tumours may increase up to five times and testicle and bladder tumours, three times more. Colon, lung, prostate, stomach, pancreas, ovary and breast tumours are approximately twice as frequent.

Bearing in mind the wide variety of tumours which could affect transplant patients it is important to consider prevention, as well as early diagnosis and treatment.

The European Code Against Cancer establishes recommendations for the prevention and early diagnosis of the disease, as well as cancer treatment in its earliest stages.

2.1 The organ donation process

The organ donation process is multifaceted and involves many different actors whose sole purpose is to recover organs and tissues for donation.

The transplant coordinator (TC) is the person who coordinates this complex process. It is the TC who is responsible for converting as many potential donors as possible into actual donors, coordinating the distribution of organs, tissues and cells to the most appropriate recipients in accordance with applicable allocation regulations.

To successfully perform this task the TC needs to efficiently manage all steps of the donation process (Figure 5). Other important TC tasks include:

- guaranteeing an adequate, efficient and safe process of tissue donation;
- promoting, protecting and auditing the living donation process and its participating actors;
- providing information and training on donation and transplantation to different sectors and groups of society, especially within the medical community;
- participating in research activities related to the development of new ways of improving the efficacy and efficiency of the donation process.

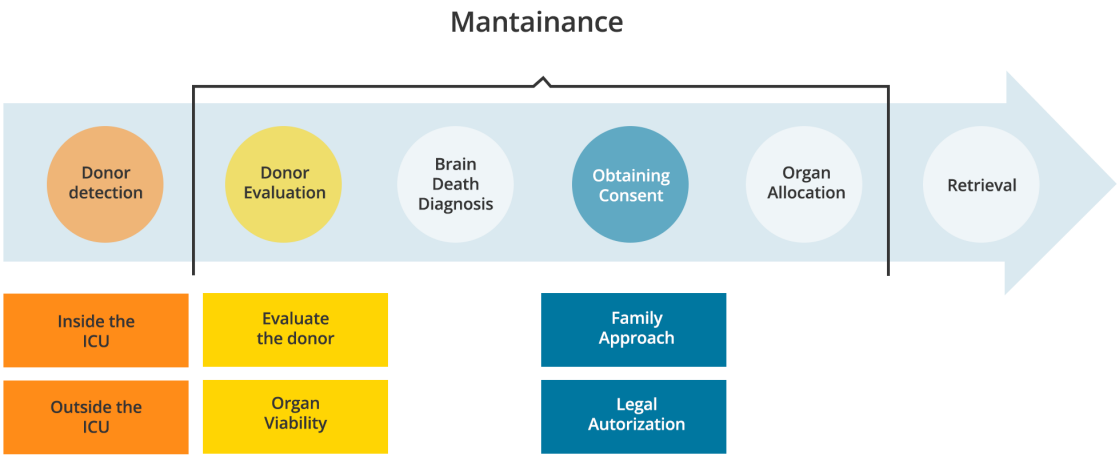

Figure 5.

2.2 The organ recovery process

TCs should take an active role in the:

Evaluation of potential donors

Assessment of all possible donor areas, promoting referral of all possible donors by their attending physicians, regardless of where donors may be.

Diagnosis of brainstem death (BD)

Evaluation of the donor's medical suitability, to ensure that no diseases are transmitted to the recipient and that transplanted organs will function normally.

- History or evidence of infective endocarditis (bacterial or fungal).
- History or evidence of rheumatic valve heart disease and/or congenital cardiac disease.
- Cardiomyopathy (viral, parasitic or idiopathic).
- Hypertrophic obstructive cardiomyopathy.
- Marfan syndrome.
- Aortic dissection (with detachment of the intima and adventitia).
- Previous cardiac or valve surgery.

Each tissue bank determines its own policy for the following conditions, which may prevent an individual from donating:

- Significant chest trauma, particularly penetrating trauma in the area of the heart including intra-cardiac injection, if the semilunar valves have been affected*.
- Open cardiac massage.
- Valvular heart disease**.
- Pneumonia in previous days without evidence of effective treatment.
- Previous cardiac surgery on the tissue to be procured**.

A chest CT-scan (*) and pre-donation echocardiograms (**), when available, can be useful tools for evaluation of valve function or damage.

Donor management

Although diagnosis of BD is the responsibility of the physician in charge of the patient, TCs should try to increase BD-related knowledge, ensuring that its diagnosis can be performed at any time in as many places as possible.

Approaching the family to offer the opportunity to donate

Maintenance of good organ and tissue perfusion to guarantee organ viability.

Organ recovery and allocation

The TC also needs to consider the administrative and legal processes involved in organ donation.

Organ recovery and allocation

This involves contacting the sharing office, operating room, anaesthesia, nursing and surgical teams, and the subsequent distribution and transport of organs to the final destination.

2.3 Basic nomenclature

To efficiently accomplish this process, the TCs and healthcare professionals involved in the donation and transplantation process should speak a common language. A basic terminology facilitates communication between professionals, allows performance assessment throughout the deceased donation process and can help identify areas for improvement. It will also enable comparison of the donation process between different centres, areas or even countries. A panel of experts recently designed a critical pathway for deceased donation as a tool that can be applied in every country, region or specific hospital, regardless of the level of development of their healthcare system or their baseline experience in deceased organ donation [10] (Figure 5). This critical pathway establishes a basic terminology and provides a common systematic approach to the deceased organ donation process, considering both donation after brainstem death (DBD) and donation after circulatory death (DCD).

Use of the correct terminology ensures accuracy throughout the organ donation process.

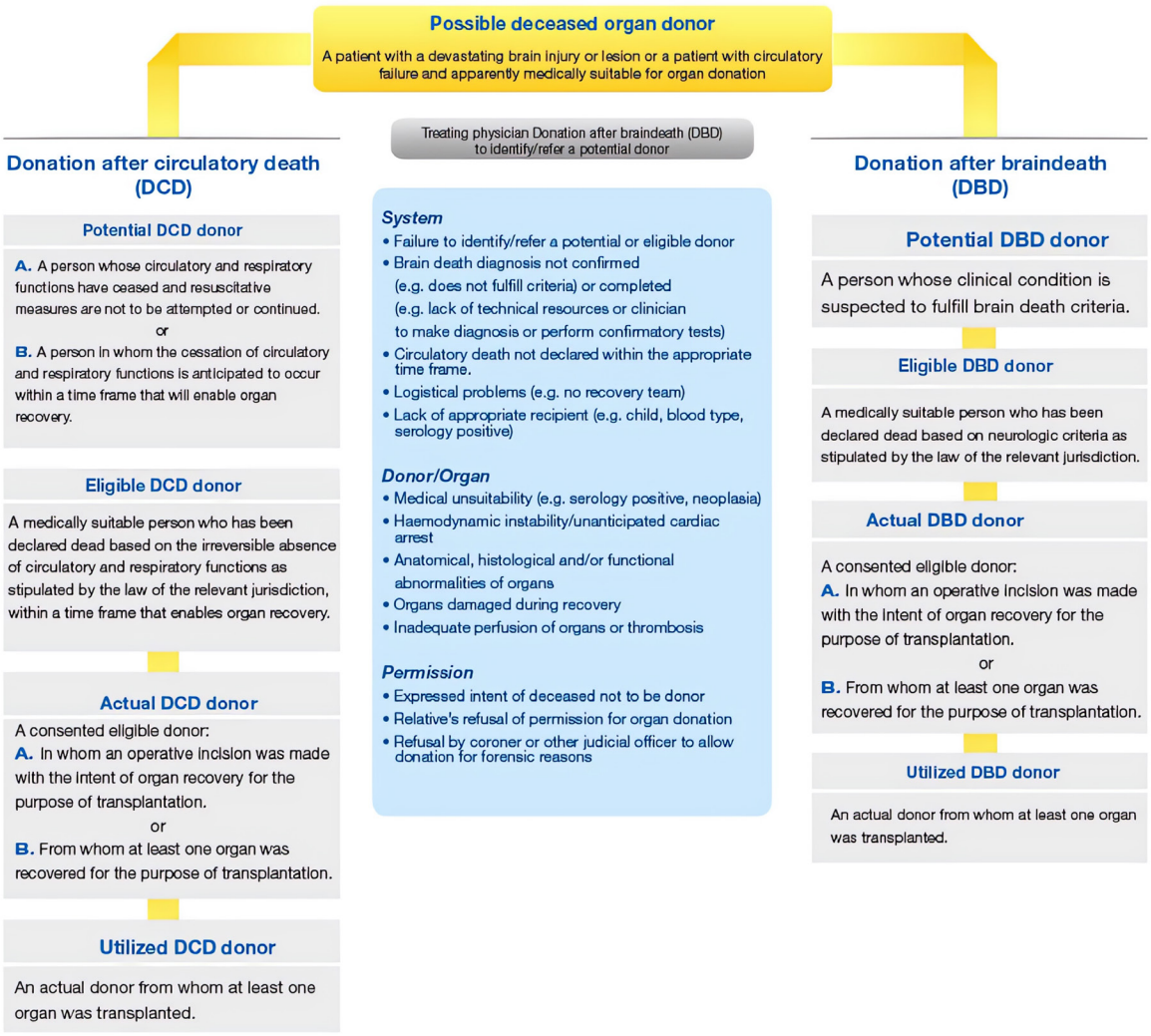

Figure 6. The donation process.

2.4 Definitions

Possible deceased organ donor - A patient with a devastating brain injury or lesion, or a patient with circulatory failure who is apparently medically suitable for organ donation.

Potential donor - A person whose clinical condition is suspected to meet brainstem death criteria (in case of DBD), whose circulatory and respiratory functions have ceased and for whom resuscitative measures are not to be attempted or continued (uncontrolled DCD), or in whom the cessation of circulatory and respiratory functions is expected to occur within a timeframe that will enable organ recovery (controlled DCD).

Eligible donor - A medically suitable person who has been declared dead based on neurological criteria as stipulated by the law of the relevant jurisdiction (for DBD donor) or on the irreversible absence of circulatory and respiratory functions as stipulated by the law of the relevant jurisdiction, within a timeframe that enables organ recovery (for DCD donor).

Actual donor - A consenting eligible donor (DBD or DCD) upon whom an operative incision was made with the intent of organ recovery or from whom at least one organ was recovered for the purpose of transplantation.

Utilized donor - An actual donor (DBD or DCD) from whom at least one organ was transplanted.

3. SECTION 3: MEASURING AND OPTIMIZING DONATION POTENTIAL AND EFFECTIVENESS

Each country, region or healthcare facility should record their donation and transplantation activity for use as a reference in assessing their performance over time, to compare their institution with other facilities/countries, to identify gaps or pitfalls, and to initiate actions to solve them.

Different measurement tools can be used to evaluate the donation activity, depending on the extent, magnitude or area evaluated.

3.1 National/regional level

The donation activity of a country or large area is normally measured as a ratio, in donors per million population (donors /pmp). The optimal donation rate has been proposed as 50 donors /pmp, although only certain areas have achieved this, and only for determined periods of time.

Spain, Croatia and Portugal are the countries with the highest annual donation rates, accounting for 33-49 donors/pmp in 2019.

3.2 National/regional donation factors (1/2)

There are several factors that can influence the magnitude and type of donation activity in a country or region.

Demography: Countries with an older population, such as western countries, have older donors than countries with younger populations (such as Asian countries). These age differences are explained by and are the consequence of other epidemiological data (cerebral bleedings, tumour deaths, etc.) that determine each country's donor profile [11] (Figure 7).

Access to the health system: Countries with public national health systems that provide a non-fragmented coverage to the population are more likely to develop integrated and efficient donation and transplantation programmes. Other factors such as the number of ICU beds per million population, the ratio of ICU beds/total acute beds, and the number of doctors and nurses available may explain the country-by-country differences in the capability to detect potential donors and maintain them adequately until the diagnosis of brainstem death has been given and organ recovery has been completed [12].

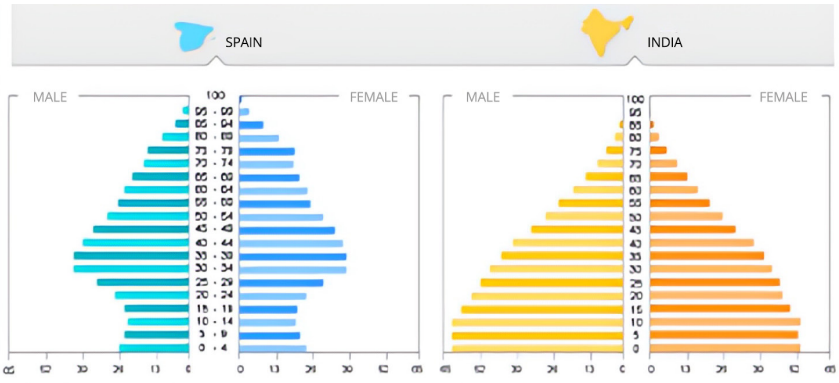

Figure 7.

3.3 National/regional donation factors (2/2)

Legal background: countries with solid legal frameworks, with definitions of concepts such as brainstem death, organ recovery after obtaining family consent, and no compensation for either donation or grafted organs, are those able to develop a consistent donation and transplant programme.

Religion, cultural and social issues: the large majority of religions take a positive stance on donation.

Other factors, such as emotional response, cultural values and spiritual issues may be even more important than religious beliefs when shaping the population's attitude towards donation [13].

3.4 Hospital level (1/2)

It is important that TCs be aware of the organ donation potential and effectiveness of their centre/area. This information is of great value for comparison of the donation activity of different periods, or between different hospitals.

There are several indexes to consider when assessing donation potential (the number of brainstem deaths expected) of a given hospital. Similarly, the effectiveness of the donation process can be evaluated by measuring the number of brainstem deaths converted into actual donors. These calculation tools are based on large datasets and are therefore reliable for the evaluation of local, regional or national activity (Table 1).

DID YOU KNOW...?

Quality assurance in the Spanish donation detection process was started by the Spanish National Transplant Organisation (ONT) in 1998 in an effort to audit the majority of donor and transplant hospitals in Spain.

Each year, the organisation publishes a report containing the most relevant data on donation activity in Spain (Table 1) [14].

Based on the information pooled from these databases, the donation effectiveness process of brainstem death donors can be summarized as follows:

- 1.5 donors / 100 hospital deaths
- 2.5 donors / 100 hospital beds / year
- 8 donors / 100 ICU deaths
- 50 donors / 100 ICU beds / year
- 49 donors (30.9-84.6) / 100 eligible hospital deaths

However, each hospital or area should continuously audit its donation process and evaluate the potential and effectiveness of its donations.

Table 2. Calculation tool to evaluate one's local, regional or national donation activity

Donation process effectiveness 1999-2011	All hospitals	Neurosurgery	
		Yes	No
Number of actual donors (AD)	15,556	13,277	2,279
AD / All ICU deaths	6.9%	7.7%	4.3%
AD / All hospital deaths	1.3%	1.6%	0.59%
AD / 100 ICU beds	38.2%	40.7%	38.1%
AD / 100 hospital beds	2.0%	2.4%	1.1%
AD / ICU admitted patients	0.67%	0.72%	0.47%

Donation potential 1999-2011	All hospitals	Neurosurgery	
		Yes	No
Number of brainstem deaths (BD)	28,056	23,634	4,422
BD / All ICU deaths	12.4%	13.7%	8.3%
BD / All hospital deaths	2.3%	2.8%	1.1%
BD / 100 ICU beds	68.9%	72.4%	54.5%
BD / 100 hospital beds	3.6%	4.3%	1.9%
BD / ICU admitted patients	1.21%	1.29%	0.91%

Potential of donation	Donor process effectiveness
	(Actual donors / Brainstem deaths) x 100
(Brainstem deaths / ICU total deaths) x100	(Actual donors / TOTAL ICU deaths) x 100
(Brainstem deaths / ICU total beds) x100	(Actual donors / ICU beds) x 100
(Brainstem deaths / ICU admissions) x100	(Actual donors / ICU admissions) x 100
(Brainstem deaths / Hospital deaths) x100	(Actual donors / Hospital deaths) x 100
(Brainstem deaths / Hospital total beds) x100	(Actual donors / Hospital beds) x 100

3.5 Hospital level (2/2)

The hospital potential of organ donation depends on several factors that should be considered when evaluating its efficacy and donor rate [15]:

- healthcare centre location and accessibility;
- size and ownership (private *vs.* public): the existence of an adequate reimbursement system for recovery and transplant activity is required that is in accordance with local estimated costs;
- presence of third level trauma services, neurosurgical department, transplant surgery programme and ethics committee;
- admission criteria policy: acute care hospitals with no restrictive policies are best candidates to hold donor programmes;
- number of ICU beds with mechanical ventilation;
- attitude of administrative and medical staff towards donation.

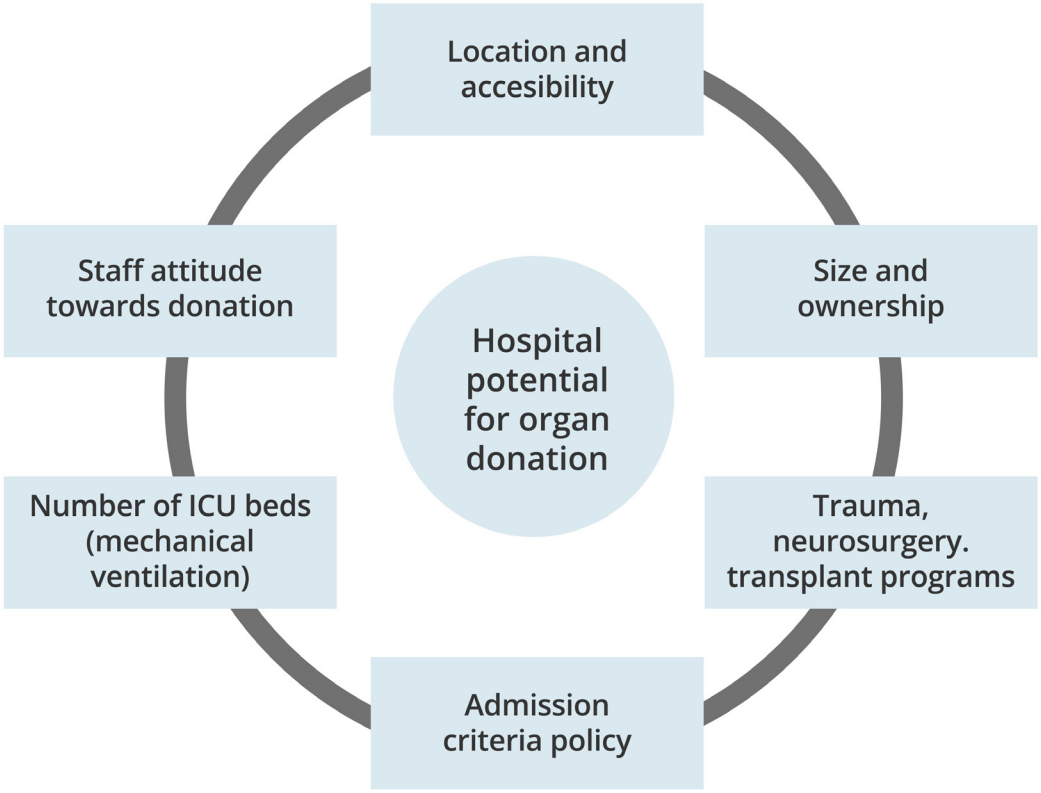

Figure 8. Hospital potential for organ donation.

3.6 Optimizing the donation process (1/2)

In most western countries, the absolute number of donors, as well as the rate of donors pmp has not significantly varied in recent years. Indeed, over a 17-year period, the number of patients on the kidney transplant waiting list increased by 22%, whereas the number of transplant procedures only increased 5% (Figure 8).

The reasons for the observed stabilization of donor rates may be attributable to several factors. Recent years have seen a decrease in the incidence of catastrophic brain injury as a result of public health initiatives that have reduced the number of motor vehicle accidents. Secondly, advances in neurocritical care management mean that many patients no longer progress to brainstem death. Finally, demographic changes have occurred in the general population. However, the main cause of organ shortage is not the lack of potential donors, but rather a failure to turn many potential donors into actual ones.

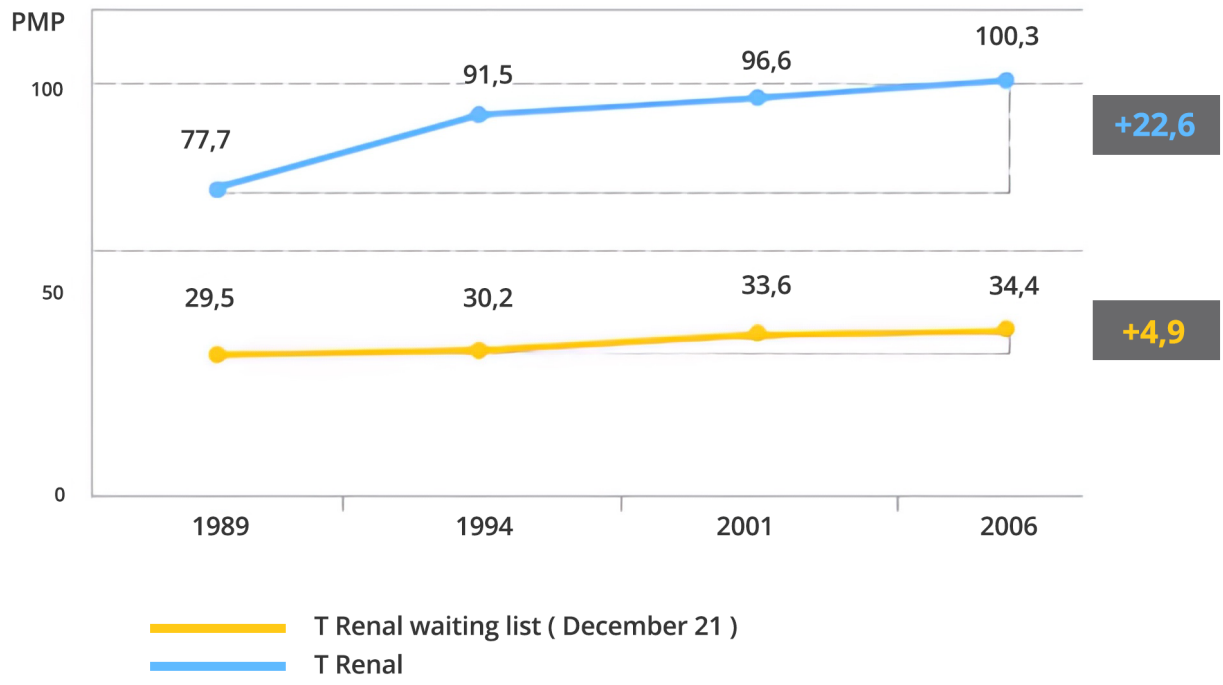

Figure 9.

3.7 Optimizing the donation process (2/2)

Every country, area or hospital should identify the main gaps and pitfalls in the donation process that may hinder the generation of donors. As an example, in 1998, the ONT began its Quality Assurance Programme for the Spanish donation detection process, in an effort to audit the majority of donor and transplant hospitals in Spain. The programme has the following objectives:

- define target organ recovery capacity, depending on the characteristics of the hospital concerned, detect gaps in the organ donation and recovery process, and analyse the reasons behind;
- the loss of potential donors, as a means of identifying the areas to be improved;
- describe the hospital factors that influence outcomes of the donation and transplantation process.

Figure 10 shows encephalic death outcomes for all Spanish hospitals between 1999 and 2011, according to the ONT programme.

Once the problems have been identified, initiatives to solve them or minimize their incidence should be promoted by national health authorities alongside the healthcare professionals directly involved in this field [16].

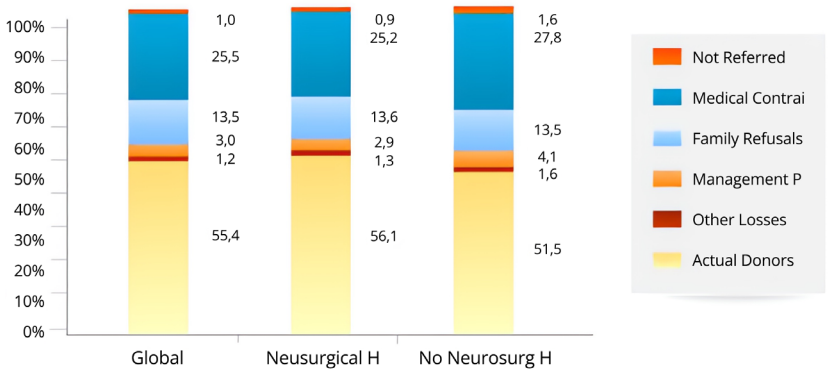

Figure 10. Encephalic death outcome. Spanish hospitals 1999-2011.

Age

In general terms, there is no age limit for receiving a kidney transplant. The recipient should have a general medical condition that allows them to undergo the surgery and receive immunosuppressive medication.

Elderly patients have a greater prevalence of vascular calcifications, which may hinder vascular anastomosis, and a greater risk of presenting an organic illness. Assessment of patients over 70 should be on an individual basis and requires a complete cardiovascular study.

Cardiovascular disease

A kidney patient has a greater risk of presenting a cardiovascular disease with complications than the general population. The first cause of long-term death in a kidney transplant (KT) is cardiovascular disease. This makes a thorough assessment of the patient's cardiovascular state necessary.

An acute or recent heart problem (myocardial infarction, angina, stent or aorta-coronary bypass, heart failure, severe valvular heart disease) can be a contraindication to receive a KT. A history of an old ischaemic cardiopathy is not an absolute contraindication but it will necessitate a careful cardiological assessment.

A recent history of cerebrovascular disease (stroke, brain haemorrhage, transient ischaemic attack, subarachnoid haemorrhage) is an absolute contraindication and a person-by-person waiting period should be considered before reconsidering inclusion on the KT waiting list. A history of previous cerebrovascular disease requires thorough individual assessment (ultrasound of supra-aortic trunks, brain CT or NMR, neurological assessment).

Patients with hepatorenal polycystic disease, a family history of intracranial aneurysms or prior subarachnoid haemorrhage should undergo a brain CT angiography and neurological assessment.

Peripheral arterial disease

Symptomatic peripheral arterial disease or aneurysm of abdominal aorta with surgical criteria should be carefully assessed prior to transplant. Treatment (angioplasty, stent, vascular prosthesis or endoprosthesis) is necessary before reconsidering inclusion on the waiting list.

Severe peripheral arterial disease with stenosis or diffuse calcifications can make vascular anastomosis of kidney graft impossible and in some centres, heterotopic kidney transplant is contraindicated.

There are two alternatives in these cases: Firstly, kidney transplant in orthotopic position (with anastomosis of kidney artery to splenic artery, graft kidney vein with its own kidney vein and pyelo-pyelic anastomosis). This technique is more complex and used by few centres. It requires simultaneous nephrectomy of own kidney and involves greater post-KT complication risks. Secondly, an aorta-iliac bypasses prior to performing kidney graft artery anastomosis to vascular prosthesis.

Pulmonary disease

Chronic obstructive pulmonary disease (COPD) or severe asthma might be contraindications for KT. Moderate cases of the disease should undergo complete assessment (spirometry, oxygen saturation, pulmonary volumes) and receive maximum optimisation of bronchodilator treatment.

Obesity

Extreme obesity (BMI >40 kg/m^2) is considered a contraindication for KT. In case of extreme obesity, lifestyle changes -and in some cases bariatric surgery- should be considered. Obesity is associated with a high risk of medical complications (diabetes, infections, venous thrombosis) as well as surgical complications.

CONCLUSIONS

- There are two kinds of donors: living and deceased. Each type of donor requires a different evaluation and donation procedure.
- Deceased donors are divided into brainstem death donors (who currently represent most donors), and donors after circulatory death.
- The organ donation process is multifaceted, involving many actors whose sole purpose is to recover organs and tissues for transplantation.
- TCs are the key element of the whole donation process.
- TCs are responsible for donor detection and valuation, approaching the family and allocation, as well as giving support in brainstem death diagnosis and maintenance of the potential donor.
- To efficiently manage the donation process, TCs should be familiar with the basic nomenclature employed, the definitions of donors, and have up-to-date information concerning the donation process.
- TCs should also be capable of assessing the donation potential of the area and healthcare centre where they undertake their professional activity, to detect all possible gaps in the donation process and find efficient ways to solve any shortfalls.

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TOPIC 1 - Unit 2

Donor detection and evaluation

ORGAN DONATION

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INTRODUCTION

The detection and identification of a future donor is the first, and most important, step in the organ and tissue recovery procedure. Identification of all possible deceased donors should ideally occur as early as possible, particularly when referring to potential donors with a devastating brain injury or lesion.

Once identified, it is mandatory to perform a global assessment of the donor in order to avoid transmission of infectious diseases and/or neoplasms and ensure that organs will function once transplanted.

The objectives of this unit are to:

- understand who can be a potential donor;
- become aware of who is responsible for donor detection and identification;
- become familiar with the different methods of donor detection and identification;
- know how to perform an adequate and exhaustive clinical evaluation of the potential donor;
- demonstrate knowledge of the absolute and relative contraindications for donation;
- understand "expanded criteria donors", their recognition and acceptance as viable sources of organs.

1. SECTION 1: DONOR DETECTION

1.1 Who becomes a potential donor?

The identification of possible deceased donors should ideally occur as early as possible, particularly when the potential deceased organ donor is a patient with a devastating brain injury that might lead to brainstem death. In such cases, the Glasgow Coma Scale is a good indicator of the neurological situation and may be used to predict eventual brainstem death, particularly when a coma score below 5 is recorded.

However, referral of possible donors might not be accepted in all local circumstances (i.e., many countries do not find it appropriate to refer possible donors if death has not yet been established). In all cases, there should be strict observance of the "dead-donor rule", by which patients may only become donors after death, and the recovery of organs must not cause the donor's death [1]. However, it should be noted that while referral means the action of making the key donation person or organization aware of the possibility of a deceased donation, it does not include any other subsequent action.

DID YOU KNOW...?

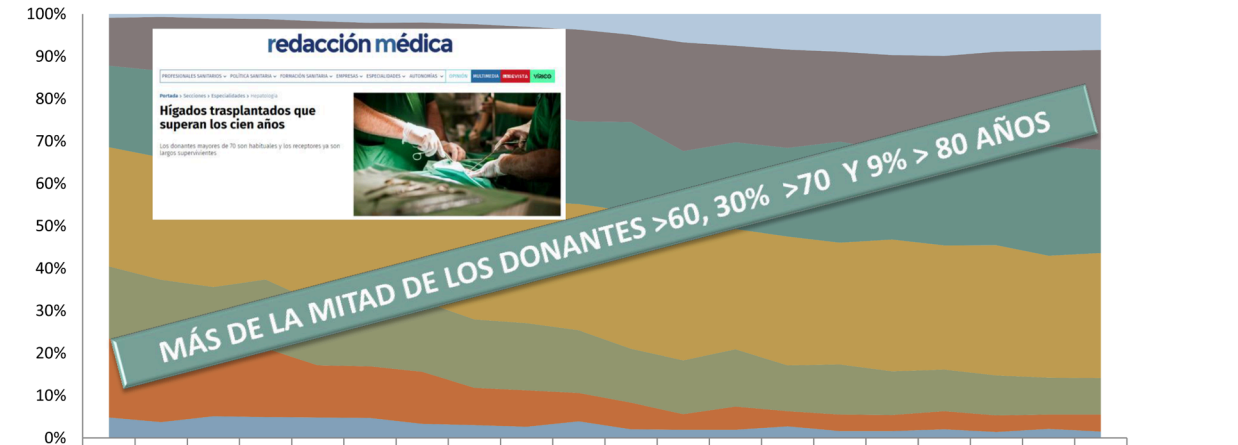
The type of donors from whom organs and tissues may be recovered varies from country to country depending on legal, cultural and organizational issues. At present, most of the organs removed for transplant come from deceased donors, although in some countries or hospitals living donors represent a significant number of donation resources.

1.2 Donor profile

Classically, the profile of a DBD donor was a young person with a brain trauma secondary to a traffic accident. However, in recent years, there has been a change in the donor profile due to a decrease in the incidence of catastrophic brain injuries thanks to public health initiatives that have reduced the number of motor vehicle accidents, advances in neurocritical care management (many patients no longer progress to brainstem death), and demographic changes in the general population. Currently, the potential donor, at least in developed countries, is a patient over 50 years of age, who has suffered a brain haemorrhage or massive ischaemic stroke. Moreover, today even patients over the age of 70 years may be considered potential donors [2-5].

However, studies have shown that referral physicians did not identify as many as 30% of donors over the age of 55 as possible donors.

TCs play an important role in updating the information on the changing profile of donors according to current reality.



	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019
≥ 80 a	0,9	0,7	1	1,2	1,7	2,1	2	2,4	3	3,7	4,9	6,7	7,5	8,4	8,9	9,7	9,9	8,9	8,7	8,5
70-79 a	11,3	12,7	13,7	15,2	16,5	16,1	17,6	18,6	20,2	21,7	20,6	25,7	22,8	23,2	21,2	22,5	22,6	21,9	22,6	23,6
60-69 a	19,2	20,4	19,7	17,5	19,9	19,8	19,2	21,9	20,9	19,5	21,1	21,4	20,5	20,9	23,8	21	22,1	23,7	25,8	24,3
45-59 a	28,1	28,8	30	28,7	30	29,2	29	29,1	28,7	29,8	32,4	28	28,4	30,4	28,7	31,1	29,3	30,7	28,8	29,5
30-44 a	17	16,3	15,5	16,2	14,7	16	16,7	16,1	15,8	14,8	12,7	12,7	13,5	10,8	11,8	10,3	9,8	9,4	8,7	8,6
16-29 a	18,6	17,2	15	16,2	12,3	12,2	12,3	8,8	8,6	6,7	6,3	3,7	5,5	3,6	3,9	3,8	4,3	3,9	3,4	4
< 16 a	4,8	3,7	5,1	4,9	4,8	4,7	3,3	3	2,6	3,9	2	1,9	1,9	2,7	1,6	1,6	2	1,4	2,1	1,5

14%

Figure 1. Age of organ donators in Spain. Source: Organización Nacional de Trasplantes (ONT).

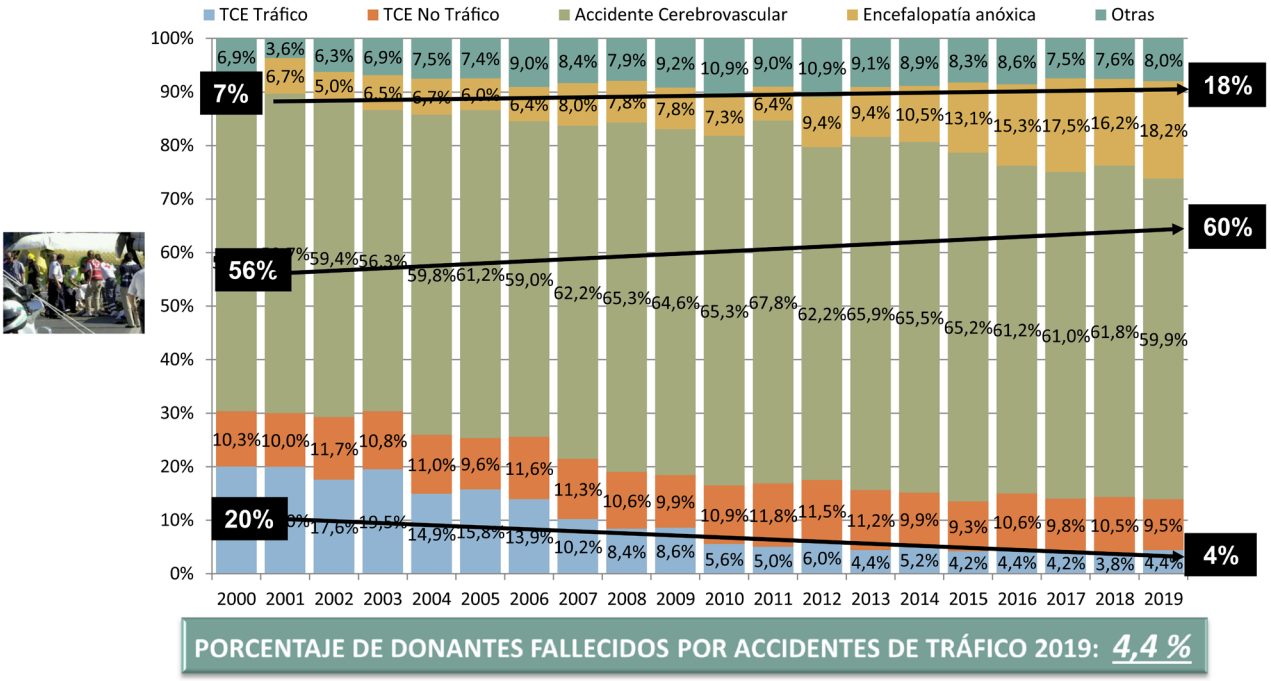


Figure 2. Cause of death of organ donors in Spain. Source: Organización Nacional de Trasplantes (ONT).

1.3 Who is responsible for donor detection?

In the most common, but not unique scenario, a patient with a devastating brain injury is attended by intensive care specialist or anaesthesiologist in the ICU or in a reanimation unit. However, this kind of patient can also be found in emergency rooms, postoperative recovery or on neurological wards. In the best-case scenario, all possible donors should be referred to a key donation person/organ procurement organization (OPO) by their physician, regardless of the patient's location.

However, many doctors do not identify or refer all possible donors to the TC. Therefore, it is TC's responsibility to monitor patients suffering from neurological deterioration wherever they are. To do so, the TC needs the support of the healthcare professionals working in each of these units in order to have accurate information regarding which patients are close to brainstem death and to ensure that the possibility of donation is always considered when brainstem death occurs. Donor detection is, therefore, a task shared between the healthcare professional in charge and the TC with a well-established and thoroughly accepted cooperation between them and hospital management.

1.4 How should we proceed?

Information about patients in the ICUs who have a serious cerebral pathology that might lead to brainstem death is essential.

The main mechanisms to obtain this information are:

» administrative methods;

» medical methods.

DID YOU KNOW ...?

TCs need certain technical resources to carry out their functions, which allow them to be contacted at any time. However, technical means of communication are no substitute for frequent visits to personnel in the ICUs, which will provide valuable information about what is happening in the hospital at any given time. The best tools for a TC are, therefore, a good pair of running shoes, good communication skills and an open mind.

1.5 Administrative methods

In almost every hospital, information concerning admissions is computerised. Therefore, it is possible for TCs to obtain a list of patients admitted to the ICU with their age and diagnosis. This is a useful tool as patients whose condition might lead to brainstem death can be identified immediately.

Using this information, with support of the physician in charge of a patient's neurological state, the TC can monitor the situation so that if brainstem death occurs, organ and tissue donation can be proposed.

1.6 Medical methods

These complement the previously described methods, because information obtained using administrative methods may lead the TC to schedule visits, if necessary, to the unit where possible or potential donors are.

The TC's tasks are to:

- monitor the evolution of neurological patients;
- increase awareness about donation amongst professionals working in the ICU, postoperative recovery, emergency room etc.

Two different methods can be adopted:

- **Active detection:** when the TC takes the initiative, adopting an open and friendly attitude, giving support whenever necessary to ensure that donation is considered, and that the TC is contacted for each case of suspected brainstem death.
- **Passive detection:** when the TC is responsible for donor evaluation (in the best of cases), but it is the patient's physician who decides that the patient is a potential donor and conducts the family interview. This method may lead to a failure to identify a significant number of potential donors for several reasons:
  - no process of donor detection is implemented;
  - incorrect clinical contraindications may be established.

EXAMPLE

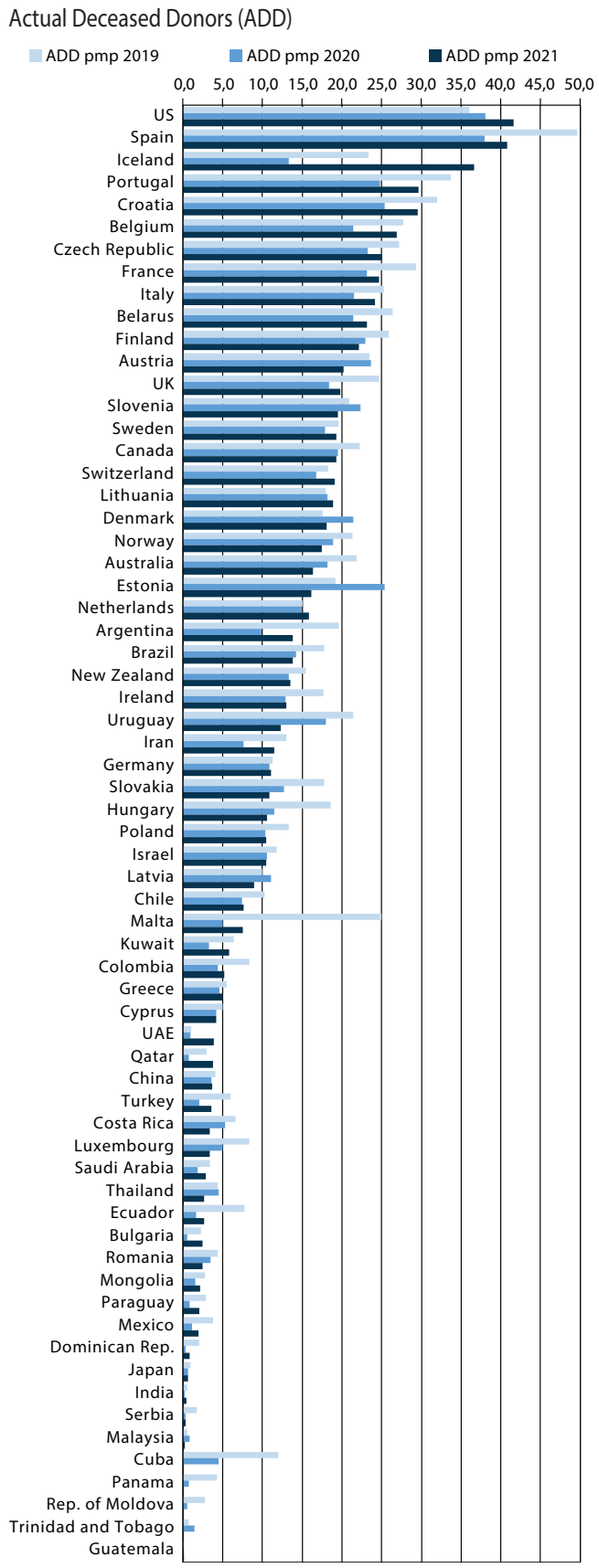
A passive detection method would be to wait in your office for a call from the ICU physician, while an active detection method would consist of daily visits to the ICU.

1.7 The transplant coordinator (TC)

The role of a TC differs from country to country, and principally depends on the location of the TC office or organ procurement organization (OPO). In some countries OPOs are located outside the hospital, which hinders a frequent pattern of visits to the locations where possible donors are. This might explain the significant number of potential donors that go undetected according to retrospective reviews of medical records, especially potential donors who may not meet [6] the standard criteria for donation (Table 1).

An alternative that can minimize this obstacle is to implement a hospital development programme based on efficient, fluent channels of communication with the objective of fostering donation awareness among ICU personnel.

In Spain, TCs are based within hospitals, and one of their tasks is active donor detection - that is, visiting ICUs and other hospital departments where potential donors are hospitalized on a daily basis. This is probably one of the key elements that has made the Spanish model so successful and placed the donation rate in Spain amongst the highest in the world (Figure 3).



COUNTRY	2019		2020		2021	
	N	PMP	N	PMP	N	PMP
Argentina	883	19,6	444	9,8	630	13,8
Australia	548	21,8	463	18,2	421	16,3
Austria	206	23,4	213	23,7	182	20,2
Belarus	248	26,4	201	21,4	218	23,2
Belgium	321	27,7	249	21,5	312	26,9
Brazil	3767	17,7	3027	14,2	2953	13,8
Bulgaria	16	2,3	4	0,6	17	2,5
Canada	828	22,2	734	19,5	734	19,3
Chile	188	10,3	141	7,4	147	7,7
China	5818	4,1	5222	3,6	5272	3,6
Colombia	417	8,4	222	4,4	268	5,2
Costa Rica	33	6,6	27	5,3	17	3,3
Croatia	131	32,0	104	25,4	121	29,5
Cuba	138	12,0	51	4,5	0	0,0
Cyprus	6	5,0	5	4,2	5	4,2
Czech Republic	288	27,2	249	23,3	268	25,0
Denmark	102	17,6	124	21,4	105	18,1
Dominican Rep.	23	2,1	4	0,4	9	0,8
Ecuador	133	7,8	29	1,6	47	2,6
Estonia	25	19,2	33	25,4	21	16,2
Finland	145	25,9	126	22,9	122	22,2
France	1924	29,4	1512	23,2	1614	24,7
Germany	932	11,3	913	10,9	933	11,1
Greece	61	5,5	48	4,6	52	5,0
Guatemala	3	0,2	0	0,0	1	0,1
Hungary	180	18,6	111	11,4	102	10,6
Iceland	7	23,3	4	13,3	11	36,7
India	715	0,5	351	0,3	552	0,4
Iran	1078	13,0	645	7,7	979	11,5
Ireland	85	17,7	63	12,9	65	13,0
Israel	101	11,7	92	10,6	92	10,5
Italy	1495	25,3	1303	21,5	1458	24,1
Japan	125	1,0	77	0,6	78	0,6
Kuwait	27	6,4	14	3,3	25	5,8
Latvia	19	10,0	21	11,1	17	8,9
Lithuania	52	17,9	49	18,1	51	18,9
Luxembourg	5	8,3	3	5,0	2	3,3
Malaysia	16	0,5	28	0,9	7	0,2
Malta	10	25,0	2	5,0	3	7,5
Mexico	500	3,8	152	1,2	260	2,0
Mongolia	9	2,8	5	1,5	7	2,1
Netherlands	258	15,1	255	14,9	273	15,9
New Zealand	74	15,4	64	13,3	66	13,5
Norway	115	21,3	102	18,9	96	17,5
Panama	18	4,3	3	0,7	0	0,0
Paraguay	20	2,9	6	0,8	15	2,1
Poland	504	13,3	393	10,4	396	10,5
Portugal	347	33,7	253	24,8	302	29,6
Qatar	8	3,0	2	0,7	11	3,8
Rep. of Moldova	11	2,8	2	0,5	0	0,0
Romania	85	4,4	66	3,4	47	2,5
Saudi Arabia	114	3,3	65	1,9	102	2,9
Serbia	15	1,7	3	0,3	3	0,3
Slovakia	98	17,8	70	12,7	60	10,9
Slovenia	44	21,0	47	22,4	41	19,5
Spain	2302	49,6	1777	38,0	1905	40,8
Sweden	198	19,6	181	17,9	197	19,3
Switzerland	157	18,3	146	16,8	166	19,1
Thailand	301	4,3	315	4,5	190	2,7
Trinidad and Tobago	1	0,7	2	1,4	0	0,0
Turkey	499	6,0	172	2,0	305	3,6
UAE	10	1,0	9	0,9	39	3,9
UK	1653	24,7	1248	18,4	1350	19,8
Uruguay	75	21,4	63	18,0	43	12,3
US	11870	36,1	12588	38,0	13863	41,6

Figure 3. Worldwide actual deceased organ donors rate 2019 (pmp). Source: International Registry in Organ Donation and Transplantation. June 2020.

Table 1. Retrospective reviews of all medical records at 177 of 177 acute-care hospitals within the New England Organ Bank (NEOB) geographic service area to determine maximum potential organ donors

	Group A: Prime donors (<55 years old with no comorbidities)	Group B: Comorbid donors (56-70 years old or <55 years old and AHT, IDDM or LBP)
Number / %	**818 / 67.4%**	**395 / 33.6%**
Identified by hospital	**94.3%**	**69.9%**
Referred to OPO	**82.8%**	**55.9%**
Converted to donor	**50.4%**	**26.8%**

Luskin et al. An alternative Approach to Evaluating Organ Procurement Organization Performance. Transplantation Proceedings, 31 353-355 (1999). Maximum potential organ donors over a 3-year period, 1994 to 1996.

1.8 Steps in donor detection

1. Identification of patients with a serious cerebral pathology and Glasgow Coma Score under 5.
2. Follow-up and identification of brainstem death when it occurs.
3. Evaluation of potential donors.

In brief:

» donor detection is the first step in ensuring higher donation rates;

» the role of the TC is crucial;

» each hospital should adopt a different approach, depending on its own characteristics and patient profile.

2. SECTION 2: DONOR EVALUATION

2.1 Introduction

One of the TC's tasks is to perform a global assessment of the potential donor and demonstrate accurate knowledge about specific organ feasibility evaluation. The objective of donor evaluation is:

» to avoid the transmission of infectious diseases and cancer;

» to ensure that organs will function once transplanted.

First, we must evaluate the donor in general, not organ by organ. After the general assessment, if at least one organ seems to be suitable for transplantation, the donation process begins.

Current donor profiles have changed in terms of age and cause of death, and donors often have associated multiple pathologies. This circumstance necessitates a detailed assessment.

National regulations and laws must be respected as they differ from country to country and will sometimes influence the donor selection process.

2.2 Cause of death

The first step is to clarify cause of death. In DBD donors, the cause of death is always due to an encephalic disease. For patients who die in cardiac arrest, it is mandatory to diagnose the cause of the cardiac arrest.

There are many clinical situations that can progress to brainstem death such as brain trauma, brain haemorrhage, anoxia, etc. that do not contraindicate donation. However, some absolute clinical contraindications for donation exist, among which, for example, are acute viral encephalitis or some central nervous system (CNS) tumours, mentioned below.

Complementary neurological tests, such as a CT, are recommended to establish the cause of death. In the case of cerebral anoxia, we need to rule out the presence of other pathologies such as primary or secondary tumours of the CNS. In cases where meningitis or encephalitis are suspected it is mandatory to perform bacteriological or virological studies.

2.2.1 Medical and social history

Complete knowledge of the donor's medical and social history is required. TCs must collect this information using all possible sources, such as relatives, friends, family physician and old hospital records.

2.2.2 Age

The donor rate may decrease or increase depending on how strictly the criteria related to age are handled.

In general, age is not currently a factor for clinical contraindication. Occasionally, after careful assessment, hearts from donors over 60 years of age have been successfully transplanted. Livers from donors older than 75 years have been transplanted even though other organs could not be recovered.

Age should be considered a risk factor when combined with other morbidity factors. Thus, higher donor age is not a contraindication in itself [2-5] but should alert us to other diseases (e.g., AHT, diabetes mellitus, etc.). In paediatric cases there is no age limit for heart or en-bloc kidney recovery, whereas surgeons are reluctant to transplant livers from children under six months of age because of the small size of the vessels and the immaturity of the organs.

2.3 Risk factors

Risk factors are defined as behavioural habits and lifestyles that increase the likelihood of disease transmission. In addition to human immunodeficiency virus (HIV) or viral hepatitis, a large number of infectious agents can be transmitted via organs or tissues. Even with negative complementary testing we must check for the following risks:

- Sexual habits (e.g., many different sexual partners / indiscriminate sexual relations).
- Toxic habits (alcoholism, drug abuse etc.).
- Travel history (to areas where malaria is endemic, prior infection, bovine spongiform encephalitis (BSE) etc.).

At times, it is difficult to rely on the information given by relatives about the potential donor's behavioural habits, especially those of a sexual or toxic nature. They are frequently unaware of the private areas of the deceased's life and may feel embarrassed or guilty when asked about such matters. Relatives, next of kin, life partners, cohabitants, friends, healthcare providers etc. should be interviewed in a confidential, sensitive manner about behaviours that may have increased the potential donor's probability of HIV, HBV or HCV infection.

Table 2. Factors identified in the literature as associated with an increased likelihood of recent HIV, HBV or HCV infection

Sexual contact
» Persons who have had sex with ≥2 partners in the preceding 12 months
» Persons who have had sex with a person known to have or suspected of having HIV, HBV or HCV infection in the preceding 12 months
» Men who have had sex with another man (MSM) in the preceding 12 months
» Persons who have had sex in exchange for money or drugs in the preceding 12 months
» Persons who have had sex with a person who had sex in exchange for money or drugs in the preceding 12 months
» Persons who have had sex with a person who injected drugs by intravenous, intramuscular, or subcutaneous route for non-medical reasons in the preceding 12 months
» Birth to a mother infected with HIV, HBV or HCV (for infants ≤2 years of age)
» Persons who have injected drugs by intravenous, intramuscular, or subcutaneous route for non-medical reasons in the preceding 12 months
» Intra-nasal use of an illicit drug (e.g., cocaine, heroin) in the preceding 12 months
» Inmate of a correctional facility (e.g., jail, prison, juvenile detention) >3 consecutive days in the preceding 12 months
» Persons who have, or have been treated for, syphilis, gonorrhoea, or genital ulcers in the preceding 12 months
» Persons who have been on haemodialysis in the preceding 12 months (for HCV only)

2.3.1 Previous diseases

In general, past diseases (except cancer) are not an absolute contraindication for organ donation. However, it is important to know the diseases that a donor has suffered, as well as when they began, what treatment was applied, how long the condition lasted and what the outcome was.

Arterial hypertension and diabetes mellitus in themselves are not absolute contraindications. We must assess their evolution and impact on specific organ function, particularly on the kidneys and heart. We could say that both are risk factors which must be considered during organ assessment.

In systemic diseases, damage of one or all organs must be considered (e.g., polyarteritis nodosa).

Pre-existing malignant diseases will be covered later in this topic.

Some neurological diseases need careful consideration. While their pathway of occurrence remains doubtful, in some cases a slow virus disease (e.g., multiple sclerosis) or prion infection (e.g., new variants of Creutzfeldt Jacob disease) must be assumed.

2.4 Current clinical situation (1/2)

The next step in the process is physical examination of the potential donor and investigation of their current clinical situation. This can only be performed by an on-site visit to the donor.

2.4.1 Haemodynamic status

Current arterial blood pressure, central venous pressure, heart rate and urine output are basic parameters of haemodynamic function. These data provide information on how good organ perfusion is and, therefore, on its function. For adults, optimal mean arterial blood pressure should be above 80 mmHg without significant inotropic or vasoactive support.

We also need to ascertain whether oliguria or anuria has occurred, and the average urine output over the last 6 to 24 hours. Normal urine output (1 to 3 ml/kg/h) correlates with a haemodynamically stable donor. An abnormal urine output only indicates an abnormal global situation that has to be corrected, but it does not provide much information on kidney function.

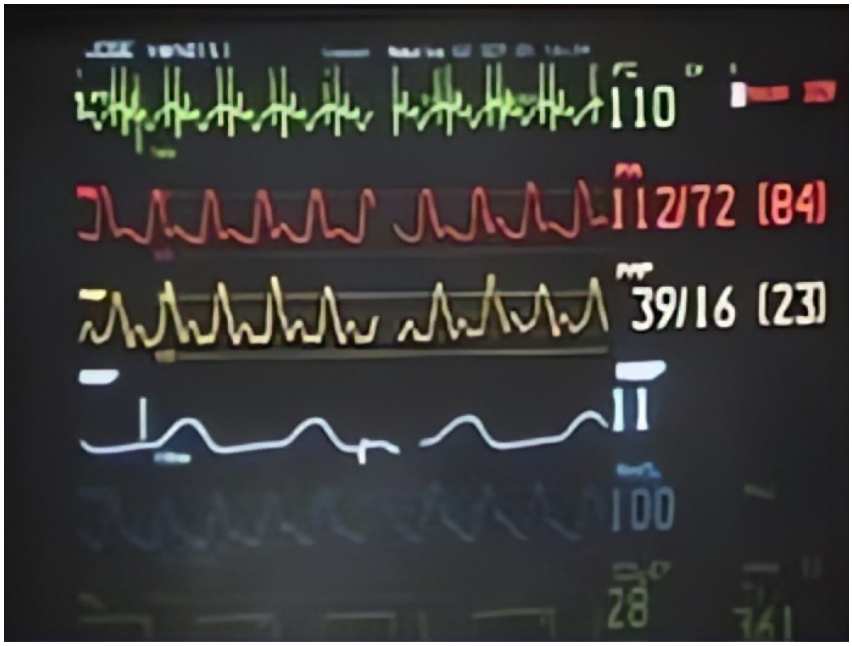


Figure 4. Hemodynamic status.

2.5 Current clinical situation (2/2)

Haemodilution due to a massive infusion of crystalloids, colloids or blood products could alter serological determinations [13] and may jeopardize tissue extraction. TCs must inform transplant teams of this possibility when there is no chance of repeating the tests with a non-haemodiluted blood sample.

Cardiac arrest as well as low blood pressure are not absolute contraindications for donation, especially in the case of kidneys and liver, with contraindication depending on the extent of organ damage caused. It is important to know when and how the arrest occurred, its cause and duration, and whether timely and adequate resuscitation was performed.

2.5.1 Current treatment

It is important to know the medical treatment that the donor is receiving at the time of evaluation, especially the magnitude of volume replacement or vasoactive support, the occurrence and treatment of diabetes insipidus as well as the administration of steroids, diuretics or insulin.

Similarly, the use of antibiotic, virostatic or fungicide medication (type, dose, time and indication for therapy) is a key factor in determining donor suitability as well as single organ viability.

Transient elevation of creatinine levels and transaminases can provide information about the presence of perfusion problems due to low blood pressure or cardiac arrest.

An elevation of creatinine (kidney) or transaminase (ASAT and ALAT >600 IU/ml) levels indicate that there is an organ with perfusion problems as a result of cardiac arrest or low blood pressure.

2.6 Physical examination

An exhaustive and meticulous examination is required, looking for:

- Injuries: thoracic or abdominal, as a cause of organ lesions.
- Tattoos/body piercing: we must investigate the time and conditions in which tattoos were performed. If the tattoo was performed within the last three months and we cannot check the conditions under which it was made (aseptic or not) the donor should be rejected, due to risk of viral HBV, HCV or HIV transmission [9,10].
- Non-medical injections of drugs: should alert us to suspect a high risk of disease transmission (e.g., HBV, HCV or HIV) due to drug abuse and its related lifestyle, sexual or toxic habits. We must examine the entire body, not only the elbow flexure, for scars, including the mouth.
- Skin cancers: most, but not all, patients with skin tumours are suitable organ donors (see tumours, especially melanoma [11]).
- Scars from previous surgery: operations for malignant diseases must be ruled out and the family interview should be helpful.
- Lesions from sexually transmitted diseases: like *condyloma acuminata*, herpes etc. [12]

2.7 Complementary testing

Blood samples should be obtained for every donor to perform several analyses.

2.7.1 General determinations

- Red and white cell count: haemoglobin and haematocrit will help identify haemodilution or volume depletion. Abnormally high values of leucocytes may suggest brain necrosis as well as infection.
- Prothrombin time and other coagulation parameters: after excluding consumption caused by bleeding or anticoagulation, its alteration is a good indicator of liver function.
- Blood gas analysis: a good marker of gas exchange (lung) and tissue oxygenation.
- Electrolytes and blood glucose: important indicators of donor maintenance quality plus the exclusion of additional organ damage due to hypernatremia (diabetes insipidus).
- Blood group.
- Evaluation of specific laboratory data for each organ: liver, kidneys, heart, lungs and pancreas.

The evolution of these determinations during ICU admission may provide you with more information on organ function (and how impaired function was recovered) than data referring to a single point in time.

2.8 Complementary examinations

» Chest X-ray (regardless of whether the donor is considered for lung donation or not). It should be reviewed by an expert (Figure 3).

» ECG (regardless of whether the donor is considered for heart donation or not). It should be reviewed by an expert (Figure 4).

» Abdominal ultrasonography. Advisable for liver, pancreas and kidney evaluation (Figure 5).

» Echocardiography. Advisable for all potential heart donors. Mandatory if: age over 40-50 years or history of arterial hypertension, recent cardiac resuscitation, recent severe thoracic trauma or receiving high doses of vasoactive drugs (e.g., norepinephrine > 0.1 ug/kg/min).

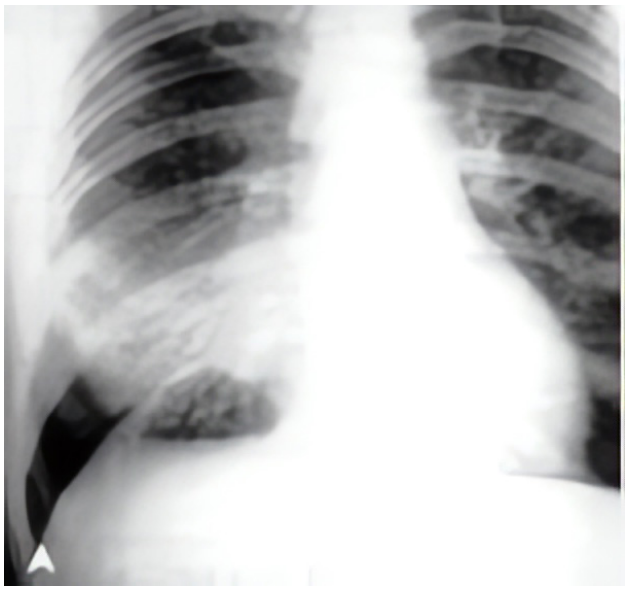


Figure 5. Chest X ray.

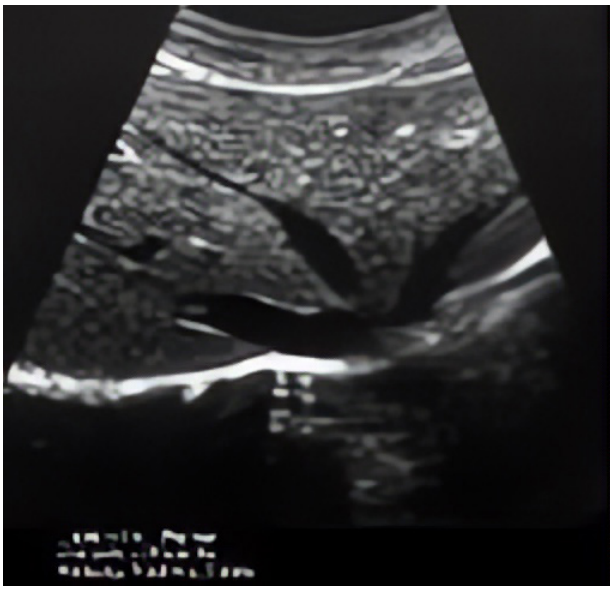


Figure 6. Abdominal ultrasonography.

2.9 Serological determinations to exclude disease transmission

There is no consensus on the best screening protocol (Table 2). It is advisable to review national legislation and be informed about any endemic infectious diseases in the region in order to set up an adequate, informative screening profile. At a minimum we have to test for:

» HIV types 1 and 2 antibodies (anti-HIV-1/2)

» Hepatitis B surface antigen (HBsAg)

» Hepatitis C antibodies (Anti-HCV)

Table 3. Basic Serological Screening of Organ and Tissue Donor (OTD): Practical considerations, Middle Europe (2001)

Characteristic	Standard criteria donors (SCD)	Expanded criteria donors (ECD)
Anti-HIV-1/2	Every prospective donor	Must be negative.
Anti-HCV	Every prospective donor	If positive, allocation only to HCV-PCR positive recipients or special cases, retrospective confirmation by HCV-PCR beneficial. Donor infectious for hepatitis C.
HBsAg	Every prospective donor	If positive, allocation only to HbsAg positive recipients or special cases. Donor infectious for hepatitis B.
Anti-HBc-total	Every prospective donor	Sometimes false positive extend testing to anti-HBs quantitative and anti-HBc-IgM for final conclusion. If anti-HBc-IgM negative and anti-HBs negative, allocate organs as indicated below, perform HBV-PCR for exclusion of viremia retrospectively. If also negative, false positive test very likely, perform second test for confirmation.
Anti-HBc-IgM	Only if anti-HBc positive	If also positive, donor has had hepatitis B recently, donor very likely to transmit hepatitis B to liver recipient (lower risk if heart or kidney is transplanted to recipient successfully hepatitis B vaccinated or with pre-existing hepatitis B). HBV-PCR retrospectively for exclusion of viremia, which is possible.
Anti-HBs quantitative	Only if anti-HBc positive	If measurable, donor had hepatitis B some time ago and has sufficiently recovered. Viremia unlikely. Donor very likely to transmit hepatitis B to liver recipient (low risk if heart or kidney is transplanted to successfully hepatitis B vaccinated recipient or one with pre-existing hepatitis B.
Anti-HDV	All donors with hepatitis B infection in areas with endemic hepatitis D	If positive, risk of liver failure due to co-infection in recipient.
Anti-CMV	Every prospective donor	If positive, risk of liver failure due to co-infection in recipient.
TPHA	Retrospectively	If positive, confirmatory testing required plus antibiotic therapy in recipient.
Toxoplasmosis	Heart donors (retrospectively?)	If positive, lymphoma induction possible in recipient.
EBV	Children, other?	If positive, lymphoma induction possible in recipient.
Prions	Currently no test	Check for future developments.
Anti-HTLV 1-2	All donors in areas with endemic infection	If positive, transmission infection may induce malignancies.

It is important to mention that some organs recovered from donors with HBsAg,

such as kidneys [13,14], liver or heart, can be transplanted to recipients infected by the same virus.

Positive antibody to hepatitis B core antigen (anti-HBc) titres indicate a high risk of hepatitis B transmission through liver transplantation [15] (Table 3) but a lower risk through heart or kidneys transplantation. Since anti-HBc screening frequently produces false positive results, it is advisable to additionally determine anti-HBc-IgM (positive, very recent infection) and anti-HBs (meaning immunization). In areas with a high rate of hepatitis D co-infection, anti-HDV antibodies should be also tested in HBsAg positive patients.

There is also some concern about when to screen for cytomegalovirus (CMV), Epstein-Barr virus (EBV), *Treponema pallidum* (TPHA), *Toxoplasma gondii* and Human T-lymphotropic virus (HTLV) 1-2. In central Europe and France, CMV and HTLV 1-2 are screened beforehand. Conversely, in paediatric patients, EBV screening occurs afterwards, and the same applies to *Toxoplasma gondii* in heart transplants.

DID YOU KNOW ...?

The use of virus polymerase chain reaction (PCR) testing is usually not available. At present no blood test is available to exclude prion infection. In general, serological determinations must be performed in a certified laboratory using a licensed reagent for diagnosis. The laboratory should have standard operating procedures that include an algorithm when positive results appear, using the same kit on the same sample.

Table 4. Risks of transmission

Donor ser. pattern	HBV DNA in blood	Risk transmission of HBV to liver recipient	Risk transmission of HBV to extrahepatic recipient
HbsAg+	Yes	Yes	Yes
HbsAg-Anti-HBs+a Anti-HBc	Unlikely	Yes, but small	Rare
HbsAg-Anti-HBs +,-Anti-HBc-	Possible	Yes, regardless of anti-HBs+ donor	Yes, but small from anti-HBs+ donor

a. Check donor history for HBV vaccination

b. Clarify false positive results, especially if HBs-

Donors with high-risk practices

Organ transplantation from donors with high-risk practices (injecting drug use, MSM, sexual intercourse with people who have high-risk practices, etc.) increases the risk of transmission of certain infections. In the past, organs were not routinely used for transplantation even though serological tests for HIV, HBV, and HCV were negative, as disease transmission can occur if the donor is in a very early stage of infection and has not yet seroconverted (window period). With the greater availability of tests based on the determination of nucleic acids in real time, the window period of a viral infection has been reduced from a period of months to approximately one week. On the other hand, the risk of viral transmission from a donor with high-risk behaviours and negative results in nucleic acid determination is less than 1 case per 1,000 donors for HCV and 1 for every 10,000 for HIV. The rejection of organs for transplantation is even

more relevant when we consider that donors are often younger and have fewer comorbidities than other donors. A careful analysis of the risk the donor represents and the benefit the transplant can bring to the recipient is essential before rejecting a donor.

It should also be borne in mind that the management of HCV-positive donors has radically changed with the appearance of new treatments for HCV with direct-acting antivirals (DAA).

Serological screening for HCV infection is required for all donors, based on the demonstration of anti-HCV antibodies by immunoassay techniques. The determination of HCV-RNA with PCR is recommended for all positive anti-HCV donors and for high-risk negative anti-HCV donors since it allows a reduction of the 40–50-day window period (from infection to anti-Ac positivity). In positive anti-HCV donors, since the infectivity of the donor depends on the existence of replication, determination of HCV-RNA with PCR also makes it possible to differentiate the HCV+ viraemic from non-viraemic donor, thus better estimating the risk of transmission, adjusting a match to the recipient and subsequent management. Transmission of infection from a non-viraemic positive HCV donor is exceptional, whereas the viraemic positive HCV donor transmits HCV infection to practically all patients, regardless of the organ transplanted. Therefore, regardless of the organ to be transplanted, the attitude should be treatment with DAA in the case of a viraemic donor (positive HCV- RNA) and specific monitoring in the case of a non-viraemic donor (negative HCV-RNA) (Table 3).

Table 5. Potential risk of organs used for transplantation from HCV-infected donors

Hepatitis C tests	Conclusion	Liver: transmission risks to consider & possible recipients to select for transplant	Non-hepatic organs: transmission risks to consider& possible recipients to select for transplant
Anti-HCV+ HCV-NAT not available	HCV viraemia cannot be ruled out*	HCV transmission occurs via the graft: Vital cases or viraemic recipients with mandatory HCV-prophylaxis/ pre-emptive treatment, as well as lifelong monitoring by serology and NAT required. In HCV *naïve* recipients, known use of grafts from HCV-viraemic donors should currently only be performed in approved study protocol and/or with informed consent in dire recipient conditions.	
Anti-HCV+ HCV-NAT+ Anti-HCV- HCV-NAT+	HCV viraemia		
Anti-HCV+ HCV-NAT-	HCV viraemia unlikely*	HCV transmission may not occur; transplantation after informed consent of recipient in study protocol possible for D+/R-. In D+/R	

+ = reactive; - = non-reactive

*HCV viraemia may be below the detection threshold of HCV-NAT. This causes a non-reactive result. Therefore, appropriate data should be collected (about the course of HCV treatment or evidence of spontaneous clearance).

Source: Guide to the Quality and Safety of Organs for Transplantation. 7th edition. EDQM. P 182. 2018.

3. SECTION 3: CLINICAL CONTRAINDICATIONS FOR DONATION

We will now review the absolute and relative contraindications for donation. Whenever there are contraindications, local teams should be asked if they wish to receive a certain organ in the specific circumstances.

3.1 Human immunodeficiency virus - HIV

Any donor who is tested and found to be positive for HIV types 1 and 2 antibodies must be rejected [16]. Techniques to detect HIV or its antibodies have improved, and window periods have reduced: third generation kits and HIV p24 antigen determination may reduce the window period to 25 and 14 days respectively. A PCR test (for RNA or DNA) reduces it to 11 days and in the future may become the technique of choice for extended safety [17].

Organ donors with negative serological markers for HIV but a medical and social history of risk (e.g., intravenous drug abuse during the past 12 months) should be ruled out since we cannot ensure a lack of disease transmission due to the previously mentioned diagnostic window.

3.2 Tumours (1/2)

In general, cancer is an absolute contraindication for organ donations except for:

- basocellular carcinoma;
- *in situ* cancer of the uterus;
- some non-metastatic tumours if they are in a cancer-free period longer than 5 years [18]. Each tumour should be analysed individually. Close cooperation with oncologists is advised. Disseminating malignant diseases, e.g., leukaemia, are always an absolute contraindication;
- some primary brain tumours.

To rule out incidental cancer, a donor autopsy is recommended. If this is not possible, a careful abdominal (intestine, liver, retroperitoneum) and thoracic (lung, pleura, mediastinum) inspection must be performed during organ extraction. In case of doubt, a biopsy is called for.

3.3 Tumours (2/2)

Primary tumours of CNS constitute 3-4% of the causes of brainstem death in organ donors. Although they rarely spread outside the CNS, distant metastases have been described in 0.4% to 2.3% of cases, [19,20] in lungs, pleura, lymph nodes, bone, liver, adrenal glands, kidneys, mediastinum, pancreas, thyroid and peritoneum.

Risk factors for transmission are a high-grade tumour, presence of ventricle-peritoneal or ventricle-atrial shunts, prior craniotomy, systemic chemotherapy and radiation therapy [21]. Patients with at least one of these factors should not be considered for donation.

The World Health Organization (WHO) provides a comprehensive classification of CNS neoplasms (Table 3), based on the specific cell type involved [59]. This WHO classification provides a parallel grading system (I to IV) for each type of tumour, depending on its behaviour and, hence, dictates the choice of therapy and predicts prognosis.

In case of doubt about the presence of an encephalic mass, it is essential to perform an autopsy after organ extraction to identify the type of tumour, especially when the cause of death was intracerebral bleeding of uncertain aetiology [22].

3.4 Acute infections

Determination of the presence of an active infection is a difficult task in donors [23]. Patients with severe traumatism or haemorrhage can present fever and leucocytosis without infection. Similarly, during and after cranial herniation, fever, very high leukocyte counts (e.g., up to 28 g/l) and haemodynamic instability may develop, simulating a SIRS-like syndrome.

In any potential donor it is important to confirm the presence of infection (generalised or localised) and the antibiotic treatment. If the donor has been under antibiotic therapy for at least 48 hours before organ recovery, it is essential to continue the same treatment in the recipient for at least 10 more days.

Absolute contraindications for donation are disseminated infections related to the donor's death, bacterial sepsis with shock and fungemia. Local infection e.g., pneumonia due to aspiration, does not constitute a contraindication for the donation of other organs that are not affected. A definitively cured infection is also not an absolute contraindication, e.g., a confirmed negative blood culture after antibiotic therapy because of bacteraemia (Table 4).

Table 6. Absolute and relative contraindications of acute infection for organ donors

Acute infection Relative contraindication	**Acute infection** Absolute contraindication
» haemodynamic stability	» disseminated infection implicated in the donor's demise.
» anatomical and functional integrity of the organ to be retrieved	» bacterial sepsis with shock and/or organic malfunction
» absence of multi-resistant microorganisms	» fungaemia
» adequate antibiotic therapy in the donor for at least 48 h.	» fungal colonization of the lung
» antibiotic therapy in the recipient for a minimum of 10-14 days post-transplant	» active tuberculosis
	» meningitis by: *L. monocytogenes; M. tuberculosis* protozoans; fungi.
	» Organ to be retrieved with known acute infection or colonized by multi-resistant bacteria

4. SECTION 4: EXTENDED CRITERIA DONOR

4.1 Introduction

While the number of patients on the waiting list continues to increase, the absolute number of donors, as well as the rate of donors/pmp has not significantly varied in recent years, at least in the West (Figure 7). As a consequence, the utilization of organs from so-called "marginal donors" has increased [24].

The term "marginal donors" is frequently used to refer to a wide range of donors who do not meet the classic screening criteria who can present different conditions that may hinder the function of any or all of their organs:

- pre-existing comorbid factors such as age, arterial hypertension, diabetes, alcoholism, smoking, medication or systemic/localised organ disease such as hepatitis, glomerulonephritis or cardiomyopathy;
- acute organ damage due to an acute event, e.g., trauma, pulmonary embolism, cardiac failure, hypoxaemia;
- insufficient therapy in the ICU before and after diagnosis of brainstem death, e.g., diabetes insipidus, volume depletion, electrolyte disorder, high doses of catecholamines or low blood pressure.

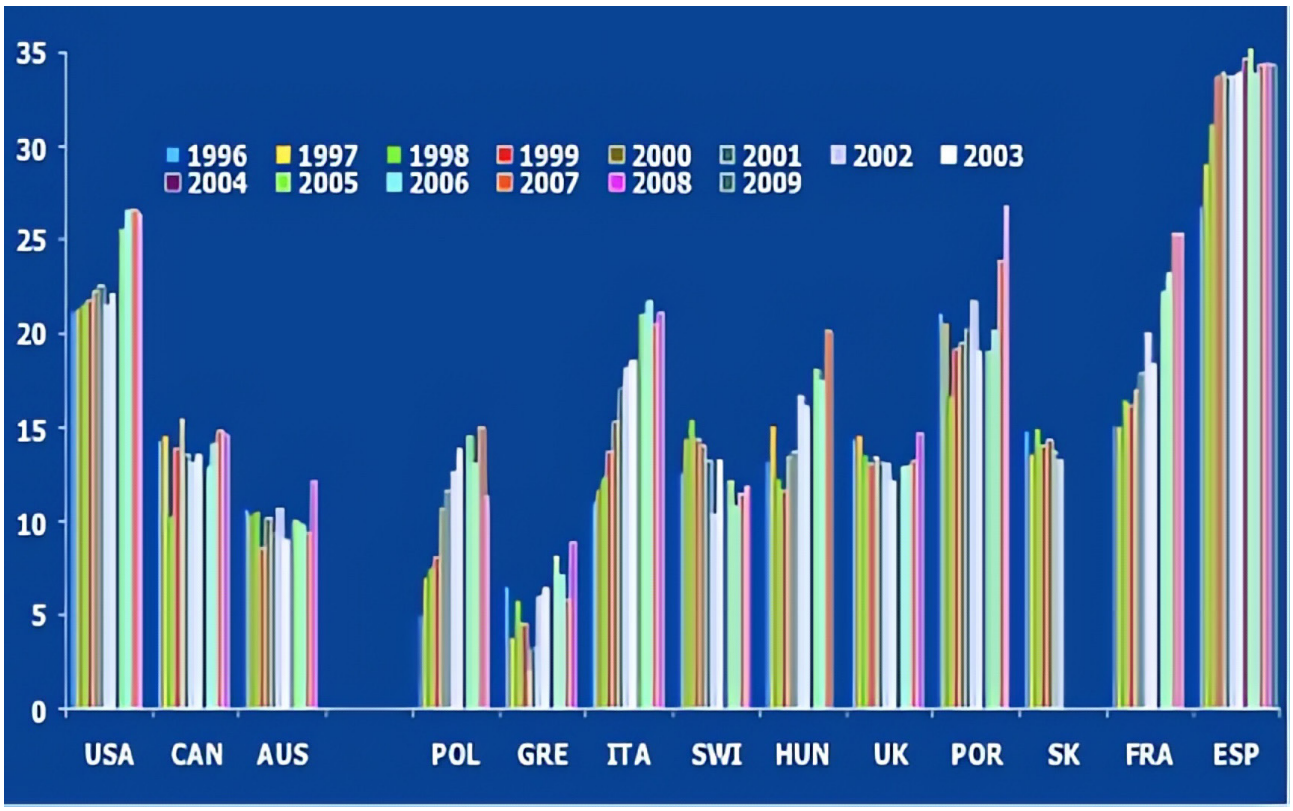


Figure 7.

4.2 Concept

Marginal donors reflect the reality of the changing profile of potential donors in developed countries. It is interesting to note that with the criteria applied 15 years ago, many of today's donors would be considered marginal. The term "marginal donor", which arose towards the end of the 1990s to refer to deceased donors who did not meet the standard criteria for donation but were suitable for transplant [25], generated conflict as this term suggested that the results were inferior, sub-optimal, and of questionable benefit [26].

Later, the concept of extended or expanded criteria donor (ECD) was defined to refer to donors who, due to extreme age and other clinical characteristics, were eligible for organ donation but expected to produce an allograft at risk of diminished post-transplant function [27]. This supposed a change in donor acceptability criteria. Factors once considered to affect donor acceptability have changed over time after having proved that they did not negatively affect the survival of the patient's graft in itself or when adequate measures are adopted [28].

4.3 Reasons for accepting ECD donors

ECD donors offer the possibility of extending the life of patients with an urgent need for a transplant or ones who would have never obtained a transplant due to their clinical conditions. Other reasons for accepting ECD donors are [29-31]:

- the shortage of organs suitable for transplant;
- a reduction in the number of young, deceased donors due to traffic and labour laws, which has resulted in a lower number of motor vehicle, industrial accidents and homicides;
- an increase in current life expectancy resulting in a larger number of older deceased donors, many of whom have died from chronic systemic medical illness related to atherosclerotic disease of intracranial and coronary vessels;
- advances in transplant technology, immunosuppressive therapy and the use of organs from individuals who die as a result of cardiac arrest.

The establishment of pre-, peri- and post-transplantation strategies to optimize organ selection, reduce cold ischaemia times, and select the adequate recipient, will reduce the difference between graft outcomes in patients grafted from ECD and standard criteria donors (SCD) [32].

4.4 Characteristics of expanded criteria donors and standard donors: general aspects

The first step to understanding the concept of ECD is to define a standard criteria donor (SCD). An SCD is a donor who is under 60 years of age, with no history of hypertension or diabetes, who had short periods of warm ischaemia time during donor medical management and did not require high doses of vasopressors. The cause of death would be traumatic head injury limited to brain, leaving thoracic and abdominal organ functions intact [33].

Clearly, SCD donors are not the typical donor we habitually encounter in our ICUs today. Some of the clinical characteristics that differentiate ECD from SCD are detailed in the Table 5 [33-34].

DID YOU KNOW ...?

In all cases, recipients must always be informed about the option of receiving an ECD organ, which requires continuous dialogue between the patient and the healthcare professionals in charge, in this case the transplant team.

Although some authors consider that ECD only applies to kidney transplants, currently this type of donor is expanding to the liver, lungs and heart.

Table 7. Standard and expanded criteria donors

Characteristic	Standard criteria donors (SCD)	Expanded criteria donors (ECD)
Cause of death	Trauma	Cerebrovascular accident, CNS tumour, intoxicated donors
Mechanism of donor death	Brainstem death status	Cardiac arrest
Deceased donor's medical history	Age = 60 years History of hypertension: NO Diabetes: NO Risk of transmitting viral infectious diseases (Hepatitis B, C, and HIV): NO	Age = 60 years History of hypertension: YES Diabetes: YES Risk of transmitting viral infectious diseases (Hepatitis B, C, and HIV): YES Metastatic tumour disease: YES
Bacterial infectious diseases: during stay in the ICU and prior to organ retrieval	NO	NO
Serological tests (results) for viral diseases such as hepatitis B, C and HIV	Negative	Any positive result that involves a risk of transmitting disease to the recipient: hepatitis B surface antigen; hepatitis C antibody, HIV antibody. Metastatic tumour disease: YES
Anatomy of the allograft: vessels and/or parenchyma	NORMAL	Abnormal: due to disease or trauma
Histological profile	NORMAL	Kidney: glomerulosclerosis, fibrosis, interstitial nephritis Liver: macro-vesicular
Functional profile	NORMAL	Kidney: serum creatinine >1.5 mg/dl Liver: elevated hepatic enzymes
Others		Split liver procedure

4.4.1 Age

Older donors present a higher incidence of hypertension and diabetes mellitus, frequently of long-standing course, lesions of parenchyma such as fatty liver and multiple simple cysts of kidneys, as well as undetected cancer, particularly of the kidney and prostate.

DID YOU KNOW ...?

The trend in the USA and some European Union countries (Spain) is a continuous increase in donor age, although the mean donor age is changing worldwide. In Spain, in 2006, it was 51.4 years (SD 18.8) while in 1992 it was 34.5 years (SD 17) (Figure 1). In the USA, while the average age of deceased donors increased steadily from 34.2 years in 1995 to 39.8 years in 2004, the percentage of donors aged 50–64 years increased from 19% in 1995 to 25% in 2004.

Data on the graft outcomes in recipients transplanted with aged donor organs are conflicting. While several clinical and experimental studies show advanced donor age as a major risk to graft failure [35-36], other studies report good transplant results for most grafts [37-39]. Hypertensive and diabetic donors adequately treated while alive can have minimal arterial and parenchyma lesions and can donate any of their organs with good transplant results.

Although the number of organs from older donors that are rejected is higher [40], the use of such donors can help reduce the waiting list. Nowadays, there is no age limit to becoming an organ donor and organs should be accepted or rejected according to their functional and structural state at the time of removal and transplantation.

4.6 Expanded kidney criteria

The definition of ECD kidneys is those with a 70% higher risk of graft failure than ideal kidneys. ECD kidneys include all those aged >60 years or donors aged 50–59 years with at least 2 of the following criteria [27]:

- cerebrovascular accident as cause of death;
- terminal serum creatinine >1.5 mg/dL;
- history of systemic hypertension.

The number of ECD donated kidneys has increased by 16% in recent years and represents an almost 60% increase in organs donated [41]. Despite the fact that these organs may have poorer outcomes due to prolonged cold ischaemia time (CIT), increased immunogenicity, and impaired function with decreased nephron mass, the recipients of ECD grafts benefit from extra years of life compared to dialysis patients on the waiting list [42]. The survival benefits of these kidneys are considerable for recipients older than 40 years of age, and patients with diabetes and hypertension [43]. Conversely, patients younger than 40 years or scheduled for retransplantation should not receive ECD kidneys [44].

Management protocols for ECD kidney transplantation should be based on potential nephron-protecting strategies. This includes minimization of cold ischaemia time, pulsatile perfusion preservation, tailored immunosuppression and adequate infection prophylaxis [45].

4.7 Expanded liver criteria (1/3)

Expanded criteria liver donors fall into 2 categories: one related to the donor condition and one related to surgical technique [46].

Donor-related issues include DCD, advanced donor age, increased cold ischaemia time, steatosis, previous malignancy, the presence of acute infections (HCV) or other high-risk donors. According to recent multivariate analyses, factors such as female donor, obesity, elevated liver function test, low blood pressure/increased pressor use and hypernatremia are not independent risk factors for poorer outcomes [47-49].

A lower 3-year allograft survival has been reported in DCD allograft recipients, supposedly because of primary nonfunction and biliary complications, all of which are mostly related to prolonged ischaemia times [50,51]. Careful selection of recipients as well as the institution of practice protocols related to organ recovery and improved surgical techniques to diminish warm and cold ischaemia times may yield better outcomes for DCD liver recipients, similar to those of DBD grafts.

4.8 Expanded liver criteria (2/3)

The liver seems to resist aging very well, possibly due to its functional reserve, regenerative capacity and dual blood supply. Several centres have proposed criteria for acceptance of an allograft from an advanced age donor such as the careful selection of donor (hemodynamic stability, normal liver function test) and graft (no steatosis on visual examination or less than 30% by biopsy) [52], as well as shorter cold ischaemic times [53].

Similarly, recipients with hepatitis C should not receive grafts from old donors since it has been proved that graft results and patient survival in such cases is poorer [54].

In the absence of additional risk factors in the donor, the use of allografts with low or moderate steatosis (30-60%) may be considered [55] with the imposition of the mandatory requirement to perform regular donor biopsies by the recovery team.

Whereas historically, hepatitis C seropositive organs were routinely ruled out, the advent of direct-acting antiviral agents has notably expanded the utilization of organs from donors with hepatitis C. There has been growing experience with liver transplantation (LT) from hepatitis C seropositive donors. Patients who receive a hepatitis C seropositive or hepatitis C nucleic acid-testing-positive liver allograft can enjoy good outcomes with a hepatitis C cure following direct-acting antiviral treatment (Figure 8).

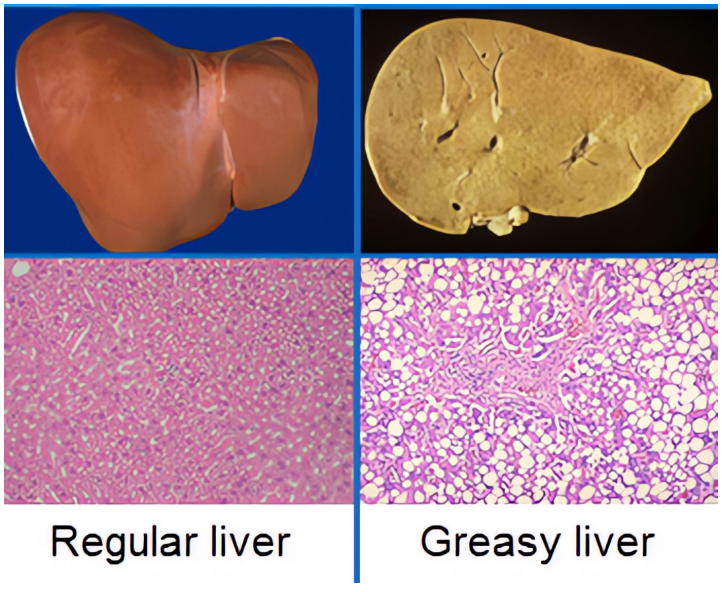


Figure 8. Steatosis.

4.9 Expanded liver criteria (3/3)

Among surgical technique-related issues we find split liver donation and living donor liver transplantation (LDLT). Split liver donation, in which one allograft is split into two transplantable allografts (segments IV-VIII going to an adult recipient and segments II y III to a paediatric recipient) has become a great source of increasing the allograft pool. When performed with the appropriate liver and the adequate technical precision, this technique has shown no significant differences in patient and allograft survival up to 5 years compared with whole liver transplantation [57].

Many institutions no longer consider living donation an extended criterion. Several authors conclude that LDLT is a feasible option when comparing the survival rate with that of deceased donation [58]. However, special care needs to be taken with both the donor and the recipient, and good surgical skills are required to remove sufficient liver parenchyma from the donor to keep the recipient alive without prejudicing the donor (at least 30% of liver parenchyma needs to be left for the donor to ensure successful recovery).

CONCLUSIONS

» With current worldwide demographic trends, TCs have to deal with ECD on a daily basis and make decisions with transplant teams about whether to accept or decline these types of donor.

» There is no consensus on the characteristics that define ECDs, or on the factors that would compel rejection of a donor as an unacceptable risk to the recipient. It is advisable to ascertain the policies about these types of donor in each country or region so as to facilitate decisions concerning issues such as allocation, dismissal and sharing.

» The patient must always be informed about the option of receiving an ECD organ, which entails continuous dialogue between the patient and the transplant team.

» Hepatitis B and hepatitis C-positive donors, with normal functional tests and anatomical integrity should be evaluated by the TC and the transplant team on individual basis.

» The increased number of ECDs is the result of organ shortages and the data available on the positive outcomes of ECD grafts.

Summary

Donor detection and evaluation is the first important step in the organ donation process.

Its correct performance is vital to guarantee safe, effective transplantation.

TCs are responsible for the adequate management of all steps involved in the donation process.

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TOPIC 2 - Unit 1

Brain death: concepts and definitions

ORGAN DONATION

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2. SECTION 2: CONCEPTS IN BRAIN DEATH 57

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Organ shortage is one of the main difficulties that may hinder the development of organ transplant programmes. Brain death (BD) deceased donors remain the main source of organ supply, and therefore the diagnosis of BD is an essential step in organ recovery.

Even though it is not the responsibility of organ donor/transplant coordinators, all healthcare professionals involved in donation and transplantation should have fundamental knowledge of BD as well as of the ethical and social aspects involved in order to:

- improve knowledge about BD;
- give accurate information concerning BD to the relatives of potential donors;
- provide support to healthcare professionals not acquainted with BD diagnosis;
- collaborate logistically (instrument management, serum drug levels, etc.) in difficult cases that may require atypical methods of diagnosis;
- comprehend the ethical aspects involved. Since nowadays BD is synonymous with death, no patient diagnosed with BD must be submitted to any further organ-perfusion support measures.

INTRODUCTION

The definition of death has long been a difficult issue to establish. It has evolved with medical knowledge and is influenced by cultural aspects. The determination of brain death has allowed the criteria for its diagnosis to be established and has enabled organ donation.

The objectives of this unit are to:

- define the concept of death as a process;
- define the concept of brain death according to different medical approaches.

1. SECTION 1: DEATH

It would seem clear that death is the end of life. However, stating that one concept (death) is the end of another concept (life) is not sufficient in itself and it is mandatory to establish some of the key points which allow us to understand the concept of death in order to diagnose it.

The concept of death has changed in step with the progress of medical knowledge but is also influenced by cultural aspects. The currently accepted concept of death is based on irreversible vital failure with the lack of any substitutes.

Another issue is that as pluricellular organisms, for human beings, death is the result of a progressive process, rather than an exact moment.

1.1 Death as a process

In biological terms, the death of a human being is not instantaneous but rather an evolutionary process during which different organ functions gradually extinguish, ending when all the body's cells irreversibly cease to function.

We know that death is a process. However, society requires doctors not only to provide a biological confirmation of death, but also to establish an exact time of death, which is to say, to establish the time of clinical death, understood as the irreversible cessation of the body's vital functions.

DID YOU KNOW...?

Although death is a process, physicians have to determine and confirm the time of the death as the event which separates the process of dying from the process of body disintegration. Therefore, death can only be confirmed retrospectively once it has occurred.

Thus, although there are cells in the body that continue functioning after a person's death, the limit established between life and death is the irreversible loss of critical function.

The concept of death has evolved throughout history. In ancient Greece, death consisted of the loss of the vital spirit, which was located in the heart. Hence, for the ancient Greeks, death was established by the lack of a pulse and breathing. In the 18th and 19th centuries, with Virchow's contribution to cell theory, death was considered a process in which the different organs and tissues progressively ceased their functions. Thus, the absence of a pulse and breathing started the process of death but the presence of signs of putrefaction (death of cells) was considered essential to diagnose death. This is why a period of 24 hours before burial was frequently included in clinical practice.

In the 20th century, Mollaret and Goulon described "coma dépassé" (literally, "a state beyond coma" [2]). Later, in 1968, at the 22nd Meeting of the World Medical Association a consensus was reached stating that the determination of death needs to be made using neurological criteria, and that the diagnosis of brainstem death and confirmation of time of death time remains the responsibility of the medical practitioner [1].

1.2 The frontier between life and death

The lack of any kind of body movement (including respiratory movements and heart pulse) has been the most accepted sign to distinguish the approach of death in the individual. This was justified because the lack of cardiac and respiratory movements was followed by a rapid and irremediable development of the multiple processes of organic decomposition (rigidity, putrefaction, etc.) identified with death.

The development of life support techniques changed the prognosis of a vast number of processes that had previously ended in death. Currently, certain diseases hitherto considered fatal (cardiogenic shock, severe respiratory failure, etc.) can be controlled using life support techniques capable of completely replacing a patient's cardiac and respiratory functions. After resolution of the acute process, the patient may not depend on the life support elements and will then be able to return to a normal life.

This has changed the concept of organic failure hitherto used to establish the frontier between life and death since nowadays the presence of severe cardiocirculatory, respiratory or neurological failure does not inevitably end in death due to the lack of substitutes for these organic functions.

At present, the complete and irreversible failure of central nervous system functions (brain death) constitutes the authentic frontier between life and death in human beings. The main reason for this statement is that complete neurological failure is irremediably associated with cessation of cardiac and respiratory functions and, consequently, the immediate start of the death process.

However, thanks to mechanical support techniques, the cessation of cardiac function can be deferred for hours or days. The situation of an irreversible absence of central nervous system functions, the inability to maintain spontaneous body homeostasis, with spontaneous cardiocirculatory function and assisted ventilation, is defined as brainstem death, and accepted in many countries as the legal death of the individual [3].

Death is a continuous process. Nevertheless, physicians who determine the diagnosis of death are also required to establish when death occurs, that is to say, the time of clinical death.

It is also necessary to know that the barrier between life and death is represented by the irreversible failure of the central nervous system, which leads to the cessation of body functions.

2. SECTION 2: CONCEPTS IN BRAIN DEATH

Not all medical schools accept the same concept of brain death. There are three different concepts for brain death: global brain death, neocortical brain death and brainstem death. Consequently, the criteria for diagnosis are different according to the concept of brain death used.

However, given that the human being has one central nervous system, does it make sense to have three different concepts of brain death? And given that the central nervous system consists of different parts, does it make sense to focus the diagnosis on one part of the CNS?

The optimal concept is, therefore, one which demonstrates the cessation of the central nervous system's function as a whole, that is to say, the cessation of all the CNS emergent functions for maintaining life: consciousness (capacity of consciousness -arousal- and content -awareness-) and the capacity to breathe. In this section we review the following subjects:

- Brainstem death
- The diagnosis of death
- Neocortical death
- Whole brain death

2.1 Brainstem death

The concept of brainstem death was developed following criteria established at the 1976 Conference of Medical Royal Colleges and Faculties (UK), with the definition set out in a document named the United Kingdom Code [4].

The definition of brainstem death establishes that there is only one type of human death: the irreversible loss of the capacity of consciousness (arousal) combined with an irreversible loss of breathing (and implicitly, irretrievable asystole).

This concept postulates that the irreversible loss of brainstem function is enough for human death because the capacity of consciousness (arousal) originates in the pons and mesencephalon. Both of these structures form part of the ascending reticular activating system (ARAS) located in the brainstem, and the capacity to breathe originates in the lower part of the brainstem.

However, this concept does not include the other dimension of consciousness: awareness, which mainly depends on the cortex. Furthermore, to maintain normal consciousness, interconnections between the ARAS, other subcortical structures and the cerebral cortex are required. Consciousness does not, therefore, only depend on brainstem function.

According to this concept, death occurs due to irreversible damage of the brainstem. It is defined by the complete absence of brainstem function, which is shown by the absence of brainstem reflexes in a clinical examination. No instrumental tests are required for the diagnosis of brainstem death.

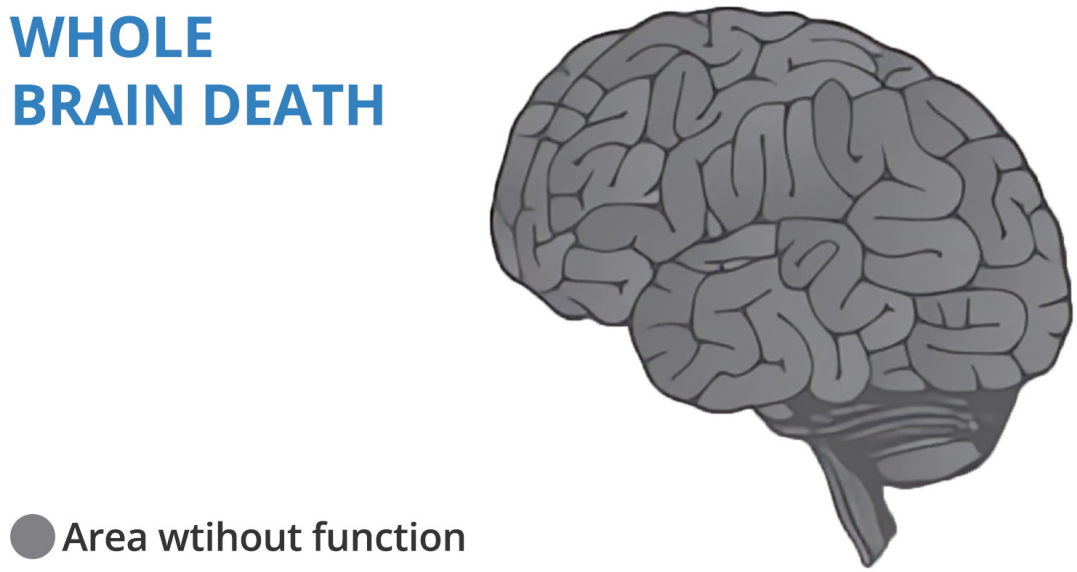

Figure 1. Brainstem death.

2.2 The diagnosis of death

Three concepts of brain death, DCD donation and somatic death. How many ways are there to die? As previously mentioned, the line between life and death is defined by the presence of an irreversible failure of the central nervous system. Of course, there are different ways to die, but there is a common final outcome, the irreversible failure of the central nervous system, which leads to the irreversible loss of the capacity for consciousness (capacity and content) combined with the irreversible loss of the capacity to breathe.

Thus, it is possible to diagnose the death of a person based on three different criteria: cardiac, brain or somatic [8].

The diagnosis of death can be based on:

2.2.1 Circulatory criteria

An irreversible cessation of cardiac and respiratory functions, which leads to the end of all brain activity, causing the death of the individual. Hence, to employ this criterion it is necessary to demonstrate the irreversible or permanent failure of circulation and breathing.

2.2.2 Neurological criteria

It is necessary to demonstrate an irreversible cessation of function of the central nervous system.

2.2.3 Somatic criteria

This is used when features of death are visible on external inspection of the corpse, such as a decapitation, hemicorporectomy, decomposition or putrefaction, etc.

Any of these criteria can be applied for the diagnosis of death, depending on the clinical setting. If the diagnosis is performed after cardiorespiratory arrest, circulatory criteria are usually employed. If the clinical setting is the intensive care unit, with the patient under mechanical ventilation, neurological criteria can be applied. When death may have occurred hours to days before, somatic criteria can be applied [8].

Internationally, there is a lack of consensus on how long circulation and respiration must cease for a person to be determined dead after cardiorespiratory arrest. Thus, there is no consensus on the waiting times required to establish death after a cardiocirculatory arrest that leads to the irreversible damage of the central nervous system. The shortest time reported is 65 seconds; however, 60 minutes after the cessation of cardiocirculatory and respiratory functions, it is impossible to restore any brain activity.

2.3 Neocortical death

This formulation has emerged recently.

Higher brain death or neocortical death is defined as the loss of what is significant for the nature of human being, which is to say, the irreversible loss of the content of consciousness -awareness- which involves crucially significant functions for human life such as reasoning, consciousness, personal identity and social interaction. Hence, the loss of awareness would be incompatible with life.

Anatomically, this is based on the permanent cessation of neocortex function.

To diagnose neocortical death, a clinical examination is used, and the presence of brainstem activity is considered not relevant.

TO KNOW MORE...

In this concept, the anatomical and physiological substrate is the neocortex. Based on this, patients with a severe irreversible cerebral hemispheric damage who are in an irreversible vegetative state are classified as dead.

In this concept, the other dimension of consciousness -arousal- is not considered. However, as previously mentioned, to maintain both dimensions of consciousness, there must be interconnections between the neocortex and subcortical structures. Furthermore, it is impossible to measure the subjective dimension of awareness.

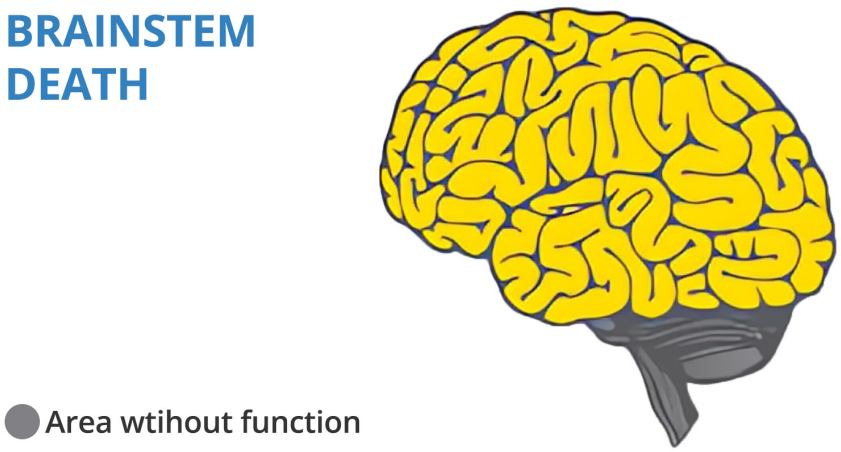

Figure 2. Neocortical death.

2.4 Whole brain death

This is the most widespread concept of brain death and considers brain death as the sum of a lack of brainstem and cerebral hemisphere activity, which is to say, the irreversible cessation of neocortex and brainstem neurological functions.

In this concept, death is defined as a cessation of the critical functions of the human organism as a whole. Hence, the irreversible loss of the body's critical emergent functions leads to the loss of the organism functioning as a whole, which means its death. This concept requires the cessation of all brain functions (including cerebral hemispheres, brainstem and other structures).

TO KNOW MORE...

The whole is more than the sum of its parts, and an emergent function is the function performed by the whole and not by its parts separately. Consciousness is the best example of an emergent function: it is basic for human life, and it depends on the integrated functioning of ARAS (arousal), cerebral hemispheres (awareness) and their interconnections.

The diagnostic criteria for this type of death include not only clinical examination, but also the use of tests that examine CNS functions (electroencephalogram, etc.) or phenomena related to brain death (cerebral circulatory arrest using cerebral blood flow tests, etc.) [5-7].

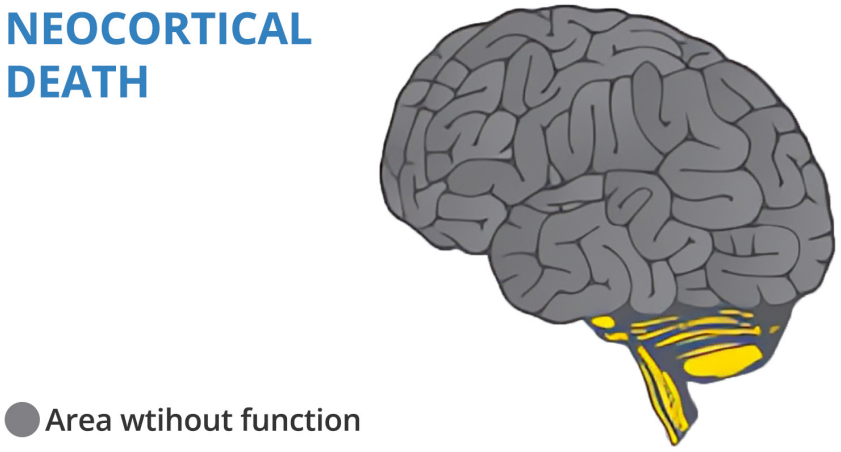

Figure 3. Whole brain death.

CONCLUSIONS

» Death is a progressive process and is determined when irreversible failure of the central nervous system is confirmed.

» The concept of death has evolved throughout history. It has not only medical implications, but also important social, ethical and philosophical reasons.

» There are three concepts of brain death: whole brain death, brainstem death and neocortical death. Thus, regarding death, it is essential to establish the concept of death and the criteria for its diagnosis.

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TOPIC 2 - Unit 2

The diagnosis of brain death

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2. SECTION 2: CLINICAL EXAMINATION FOR THE DIAGNOSIS OF BRAIN DEATH 69
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INTRODUCTION

It is important to know the protocol for the diagnosis of brain death (who is the person in charge of establishing it, where and how it must be done). The patient must meet some requirements before the process of diagnosis can go ahead. In this regard, clinical examination and complementary tests need to be performed. It is essential to know the pathophysiology of the central nervous system in order to be able to conduct the clinical examination, which must be methodical.

The objectives of this unit are to:

- learn how to perform the clinical examination of brain-dead patient;
- know how to interpret the complementary tests.

1. SECTION 1: DIAGNOSIS OF BRAIN DEATH: WHO AND HOW. CONTEXT (ELEMENTS) THAT SUPPORT IT. NECESSARY PERIOD FOR DIAGNOSIS

Brain death is a very important diagnosis for both clinical and legal reasons. Thus, it is mandatory to establish the optimal framework to perform the diagnosis.

There are some key issues to consider when conducting the diagnosis. Who should perform it? The physician in charge of the patient or another doctor? There are some clinical conditions to comply with before starting the clinical examination. It is also necessary to highlight that there are certain pathophysiological phenomena related to brain death which facilitate its diagnosis.

Another important issue is whether it is necessary to wait some time before repeating the clinical examination or complementary tests to certify the patient's death.

In the diagnosis of brain death, as in any other diagnosis, it is essential to differentiate between what is a medical diagnosis and what it is a legal one. A legal diagnosis consists of establishing a diagnosis that meets the minimum requirements established by the law. On the other hand, performing a medical diagnosis is to do so according to the best medical knowledge available. Therefore, a medical diagnosis will always be equal to or more complete than a legal one.

1.1 Who should make the diagnosis?

The physicians attending the patient should perform the diagnosis of brain death. They need to be experienced in neurological diagnosis. If instrumental tests are required for the diagnosis (EEG, evoked potentials, arteriogram), they are best carried out and interpreted by specialists (neurophysiologists, radiologists, etc.), although this is not essential. In some countries, legal requirements demand the participation of three doctors in this diagnosis, one of whom must be a neurologist or neurosurgeon and another one a physician of the unit where the patient is admitted.

The transplant procurement management (TPM) coordinator should never participate in or be part of the team of doctors who make the diagnosis of brain death, in order to avoid any appearance of there being possible conflicts of interest. However, the TPM coordinator may assist and guarantee that the diagnosis has been made correctly, as well as providing the best instruments to do it.

Before conducting the diagnosis of brain death, it is essential to rule out possible situations which may mimic brain death but could be completely reversible.

1.2 How should the diagnosis be conducted?

First, the cause of brain damage (head injury, stroke, brain tumour, anoxia, etc.) must be known, in order to establish the irreversibility of the process.

It is also necessary to exclude certain conditions that could simulate brain death in a patient, such as severe systemic arterial hypotension, severe hypothermia, metabolic disturbances, or the effects of certain drugs. Thus, before diagnosis, some requirements are mandatory:

Absence of systemic arterial hypotension

Systemic arterial hypotension can decrease cerebral blood flow, so blood pressure must be normalized (according to the age and medical history of the patient) before proceeding with the clinical examination.

Absence of hypothermia

Accidental or induced hypothermia is a factor which leads to a general decrease in brain activity, even attenuating brainstem reflexes, above all if the temperature is lower than 28ºC. The patient must be examined with a corporal temperature higher than 32ºC, but it is advisable to obtain a corporal temperature equal to or higher than 35ºC.

Metabolic disturbances: in brain dead patients, the most common metabolic abnormality is hypernatremia, which is secondary to diabetes insipidus. There is also a lack of secretion of other pituitary gland hormones. There are other metabolic or endocrine causes that may contribute to a coma, such as hypothyroidism, panhypopituitarism, adrenal dysfunction, uraemia and hepatic failure. Disorders of sodium, phosphate, magnesium and glucose balance could affect the response to brainstem tests, but the only metabolic disturbance to avoid before performing the clinical part of the diagnosis is hypernatremia higher than 165 mEq/L.

Pharmacologic agents: CNS-depressant drugs such as barbiturates (thiopental, phenobarbital) or benzodiazepines (midazolam, etc.) or other types of drug (e.g., propofol) can mimic the absence of brainstem function.

In the case of previous administration of such drugs, there are some possibilities to consider such as:

- using antagonists (flumazenil – Figure 1) in the case of drugs that can be antagonized (benzodiazepines);
- postponing clinical examination until the half-life of the drug has elapsed four times (Table 1);
- measuring serum level of the drug. If the neuro-depressant drug is within a therapeutic range, there is no contraindication for performing the clinical test.

There are other types of drugs that have to be antagonized before performing the clinical examination, such as neuromuscular blocking agents (depolarizing and non-depolarizing). If the patient is under the effects of one of them, an antagonist must be used (for rocuronium, which is an aminosteroid, non-depolarizing neuromuscular blocking agent, there is an antagonist available: sugammadex). Otherwise, it is necessary to wait four times the half-life.

Flumazenil is an imidazo-benzodiazepine antagonist that blocks the benzodiazepine´s receptor by a competitive interaction. The recommended initial dose in the intensive care environment is 0.2 mg intravenously administered in 15 seconds, adding doses of 0.1 mg each 60 seconds if necessary, until administering a total dosage of 2 mg. It is mainly eliminated through hepatic metabolism. The half-life of flumazenil is shorter than benzodiazepine´s half-life, so in patients who are alive, re-sedation induced by benzodiazepines can be observed after metabolizing the flumazenil, sometimes requiring continuous intravenous perfusion of flumazenil.

Figure 1. Flumazenil.

Table 1. Half life of some neurodepressor drugs frequently used in ICU

Midazolam	1-4 hours
Diazepam	20-70 hours
Propofol	30 min-4 hours
Morfine	2-3 hours
Droperidol	1,5-2 hours
Fentanyl	30 min-90 min
Remifentanyl	33 week of gestation
Thiopental	6-80 hours

1.3 Related pathophysiological findings: elements that support a diagnosis of brain death

There are some cerebral pathophysiological phenomena that are present when there is an irreversible loss of function of the cerebral hemispheres.

To establish the diagnosis of brain death, it is mandatory to demonstrate the loss of function of the brainstem and the loss of the function of the cerebral hemispheres. Proving the absence of brainstem function can be achieved by performing a clinical examination but, to prove the loss of function of the cerebral hemispheres cannot, so it is necessary to draw on to a complementary test that can demonstrate one pathophysiological phenomenon present in brain death (Table 2). The demonstration of such phenomena can be very useful to establish a diagnosis and the irreversibility of the process.

It is important to highlight that the presence of such phenomena is not synonymous with brain death since there may be function in the brainstem. So, it is possible to find, for instance, a patient with neurological brainstem activity but a flat electroencephalogram (EEG).

However, it is also important to stress that not all these tests have the same accuracy in diagnosing brain death. Neurophysiological and cerebral blood flow tests are the most accurate ones.

Table 2. Intracranial pathophysiological phenomena related to brain death

Cerebral circulatory arrest
Absence of bioelectric activity of the cortex
Decrease of $CMRO_2$
Other phenomena

1.4 Required period to establish the diagnosis

When the first criteria of brain death were described (Harvard Medical School Criteria), the clinical and complementary signs had to be sustained for at least 24 hours before confirming the diagnosis of brain death.

Medical knowledge has evolved, but national regulations and guidelines have not always kept pace with medical knowledge, so there are frequently discrepancies between the different guidelines regarding the necessity of a waiting period between clinical examinations, and about how long it is necessary to wait.

For the adult population, based on medical knowledge, it makes no sense to have to repeat the clinical examination or the complementary test after having established a diagnosis of brain death, because once this diagnosis has been made there cannot be any possible differential diagnosis.

KEY POINTS

- The physician in charge of the patient is the healthcare professional who must perform the diagnosis. It is not only necessary to know the pathophysiology and perform a clinical examination but also to have the results of complementary tests. This means that the doctor has to be well trained in how to correctly perform the diagnosis of brain death.
- It is mandatory to comply with certain clinical pre-conditions, in order to exclude situations which could interfere with the diagnosis, before proceeding with the diagnosis itself. The patient must be kept hemodynamically stable, without neuro-depressant drugs. It is also mandatory to keep the body temperature higher than 32ºC (higher than 35ºC if possible).
- In the general adult population, it is not necessary to repeat the diagnosis.
- There are some phenomena related to brain death. They facilitate diagnosis, but do not certify brain death (e.g., it is possible to have a patient who is alive with a flat EEG, under high doses of barbiturates).

2. SECTION 2: CLINICAL EXAMINATION FOR THE DIAGNOSIS OF BRAIN DEATH

The clinical examination for brain death shows the absence of brainstem function by demonstrating the absence of bilateral reflexes of the brainstem.

Before carrying out diagnostic tests that may damage the brain, it is advisable to perform tests that do not have any such effects, in order to prevent further damage if death has not yet been confirmed. Therefore, the apnoea test should be the last clinical examination performed.

It is therefore recommended to systematize the neurological examination of patients, following a protocol.

Table 3. Clinical examination protocol to demonstrate brain death

Abscense of photomotor reflex
Absence of corneal reflex
Absence of facial movements
Absence of spontaneous muscle movements
Absence of oculovestibular reflexes
Absence of oculocephalic reflexes
Absence of nausea reflex
Absence of cough reflex
Absence of oculocardiac reflex
Absence of response to atropine
Absence of spontaneous breathing

2.1 Pupillary light and corneal reflex

2.1.1. Absence of pupillary light reflex (PLR)

In brain death, there is no change in the size of the pupil when illuminated by a bright light. There is no pupillary constriction when the pupil is directly illuminated with a light (direct pupillary reflex) nor when the contralateral pupil is illuminated (consensual pupillary reflex). Direct trauma to the eyes, and high-dose adrenergic agents and atropine should be considered as possible confounding causes of dilated and arreflective pupils.

2.1.2 Absence of corneal reflexes

In brain death, when the cornea is stimulated (use a cotton swab preserving the central cornea from damage) there is neither motor (no blinking, no withdrawal) nor vegetative (no tearing, no reddening) response.

2.2 Facial and muscle movements

2.2.1. Absence of facial and spontaneous muscle movements.

This part of the clinical examination must be divided into four parts:

a. After stimulating the trigeminus area: no facial motor responses are observed after making a stimulus in the area innervated by the trigeminus.
b. After stimulating the trigeminus area: no corporal motor responses are observed after making a stimulus in the area innervated by the trigeminus.
c. After stimulating the spinal territories: no facial motor responses are observed after making a stimulus in the area innervated by the spinal.
d. After stimulating the spinal territories: in most patients with brain death there are no somatic motor responses (in neck, thorax, abdomen or limb muscle groups) after stimulating somatic territories. It is possible, however, to detect somatic motor responses (sometimes extremely complex) in certain patients with brain death when the stimulus occurs in any of the previously mentioned territories (neck, thorax, abdomen or limbs). These are called medullary or spinal reflexes, the presence of which does not invalidate the diagnosis of brain death. These motor responses can also be found in a situation of ischemia-anoxia of the spinal cord (for example, when clamping the aorta during organ extraction), and are similar to a cough response (sudden contraction of all the respiratory muscles). They do not invalidate, however, a diagnosis of brain death since the stimulus is produced in the spinal territory.

2.3 Not everything is what it appears to be

In brain dead patients, it is possible and also frequent to see motor spinal cord activity, so it is essential to recognize it and differentiate it from the encephalic motor activity.

Thus, brain dead patients can present spontaneous (Lazarus sign, repeated flexing of the toes) and reflex (cremasteric, cutaneous abdominal and plantar reflex) motor spinal cord activity. During organ recovery, motor abdominal reflexes have been seen in up to 60% of cases.

Therefore, knowledge of pathophysiology is important to avoid any anxiety on the part of the patient's relatives if they see this type of spinal-generated movements (Table 4).

Table 4. Reflex and spontaneous movements spinal-cord mediated

Flexor plantar reflex
Flexor withdrawal reflex
Abdominal reflex
Cremasteric reflex
Anal reflex
Bulbocavernous reflex
Cervicoabdominal reflex
Cervicoflexor reflex
Bringing one or both arms up to the face
Sitting up (Lazarus sign)

2.4 Vestibulo-ocular reflex, oculocephalic, nausea and cough reflex

2.4.1 Absence of vestibulo-ocular reflex

After elevating the head 30º, 50 ml of saline at 4ºC are injected into the auditory conduct (previously eliminating any existing earwax and ensuring integrity of the tympanum membrane). With the eyelids open, no ocular movements are observed after irrigation (in normal conditions, in living patients, we observe nystagmus with the injection of cold saline).

2.4.2 Absence of oculocephalic reflexes

The eyelids are kept open while the head is moved abruptly from side to side, maintaining the final position of the head for one second per side. Unlike the normal response, the eyes follow the direction of the head movement.

2.4.3 Absence of nausea reflex

No response is obtained when stimulating the base of the tongue and the posterior wall of the pharynx with a probe.

2.4.4 Absence of cough reflex

No response is obtained when repeatedly introducing a probe through the endotracheal tube down the lower respiratory tract. This is usually the last reflex to disappear.

2.5 Oculocardiac reflex and the absence of response to atropine

2.5.1 Absence of oculocardiac reflex

In living persons, the normal response is a slowing of the heart rate of more than 10% and a decrease in blood pressure of more than 35% following compression of the eyeballs. There is no response in the case of brain death.

2.5.2 Absence of response to atropine test

In brain dead patients, when 0.04 mg/kg of intravenous atropine is administered, there is no increase in heart rate, or the heart rate has an increase of less than 10% above baseline frequency. This test examines the nucleus of the vagus nerve. This reflex has to be performed after examining the pupillary light reflex. Atropine should be injected in an independent venous line, without mixing it with other drugs, especially chronotropic drugs (dopamine, dobutamine, etc) that could interfere with the test results.

2.6 Absence of spontaneous breathing

2.6.1 Apnoea test

This is the final clinical test to be performed in the clinical part of the diagnosis of brain death. The purpose of performing the apnoea test is to demonstrate the absence of the respiratory centre. The respiratory centre is located in the terminal part of the brainstem, i.e., the medulla oblongata and the pons. The dorsal and ventral respiratory group (both in the medulla oblongata) and the pontine respiratory group, which includes two areas known as the pneumotaxic centre and the apneustic centre. In normal conditions, the respiratory centre is stimulated with $PaCO_2$ followed by PaO_2, finally followed by changes in pH levels. The minimum level of $PaCO_2$ to trigger the respiratory centre is a $PaCO_2$ >60 mmHg or an increase of $PaCO_2$ >20 mmHg more than the baseline value, for patients with chronic obstructive respiratory disease who retain CO_2 (normal $PaCO_2$ 35-45 mmHg; patients with COPD often present compensated respiratory acidosis with $PaCO_2$ >45 mmHg). This test consists in achieving a $PaCO_2$ equal to or higher than 60 mmHg (or an increase higher than 20 mmHg above the baseline value) and checking that there is no spontaneous ventilatory trial, thus demonstrating the absence of function of the respiratory centre.

How can this be done? It is easy and SAFE to perform by following the steps below:

Step 1:

Pre-oxygenate the patient with a 100% FiO_2 at the beginning of the clinical examination (before performing pupillary light reflex).

Step 2:

Take a sample of baseline $PaCO_2$.

Step 3:

Period of apnoea. The patient is disconnected from the ventilator and a probe with an O_2 flow of 6 L/min is introduced through the endotracheal tube. For patients with unstable respiration who it is impossible to maintain disconnected from the ventilator for a prolonged time, another technique can be employed: maintain the patient connected to the ventilator in spontaneous mode ventilation with PEEP but without support pressure or triggering by pressure (not by flow, to avoid autocycling

of the ventilator). In older ventilators, the inspiratory branch can be disconnected and connected to a T-tube with oxygen 6 L/min, using a PEEP security valve in the expiratory branch. The time necessary to have the patient disconnected from the ventilator depends on the baseline $PaCO_2$. Since it is known that $PaCO_2$ increases 3 mmHg per minute of apnoea, it is possible to calculate the time of apnoea to reach a $PaCO_2$ of 60 mmHg (e.g., if the baseline $PaCO_2$ is 45 mmHg and the increase of $PaCO_2$ per minute of apnoea is 3 mmHg, it will be necessary to wait 5 minutes, to reach a $PaCO_2$ of 60 mmHg.).

Step 4:

Once the necessary time has elapsed, a second sample must be taken to check $PaCO_2$ value. Respiratory movements are not observed either during the test or after reaching target $PaCO_2$.

Step 5:

Restart mechanical ventilation.

Summary

KEY CONCEPTS

Clinical examination has to follow a protocol. Tests which could damage the brain must be performed at later stages.

The absence of brainstem reflexes must be bilateral. It is necessary to examine PLR, corneal reflex, facial and muscle movements, vestibulo-ocular reflex, oculocephalic reflex, nausea reflex, cough reflex, oculocardiac reflex, response to atropine and spontaneous breathing (apnoea test).

To understand pathophysiology, it is important to know the pathways of the cranial nerves.

3. SECTION 3: INSTRUMENTAL TESTS

3.1 Are all these tests necessary for a diagnosis of brain death?

There is no single instrumental test that demonstrates the absence of all neurological functions in the CNS. However, there are different instrumental tests that demonstrate the presence of phenomena closely related to brain death, such as cerebral circulatory arrest, absence of bioelectric activity or a decrease in cerebral aerobic metabolism.

Within the concept of brainstem death, once the clinical prerequisites are met, the mechanism of brain damage is well-known, and when the clinical examination has been completed, it is possible to establish a diagnosis of brainstem death.

However, in this concept of brain death, the diagnosis of death requires a clinical examination in addition to the demonstration of at least one of the phenomena clinically related to brain death. It is not necessary to use all of the available methods to diagnose brain death. As in any other medical diagnosis, the method should be selected according to the sound judgment of the clinicians performing the diagnosis. So, to establish the diagnosis, it is mandatory to perform a complete clinical examination plus one ancillary test which demonstrates the absence of bioelectric cerebral activity (EEG) or the presence of the arrest of cerebral circulation (doppler, arteriography or gammagraphy), and the test chosen will be selected according to its availability at the centre where the patient is admitted.

For the diagnosis of brain death, it is mandatory to perform one of the four validated tests: EEG, transcranial doppler, cerebral gammagraphy or cerebral arteriography. These tests have a positive predictive value of 100%, that is to say, if the test is positive in detecting an absence of electrical activity in the cortex (EEG) or in the detection of an absence of cerebral circulation in the circle of Willis, there is no possibility of having a false positive result.

It is mandatory to perform one validated test but, from a medical point of view, it is sufficient to perform one of the complementary tests once. As with any other medical diagnosis, the ancillary test should be selected according to the sound judgment of the clinicians performing the diagnosis, but it must one of the previously mentioned validated tests.

3.2 Electroencephalogram

Existing cerebral electrical activity is documented with an EEG reading obtained over 30 minutes with amplification characteristics of 2 microvolts/mm, frequency bands between 0.3 and 30 Hz, electrodes spaced at least 10 cm apart, placed at frontal, temporal, occipital and parietal regions, and with painful stimulation of the patient.

Electric brain silence, a null recording or a flat EEG (Figure 2) are considered as no activity.

In the EEG of some brain-dead patients, it is possible to register some electrical activity due to cardiac activity. In such cases, the EEG shows spikes that coincide with the QRS complex of the ECG [1].

Figure 2. EEG.

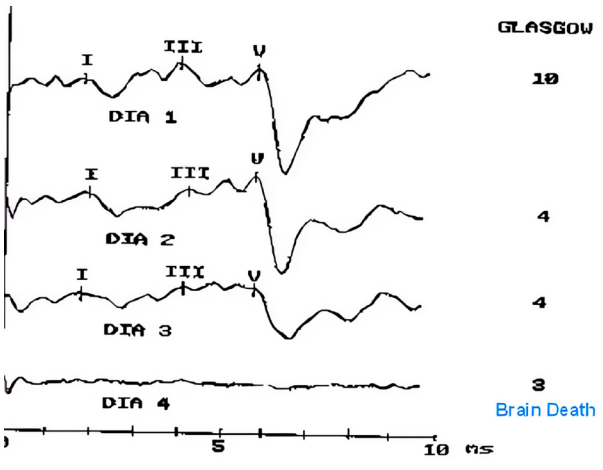

Figure 3.

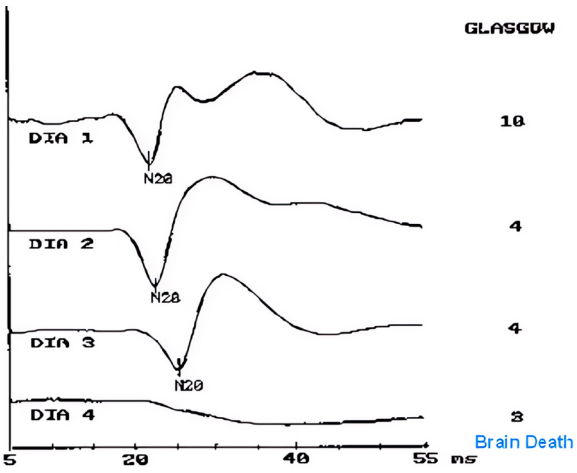

Figure 4.

3.3 Transcranial Doppler sonography

Transcranial Doppler (TCD) is a well-established complementary test for the diagnosis of brain death. It is a non- invasive, validated, test that is easy for a well-trained specialist to perform.

TCD enables insonation of the main intracranial arteries to establish the velocity of blood flow. In case of brain death, there is cerebral circulatory arrest, and four arrest patterns (which are four consecutive steps of the same phenomenon, but all have the same meaning, which is to say, an absence of cerebral circulatory arrest). An effective technique, TCD is used to detect, monitor and diagnose other diseases in patients suffering from traumatic brain injuries, subarachnoid haemorrhages, etc.

The technique is efficient in diagnosing the progressive circulatory cessation of large intracranial arteries that occurs in brain death. A decrease in the mean and diastolic velocities and a significant elevation of the pulsatility index are associated with an increase in intracranial pressure.

The use of TCD has the advantage that it is frequently performed at the patient's bedside, or even by means of permanent monitoring. Its use has proved that the cessation of cerebral circulation is a process that begins (especially in a supratentorial pathology with intracranial hypertension) with a progressive decrease in diastolic flow speed, followed by:

1. a separation of the diastolic and systolic wave (Figure 5);
2. an inversion of the diastolic flow wave (reverberant flow) (Figure 6),
3. a disappearance of the diastolic wave (systolic spikes); and
4. the absence of any sonographic signal (Figure 7) (mainly in patients with over 24 hours of cerebral circulatory arrest) [3-5].

3.4 Cerebral angiography

A cerebral angiographyof the 4 vessels in patients with brain death can be extremely valuable for the diagnosis of cerebral circulatory arrest. Cessation of circulation is not instantaneous, but progressive. Different patterns, all compatible with brain death, can be observed:

a. Total arrest of arterial contrast and lack of vein filling. With retrograde disappearance of the contrast material (Figure 5).

b. The cessation of cerebral circulation in the polygon of Willis.

c. Extreme slowing of arteriovenous circulation time. A lengthening of over 15 seconds is not compatible with cerebral function.

Digital subtraction intravenous angiography is also successfully used to verify cerebral circulatory arrest and is based on the same principles as conventional arteriography. One of the greatest disadvantages of these techniques is that they cannot be performed at the bedside, which implies the patient has to be moved from the intensive care unit to the site of the test (with less monitoring and possibility of treatment).

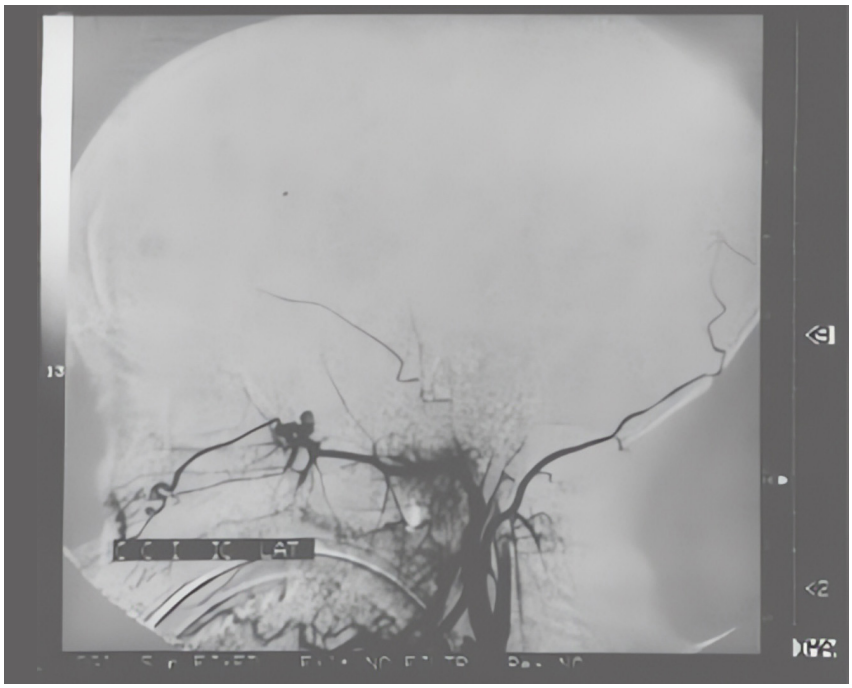

Figure 5. Total arrest of arterial contrast and lack of vein filling.

3.5 Isotope perfusion studies: cerebral gammagraphy

Nuclear medicine also offers interesting possibilities for the confirmation of brain death, particularly since the recent development of lipophilic radio substances: tracers capable of crossing the intact blood-brain barrier and revealing high extraction at first as well as prolonged brain retention. I-123-IMP and ^{99m}Tc-HMPAO are the substances mainly used to certify brain death.

Their use reveals no differences regarding results, although ^{99m}Tc-HMPAO is more frequently used more due to its wider availability. Angio gammagraphy with ^{99m}Tc-HMPAO consists of 2 phases: the first evaluating cerebral blood flow, and the second phase, 5-10 minutes after injection, when static images are obtained in anterior, lateral right and lateral left projection, evaluating parenchymal capture. Gammagraphy with ^{99m}Tc-HMPAO is easy to perform, highly sensitive and specific, and does not interfere with the patient's clinical conditions or the administration of neuro-depressant drugs [6,7].

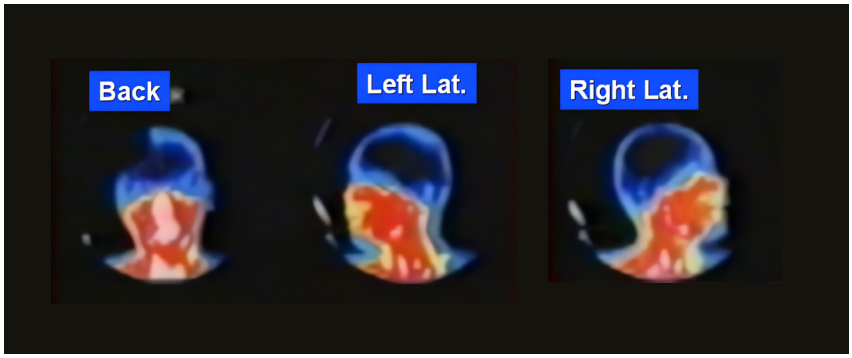

Figure 6.

Summary

KEY POINTS

- Any single instrumental test may demonstrate the absence of all neurological functions in the central nervous system, but some these tests are also able to confirm the presence of phenomena closely related to brain death.
- A well-established cause of brain damage, compliance with clinical prerequisites, a clinical examination for brain death and one complementary test suffice to diagnose brain death.
- The choice of the complementary validated test is at the discretion of the physician and depends on the availability of the testing method.

4. SECTION: 4 SITUATIONS OF CONFLICT

There are two frequent situations of conflict that may arise in the diagnosis of brain death: diagnosis in children and diagnosis in patients under the effects of central nervous system depressant drugs.

Brain death diagnosis in children. During the first period of life, due to neurological immaturity, some brainstem reflexes have not yet developed or emerged. This can make the clinical examination for brain death in children more difficult.

Brain death diagnosis in patients under barbiturates. It is frequent for patients in the ICU to be under treatment with barbiturates, which could interfere with a clinical examination for brain death by mimicking an absence of brainstem reflexes. However, this usually occurs in patients who are administered high doses of barbiturates, which is not likely to happen within the recommended therapeutic range.

Table 5. In the last 12 to 15 weeks of gestation there are rapid changes in the neurological development

Suction and rooting reflexes	32-34 week of gestation
Auditive response	30-32 week of gestation
Photomotor reflex	30-32 week of gestation
Oculocephalic reflex	28-32 week of gestation
Corneal reflex	28-32 week of gestation
Moro reflex	28-32 week of gestation
Response to increase of $PaCO_2$	33 week of gestation

4.1 Diagnosis in infants and children

It can be difficult to confirm the loss of central nervous system functions when performing a clinical examination of patients in their first weeks of life. This is due to neurological immaturity, as some brainstem reflexes may not have developed or emerged yet, making newborn patients more vulnerable to exogenous aggressions. In the last 12 to 15 weeks of gestation there are rapid changes in neurological development (Table 5).

In children, guidelines recommend performing the clinical exam twice. It must be repeated after a waiting period [10].

» In-term newborns (>37 weeks gestational age) to 30 days of life: 24-hour waiting period.

» Children >30 days to 18 years: 12-hour waiting period.

It is also mandatory to perform one complementary validated test. It is important to consider that infants may have persistent cerebral blood flow in brain death (expansive skull fractures), so in these cases it is mandatory to perform an electroencephalogram as complementary test.

DID YOU KNOW?

It can be difficult to confirm the loss of central nervous system functions when performing clinical examinations of patients in the first weeks of life. This is due to neurological immaturity, as some brainstem reflexes may not yet have developed or emerged, making newborn patients more vulnerable to exogenous aggressions. In the last 12 to 15 weeks of gestation there are rapid changes in the neurological development.

In newborn children and infants up to the first 6 months of life the absence of sucking reflex must be demonstrated. To do so, a dummy or the tip of a finger is introduced into the patient's mouth to check whether the child sucks. If there are no movements, the reflex is absent.

Another reflex which must be absent in brain dead children is the rooting reflex. In normal conditions, after stimulating the cheek, the patient turns towards the stimulated cheek and its mouth begins to make suction movements. This reflex must be absent in brain death.

4.2 Diagnosis in patients under barbiturates

The administration of high doses of barbiturates can interfere with the clinical examination and EEG of patients in whom brain death is suspected. There is no unanimously accepted approach. While certain authors wait until levels of barbiturates in plasma decrease to certain levels, others wait until these levels reach zero. It is true that in certain cases of barbiturate therapy or intoxication, reversible electric brain silence has been reported.

However, it is also true that the levels of barbiturates in plasma at the moment of recording were approximately 100 mcg/ml. Since in our experience the levels of thiopental (used for the control of intracranial hypertension) in plasma were never greater than 10 mcg/ml, the safety range is wide enough to consider a decrease of barbiturates to therapeutic levels as sufficient.

Summary

KEY POINTS

» Generally speaking, it is not necessary to repeat a clinical examination, but in children up to the age of 18 years it is a legal requirement to do so, with a range of time that varies according to the age of the patient.

» In patients under barbiturates, clinical examination of brain death could be mimicked, but this mainly occurs when barbiturate values are very high. Thus, levels need to be measured. In most cases, barbiturates administered within the recommended therapeutic range do not interfere with the diagnosis.

CONCLUSIONS

The diagnosis of brain death should be performed by the physician in charge of the patient. Hence, it is essential that doctors should be well-trained in the diagnosis of brain death.

- It is mandatory to comply with certain clinical prerequisites before establishing a diagnosis of brain death. It is necessary to have a well-documented cause for death. Haemodynamic stability is required. Moderate to severe hypothermia needs to be avoided (the temperature cannot be lower than 32ºC). The patient cannot be under the effects of neuro-depressive drugs, neuro-muscular blocking drugs or anticholinergics.
- Clinical examination must be methodical and complete. The absence of brainstem reflexes is compatible with the absence of brainstem function.
- There are some phenomena related to brain death. Tests capable of demonstrating the presence of such phenomena need to be performed, according to their availability in the units.
- Diagnosis must include demonstration of the cessation of all brainstem reflexes (by means of the clinical examination) plus demonstration of the cessation of cerebral hemisphere function (through performing one complementary validated test once).

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TOPIC 3 - Unit 1

Donor management

ORGAN DONATION

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CONCLUSIONS 100

Donor management and organ evaluation are two important steps along the path from donor to recipients.

Each year, potential donors are lost due to cardiovascular collapse that can be avoided with intensive management. Knowing the consequence of brain death on physiology can help doctors avoid cardiovascular collapse. Furthermore, this intensive management can improve organ function, leading to an increase in the number of organs recovered. Even through there are not sufficient scientific publications in this field, there are some major articles that provide information about how to improve donor management, which is increasingly becoming management of the organs themselves.

Organ evaluation must be performed while donor management is being undertaken. When considering a potential donor, their general characteristics must be taken into account. During donor evaluation, we may encounter infectious disease or malignancy, which can increase the risk for recipients. As the population ages, the risk-benefits of using organs from older donors must be discussed and it is important to conduct a specific evaluation of the organs.

Conducting intensive donor management and a performing a good evaluation of both donor and organs can improve the number of organs available for transplantation.

INTRODUCTION

Once the diagnosis of brain death (BD) has been established, management must be redirected and centre on the support and protection of the organs to be transplanted. The reason for this is that major pathophysiological changes may occur in the cardiovascular and respiratory systems during this process, and changes may also arise in hormonal and metabolic balance [1, 2].

This unit is aimed at health professionals working in or about to join medical units where donor care might be provided.

The goal of donor management is to:

- treat the complications associated with the onset of brain death;
- optimize the quality of organs;
- assess organ function;
- seek and confirm the absence of contraindications to donation.

1. SECTION 1: GLOBAL CARE

Management of a potential donor must start very early, even before the final diagnosis of brain death.

Indeed, in terms of ICU care there is little difference between the management of a severely ill patient with multiple organ failure and a potential donor. Only treatments provided for neurological reasons (osmotherapy, goals in cerebral perfusion pressure, surgery) can be stopped. All other treatments and care (infection prevention, nursing, inotropes, mechanical ventilation) must continue.

During the ICU stay, due to the pathophysiological consequences of brain death, some elements require specific attention [3]. In this section we will review:

- Management goals
- Instability
- Temperature management
- Haemoglobin levels – coagulopathy
- Infection
- Standard care
- Donor management protocols

1.1 Management goals

Donor management = Intensive Care Unit Management

The goal of ICU-care donor management is to maintain homeostasis.

The French recommendations, published in 2005 [4], proposed the following goals (for further details refer to the dedicated section):

- Mean arterial pressure: 65 - 100 mmHg
- Diuresis: 1 – 1.5 mL/kg/h
- Haemoglobin: 7 - 9 g/dL
- Blood lactate: normal
- PaO_2 >80 mmHg
- Temperature: 35°5 - 38°C

To manage a potentially unstable donor, it is essential to ensure the following:

- Continuous monitoring: ECG, arterial pressure, SpO_2, $EtCO_2$
- Arterial line for invasive blood pressure monitoring and extraction of blood samples (*)
- Central venous access to administer treatment (*)
- Active heating system with temperature monitoring
- Urinary catheter
- Gastric tube

(*) For perioperative (surgical and anaesthesia) purposes, and even more so if thoracic surgery is planned, it is preferable to insert the arterial line in the left radial artery and a central venous access in the right jugular vein.

DID YOU KNOW...?

Some data suggest that intensivist-led management provides better results [5]. Establishing intensive, focussed donor management could reduce the number of deceased donors lost due to cardiovascular collapse [6]. Achieving goals in loss reduction is associated with an increase in the number of organs available [7].

1.2 Instability

The most frequent event that occurs after brain death is hypotension, and Figure 1 shows the incidence of other events.

For an ICU patient, instability may be due to preventable reasons:

- Hypovolemia
- Pneumothorax
- Cardiac arrhythmia (see Section 2)
- Inadequate ventilator settings
- Metabolic abnormalities
- Disconnection of catecholamine administration (catheter, syringe), ventilator, etc.

Unpredictable cardiac arrest can occur during ICU care, surgery, and particularly during high-risk procedures (transport), so continuous monitoring is a requirement. Treatable reasons must be searched for and epinephrine administration, chest compression, optimization of mechanical ventilation or defibrillation (if indicated) must be attempted. In cases of brain death, atropine is ineffective. If these procedures fail, organ function may be preserved using DCD donor perfusion techniques.

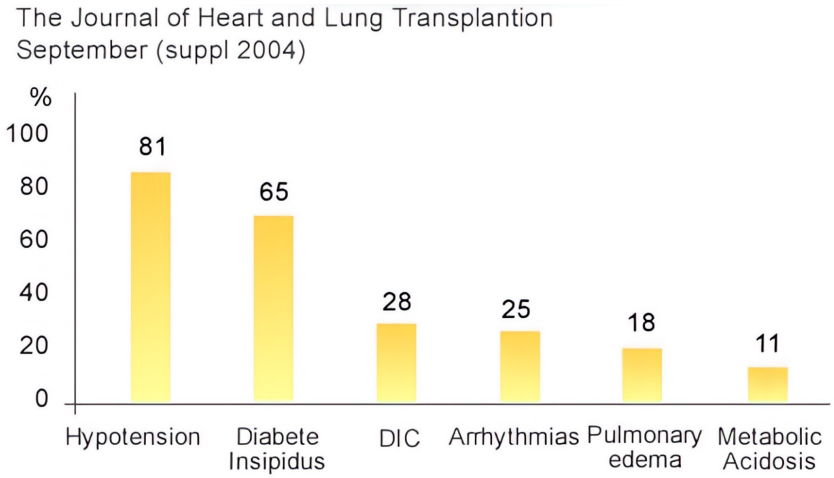

Figure 1. Physiological changes during brain stem death. Lessons for organ donor management.

1.3 Temperature management

Monitoring body temperature is another fundamental element of organ donor management.

After BD, hypothalamic control of temperature is lost, which leads to donor poikilothermia, producing a progressive loss of body heat.

Hypothermia has several consequences:

- Deterioration of haemodynamics: vasoconstriction and cardiac instability.
- Arrhythmias (general conduction delay), T wave inversion, QT lengthening, appearance of J wave (between 32-33 ºC).
- Atrial fibrillation.
- Ventricular fibrillation if temperature is less than 30ºC.
- Renal function disorders, due to a reduction of glomerular filtration and the incapacity to maintain tubular concentration gradients (cold diuresis).
- Coagulation disorders.
- Left shift of the oxygen-haemoglobin dissociation curve, with a reduction of free oxygen delivery in tissues.

Prevention is key and can be achieved using continuous temperature monitoring, heated intravenous solutions, humidification and heating of respiratory gases.

Electric blankets are necessary to maintain body temperature above 35°C.

KEY IDEA

Hypothermia must be systematically prevented.

1.4 Haemoglobin

Anaemia can occur in a potential donor, and this is more frequent when the patient has suffered a trauma. To provide correct oxygenation and blood coagulation it is essential to maintain haematocrit (Hct) above 30% or haemoglobin between 7 and 9 g/dl. However, in the case of a planned thoracic surgery, haemoglobin levels must be higher to improve heart condition and prevent anaemia after a sternotomy [8].

1.5 Coagulopathy

Donor coagulopathy is multifactorial, and previous medication (warfarin, aspirin) may be a contributory factor. The release of fibrinolytic agents from ischaemic-necrotic brain tissue can be the initial cause of coagulopathy. In common with severe brain trauma patients, organ donors may present signs of disseminated intravascular coagulation [9]. Dilution due to fluid loading can also prolong coagulation times.

DID YOU KNOW...?

Transfusions can be performed on deceased donors to improve the quality of the organs to be transplanted.

Transfusion is reserved for donors who present blood loss, haemodynamic instability or changes in coagulation parameters that will interfere will surgery. Suggested goals are:

- Platelets >50 g/L
- Fibrinogen >1 g/L
- PT <15 sec
- PTT <38 sec

1.6 Infection

Infection is a problem in organ donation as it can alter organ function and may also be transmitted to recipients.

Prevention of acquired infection during ICU stay is important

The presence of bladder catheters, nasogastric tubes and catheters may promote the entry of microorganisms in the donor.

A frequently encountered problem is lung colonization or infection due to trauma or mechanical ventilation.

Recommendations to prevent infections include endotracheal suctioning, avoidance of supine position (the patient needs to be positioned at a minimum of 30º, head up) and hand hygiene.

Diagnosis of infection or colonization is essential

Bacteriological samples must be taken.

Treatment of the diagnosed infection is critical

Potential BD donors may present respiratory superinfections secondary to bronchoaspiration or prolonged mechanical ventilation. Prophylaxis with broad spectrum antibiotics is debatable.

KEY IDEA

Donor-related bacteriological information must be reported to the transplant teams.

1.7 Standard care

Apart from the treatment given to the potential donor, further care must be provided as follows:

- Maintain head of bed at an elevation of 30-40º
- Routine pulmonary suctioning
- Artificial tears to prevent corneal drying
- Prevention of pressure ulcers

» Plan repeated blood analyses

» Laboratory tests of coagulation, blood gas, electrolyte

» Bacteriological samples

» Plan repeated urinary analysis and urine dipstick to detect glucose

Beware of spontaneous and reflex movements in potential BD donors [10].

1.8 Time optimization

Organizing a surgical procedure can take time. It is important to maintain efficient donor care to avoid the degradation of organs. Moreover, this time can be used to improve the function of organs (lungs, kidney etc.) during the ICU stay, as suggested by some authors [11] (Figure 2).

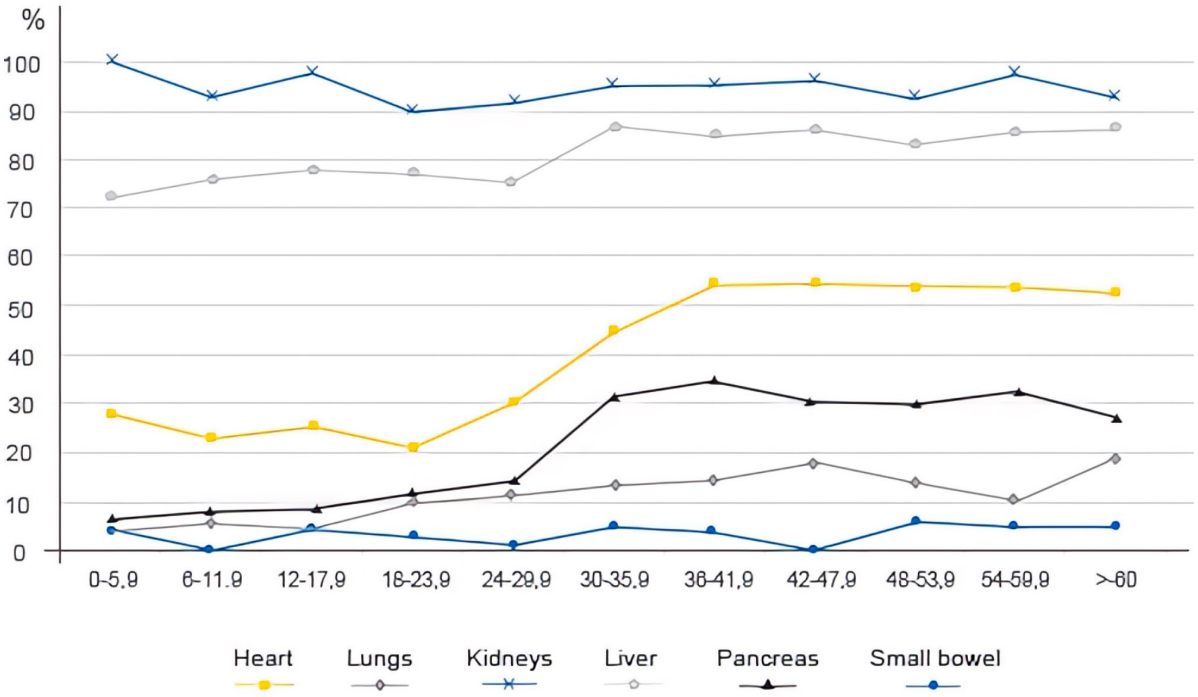

Figure 2. Individual organ procurement rates.

1.9 Donor management protocols

The management of a potential donor is a multifaceted task similar to the care of an ICU patient and requires significant medical and paramedical involvement, conducted in active collaboration with the transplant coordinator. Efficient management can improve organ function, which favours a better outcome in the recipients. Treatment must be maintained until the organs are recovered.

"What is beneficial and helpful for an ICU patient is good for the donor and thus is advantageous for the recipient."

This can be achieved by following universal standardized protocols and algorithms [12], and also requires a high degree of professionalism from the people involved in the organ donation.

2. SECTION 2: HAEMODYNAMIC MANAGEMENT

Haemodynamic instability is a major problem in the management of a potential donor because it occurs frequently and can cause serious complications (altered organ perfusion, cardiac arrest, etc.)

This instability may occur as a result of:

» brain death;

» the initial aggression that led to the brain death (trauma, cardiac arrest, subarachnoid haemorrhage, etc.);

» the patient's past medical history (hypertension, myocardial ischaemia).

The incidence of post-transplant acute tubular necrosis and liver failure is substantially higher when donor systolic blood pressure is below 80 mmHg.

The goal in hemodynamic management is to maintain adequate circulating volume, cardiac output and perfusion pressure to ensure optimal oxygen supply to tissues.

Several issues will be further discussed:

» Pathophysiology

» Hypotension/hypertension

» Hypovolemia/vasoplegia

» Cardiac dysfunction

» Monitoring

» Fluid loading

2.1 Pathophysiology

Initially, there is a massive sympathetic discharge (a "sympathetic storm") which results in a hypertensive crisis together with severe cardiovascular disturbances. This is followed by a second phase, induced by a profound reduction in the sympathetic discharge. The inotropic and chronotropic status of the heart deteriorates, resulting in a reduction of cardiac output [13].

Brain death causes dysfunction of the vasomotor centre and a reduction in catecholamine release, which results in vasodilatation due to the reduction of peripheral vascular resistance [3].

Deterioration of cardiac function is may be due to a number of different factors including hormonal deficiency (reduction of free thyroxine, cortisol, arginine vasopressin and insulin levels), increased anaerobic metabolism, and spinal shock [1]. Moreover, Salim et al. recorded cardiac ischaemia in about 30% of donors [14].

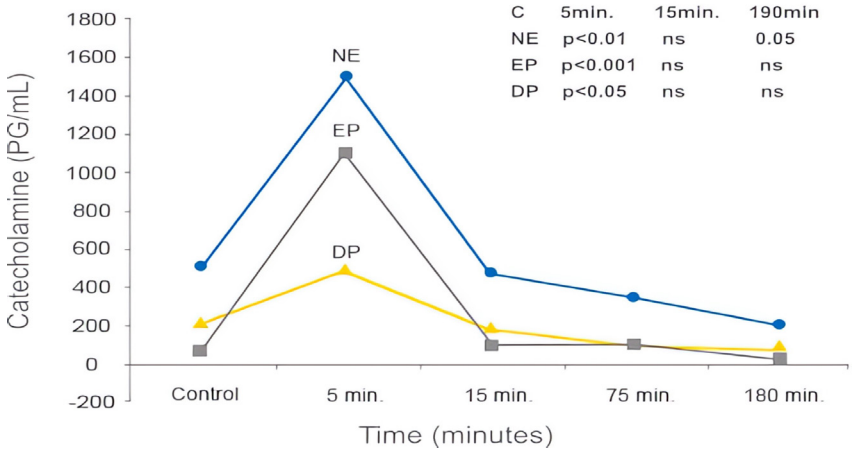

Figure 3. Changes after brain death.

2.2 Hypotension

Hypotension is one of the most constant pathophysiological disorders and can be defined as a mean arterial blood pressure (MAP) of <60 mmHg (below the objective: 65 to 100 mmHg). It is induced by several factors and requires a structured approach in order to make a differential diagnosis.

The three main reasons for hypotension are:

- hypovolemia (see Section 2)
- vasodilatation (see Section 2)
- cardiac dysfunction (see Section 2)

2.3 Hypertension

Hypertension (MAP >90 mmHg) is rare following brain death but occurs during the evolution of brain death. It is the consequence of the intense catecholamine storm seen during herniation. It usually requires no treatment, however if this hypertension is secondary to stimulation, it must be stopped. If treatment is considered necessary, a quick-acting agent with a short half-life, such as esmolol, can be proposed with close monitoring [15].

During surgery, the administration of opioids is suggested in order to prevent the hypertension induced by spinal reaction.

DID YOU KNOW?

Christopher Pallis (1923-2005) was an eminent neurologist and intellectual leader of the brainstem death school in the UK. He was also an intellectual socialist. Under the pennames of Martin Grainger and Maurice Brinton, he wrote many literary works for Solidarity, a British libertarian socialist group.

2.4 Hypovolemia / Vasodilatation

Hypovolemia and vasodilatation are frequent when managing a potential donor and can induce hypotension. A hemodynamic exploration may be required.

Absolute hypovolemia

- Initial injury
  - Inadequate resuscitation
  - Fluid leaking into interstitial space
  - Decrease in intravascular oncotic pressure
- Fluid restriction to treat cerebral oedema, administration of diuretics or mannitol.
- Hyperglycaemia-induced osmotic diuresis
- Diabetes insipidus (DI)
- Hypothermic “cold” diuresis

Effective hypovolemia: vasodilation

» Loss of vasomotor tone

» Hypothermia treated with rewarming

» Sepsis

» Adrenal insufficiency

In cases of hypovolemia, fluid loading is recommended (see Section 2).

In some countries, dopamine is recommended in cases of vasoplegia, but this can induce tachycardia and arrhythmias. Some recent papers report the beneficial impact of dopamine administration on kidney function (possibly due to an immunomodulatory effect) [16, 17]. In other countries, norepinephrine is the first catecholamine used.

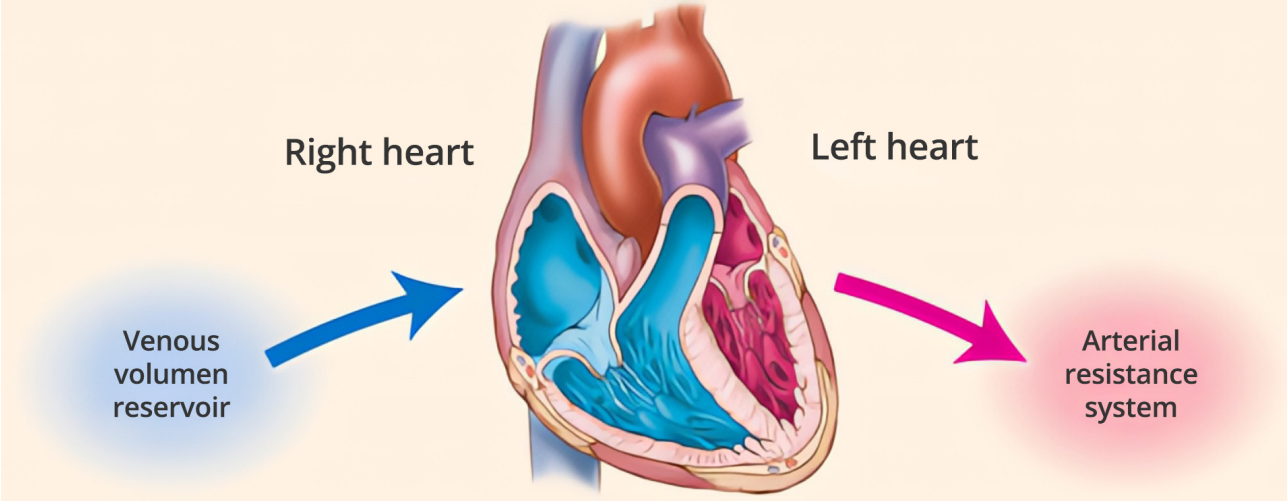

Figure 4. Hydraulic model.

Table 1. Section 2 summary

Hypovolemia	Cardiac dysfunction	Vasodilation
Absolute hypovolemia	Preexisting disease	Spinal shock
Initial injury » Inadequate resuscitation » Fluid leaking into interstitial space » Decreased intravascular oncotic pressure after crystalloid resuscitation	Initial injury » Myocardial contusion » Pericardial tamponade » Myocardial ischaemia or infarction	Catecholamine depletion
Treatment for intracranial pressure » Fluid restriction » Urea » Diuretics » Mannitol	Process of brain death	Loss of vasomotor control and autoregulation
Hyperglycaemia-induced osmotic diuresis	Catecholamine damage	Relative adrenal insufficiency as a result of trauma or critical illness
Diabetes insipidus	Ischaemia-reperfusion injury	Endocrinopathy of brain death
Hypothermic “cold” diuresis	Metabolic depression	Acquired sepsis
Effective hypovolemia	Acidosis	
Loss of vasomotor tone and pooling in venous capacitance bed	Hypothermia	
Hypothermia treated with rewarming	Hypophosphatemia	
	Hypocalcaemia	
	Hypoxia	
	Endocrinopathy of brain death	
	Volume overload resulting in congestive heart failure	
	Arrhythmias	
	Catecholamines	
	Ischaemia	
	Hypokalaemia	
	Hypomagnesemia	

2.5 Cardiac dysfunction

This can be defined by echocardiography with LVEF <45%. (Figure 5).

Several conditions can induce cardiac dysfunction:

- preexisting disease
- initial injury: myocardial contusion, pericardial tamponade, myocardial ischaemia
- process of brain death: catecholamine storm induced, ischaemia-reperfusion
- metabolic depression: acidosis, hypothermia, hypophosphatemia, hypocalcaemia, hypoxia, endocrinopathy of brain death
- volume overload in chronic heart failure
- arrhythmias induced by catecholamine, ischaemia, hypokalaemia can lead to ventricular tachycardia

This dysfunction can be reversible and therefore must be re-evaluated [18, 19]. Some conditions are preventable (hypothermia) or treatable (cardiac arrhythmia). Cardiac echography is a recommended examination to make the diagnosis, search for an aetiology and monitor changes in cardiac function (Figure 6).

In the case of cardiac dysfunction, dobutamine or epinephrine are recommended for their inotropic proprieties. Section 3 discusses hormonal resuscitation.

KEY IDEA

Arrhythmias must be prevented. Cardiac dysfunction can be reversible with donor management [18].

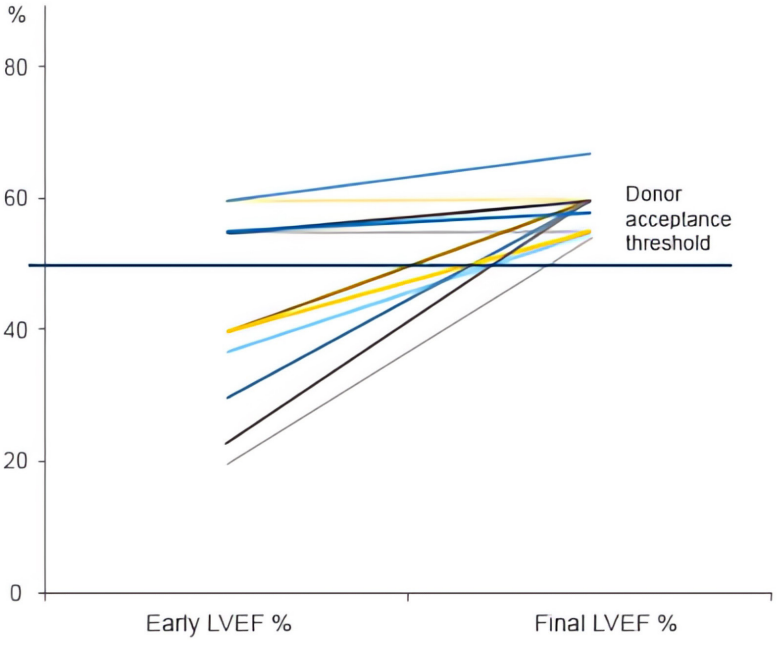

Figure 5. LVEF.

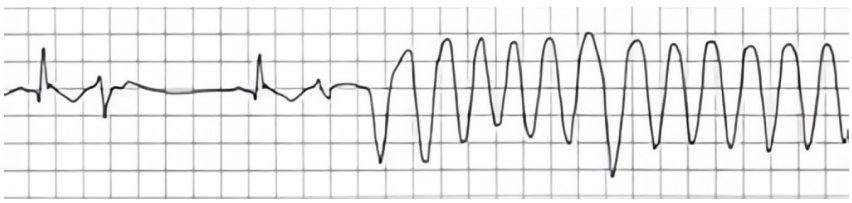

Figure 6. Onset of ventricular dysfunction.

2.6 Monitoring

Due to the multiple factors that may cause haemodynamic instability, exploration and monitoring of the haemodynamic situation is mandatory in order to adjust treatment:

- fluid loading in persistent hypovolemia;
- inotropes in cardiac dysfunction;
- vasoconstrictors in vasoplegia.

The optimal treatment for each organ can be different: preventing fluid overload in lungs, administering excessive catecholamine in heart (see Table 2). Monitoring is mandatory for a potential donor, and this is even more necessary in cases of instability (not responding to usual measures, chronic heart disease etc.).

Tools usually used in the ICU can provide helpful information about the donor's haemodynamic status. Physicians will make better decisions when using the tools available in their units, such as Swan-Ganz catheters, PiCCO®, Vigileo®, echocardiography, in addition to standard parameters such as cardiac output, filling pressure, SvO_2, CVP. Base excess and lactate monitoring have also been shown to be efficacious in providing guidelines for fluid administration and resuscitation [2, 19-23].

Monitoring is the most efficient way to improve organ function when there is a situation of instability.

Table 2. Ideal condition

	Heart	Lung	Liver	Kidney
Fluid balance	Pos	Neg	Pos	Pos
Vasopressors	No	Yes	-	Yes
Corticosteroids	-	Yes	+/-	-
Polyuria	No	Yes	No	Yes

2.7 Fluid loading

Hypovolemia is very frequent in potential donors. It must be corrected to improve organ perfusion.

First line treatment in hypotension: crystalloids are the first product to be given. In 1996, a study showed that the kidney graft function of braindead organ donors resuscitated with 6% hydroxyethyl starch (HES) 200/0.6 was impaired in comparison with 3% gelatin [24]. After several years of debate and changes in HES properties, as well as conflicting studies, the European Society of Intensive Care Medicine (ESICM) published the results of a task force on fluid loading: "We recommend not using HES or gelatin in organ donors outside the context of clinical trials (grade 1C)." [25, 26]. In 2013, the FDA and the EMA suggested stopping the use of HES in critically ill patients due to the risk of death and kidney injury [27].

In fact, it appears that using HES can be deleterious for kidney function, whereas gelatin must be used with caution. However, fluid administration is recommended only when suggested by advanced haemodynamic parameters.

KEY IDEA

Use advanced haemodynamic parameters to avoid useless or harmful fluid loading. Beware of HES.

3. SECTION 3: ELECTROLYTE AND ENDOCRINE MANAGEMENT

It is not easy to maintain fluid and electrolyte balance in potential BD donors. Knowing the pathophysiological consequences of brain death can help to prevent them, and avoid severe complication such as arrhythmia, alterations of organ function (hypernatremia can be deleterious for the liver and kidney [28, 29]) or cardiac arrest.

Another important point is the consequence of brain death on endocrine function.

The next section covers:

- Pathophysiology
- Polyuria
- Glycaemia
- Hormonal disorders induced by brain death
- Corticosteroids hormone replacement therapy

3.1 Pathophysiology

After brain death, loss of anti-diuretic hormone (ADH) secretion can induce losses of free water and electrolytes responsible for hypernatremia, hypocalcaemia, hypomagnesaemia, hypokalaemia, and hypophosphatemia that favour the onset of cardiovascular instability.

Excessive glucose-containing fluids may cause hypernatremia and hyperglycaemia, which result in an increase in intracellular dehydration and polyuria.

Moreover, for potential BD donors, fluid replacements with sodium-rich solutions with increased osmolarity due to hypohydration may cause hypernatremia within a few days, which is difficult to correct. On the other hand, hypernatremia is a negative prognostic factor for liver and kidney graft function [28,29].

Rehydration should be carefully carried out to avoid pulmonary oedema, cardiac overload or hepatic congestion.

Normovolemia should be restored before starting any vasopressor drug therapy.

3.2 Polyuria

Defined by urine output >2-4 ml/kg/h.

The causes are:

- physiological diuresis after prior fluid administration
- osmotic diuresis due to previous therapy (mannitol, diuretics)
- hyperglycaemia
- DI

Diabetes insipidus occurs in 38% to 87% of cases and is caused by a deficiency of ADH secreted by the hypothalamus.

In polyuria, DI is confirmed in the case of low urine density <1005 and an increase in natremia or plasma osmolality >300 mmol/kg.

As soon as the diagnosis is made, treatment must be started:

» Correction of fluid loss with a low-sodium solution with the correct ion supplement (calcium, magnesium and phosphate)

» Administration of analogue ADH

Desmopressin (DDAVP), a synthetic analogue of natural ADH (arginine vasopressin), has a selective action on V2 receptors with an antidiuretic effect. It is the drug of choice. Its latency time is 15 to 30 minutes, and it has a prolonged action (5-12 hours). It must be administered as an intravenous bolus of 1 µg/8-12 hours to achieve correct diuresis (for vasopressin see Section 3).

KEY IDEA

When DI is diagnosed, start administering desmopressin to avoid hypovolemia and electrolyte abnormalities.

3.3 Glycaemia

Glycaemic control is often altered in potential BD donors due to hypersecretion of adrenal hormones, glucose solutions, glucocorticosteroids and catecholamine treatment, hypothermia and changes in pancreatic microcirculation.

This may lead to fluid and electrolyte imbalances such as metabolic acidosis, osmotic diuresis, dehydration and hypovolemia.

Therefore, potential BD donors should be strictly controlled using insulin in continuous intravenous infusion, as absorption by other administration routes is variable and difficult to control. The dose to be administered ranges between 0.5 and 7 IU/hour of rapid-acting insulin.

It is recommended to measure serum glucose every 4 hours and obtain finger stick glucose (FSG) using a blood-glucose meter every 2 hours. In case of hyperglycaemia, a search for glycosuria is needed.

KEY IDEA

Watch for glycaemia and glycosuria. Treat with IV insulin.

3.4 Hormonal disorders induced by brain death

Levels of a thyroid hormone, triiodothyronine (T3) decrease in donors and do not respond to exogenous administration of thyrotropin-releasing hormone (TRH). Some publications report a favourable effect of T3 administration [30,31], whereas a recent randomized study showed no effect [32]. T3 is not widely employed, and its use is still debatable.

Vasopressin acts on the V2 receptors on renal cell membranes, increasing water reabsorption and reducing diuresis, while in higher doses it acts on the V1 receptors on blood vessels, causing vasoconstriction in the pulmonary, mesenteric, hepatic and coronary territory and reducing renal flow without increasing its effect on diuresis. The duration of its action is approximately 2-3 hours, and it should preferably be administered via continuous infusion. The doses recommended by various authors range between 0.4–5 UI/h of vasopressin intravenously, allowing a decrease in the dose of other catecholamines.

3.5 Corticosteroids

Dimopoulou et al. reported low levels of cortisol, even lower than those of brain trauma patients, with a failed response to ACTH stimulation. The meaning of these findings has not yet been explained [33].

The administration of high doses of methylprednisolone in BD donors can reduce immunological activation and improve both short and long-term outcomes for most transplanted organs [34, 35]. However, cortisol administration can induce adverse reactions (liver necrosis) [36].

Recently, Dhar et al. demonstrated that low dose corticosteroids did not result in worsened pulmonary or cardiac function in comparison to a high dose. The authors concluded that a high dose of corticosteroids is not required [37].

3.6 Hormone replacement therapy

The use of hormone "cocktails" in donor management is recommended in some English-speaking countries [38,39]. Rosendale et al. published a retrospective study on the use of T3, arginine vasopressin, methylprednisolone (MP) and insulin as part of a general donor management protocol, but their conclusions are debatable [40]. Wood suggests that it would be wise to reserve hormone replacement therapy for unstable donors [41].

In a randomised prospective study, Venkateswaran et al. evaluated the cardiac index between initial and final assessment in donors receiving or not receiving T3 or MP during donor management. Neither T3 nor MP, alone or in combination, appeared fundamental to the improvement of the cardiac index after active management [42].

Salim et al. conclude that additional research is still necessary (regarding timing and the effect of steroids) [43].

One possible explanation for such conflicting results may be the duration of brain death before recovery.

4. SECTION 4: VENTILATION MANAGEMENT

Many conditions can alter lung function. Lungs are the organs most often deemed medically unsuitable, and only 10–20% of lungs from multiple organ donors are used for transplantation. Aggressive donor management has a direct impact on organ function [44].

Ventilation management aims to:

- Maintain correct tissue oxygenation for the organ
- Improve lung function, making them suitable for transplantation

Donor ventilation support requires close attention during management, considering that up to 15% of all donors present acute respiratory distress syndrome (ARDS) or acute lung injury (ALI) [47].

This section deals with:

- Hypoxemia
- Pulmonary care
- Infection / Corticosteroids

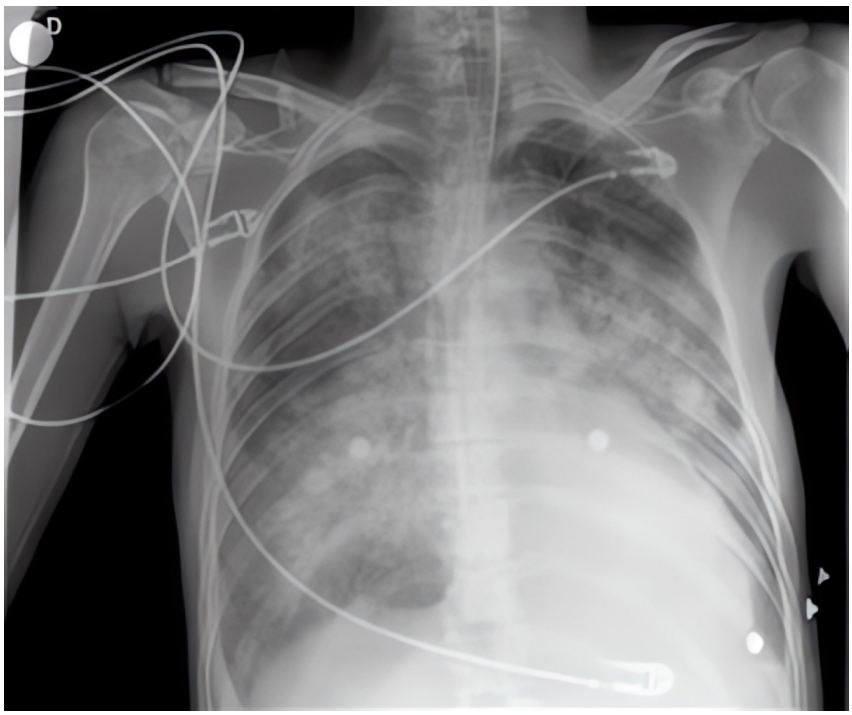

Figure 7. Pulmonary oedema.

4.1 Causes of hypoxemia

Neurogenic pulmonary oedema: at the onset of BD, particularly in young donors, this may occur due to an abrupt increase of circulating catecholamine.

First, the catecholamine storm will produce a sympathetic alteration of capillary permeability, together with haemodynamic changes that lead to increased hydrostatic pressure and capillary-alveolar membrane damage. On the other hand, the activation of inflammatory mediators due to brain ischaemia, organ ischaemia and endothelial activation will impair lung function [45].

- Inhalation pneumonia
- Nosocomial pneumonia
- Fluid overload
- Left ventricular dysfunction
- Lung atelectasis related to prolonged mechanical ventilation

4.2 Pulmonary care

It is important to follow standardized protocols that optimize and maintain optimum lung function and increase the number of potential grafts [46-48]. Following these protocols, respiratory management of potential BD donors should include the use of low FiO_2 to avoid pulmonary toxicity, use of positive end-expiratory pressure (PEEP) to reduce atelectasis, avoidance of fluid overload, and preventive measures required to avoid respiratory superinfection.

4.3 Protective ventilation

The use of a lung-protective strategy in potential BD organ donors has increased the number of eligible and recovered lungs compared with conventional strategies. In the protective strategy, potential BD donors should receive ventilation with low tidal volumes (6 to 8 mL/Kg of predicted body weight) and PEEP of 8 to 10 cm H_2O. A closed circuit must be used for tracheal suction (Figure 8). An apnoea test should be performed with the ventilator in continuous positive airway pressure mode. Finally, recruitment manoeuvres are recommended after any disconnection from the ventilator [49, 50] (Table 3).

Table 3. Protective ventilator settings

Protective ventilator settings
TV 6 to 8 ml/kg
PEEP 8 to 14 cm H_20
CPAP for apnoea test
Closed suction system
Recruitment manoeuvres

4.4. Infection / Corticosteroids

Diagnosis of respiratory infection must be accurate. The use of a flexible bronchoscopy, bronchoalveolar lavage and sample taking with the protected-specimen brush technique is recommended [51, 52].

Corticosteroids

The use of corticosteroids has been suggested to reduce an inflammatory response that determines preclinical lung injury, thereby increasing the potential number of lung donations. The use of methylprednisolone at doses of 15 mg/kg has been shown to improve gaseous exchange and is an independent predictor of successful lung transplantation [53]. Recently, Dhar et al. demonstrated that low dose corticosteroids did not result in worsened pulmonary or cardiac function in comparison to high doses. The authors concluded that high dose corticosteroids are not necessary [37].

Transport to the OR

Ventilation for around 20-30 minutes with FiO_2 = 1 is advisable before donor transfer to the operating theatre.

CONCLUSIONS

- Donor management is an “intensive” job.
- Improving management is a way to improve organs (both number and function).
- Knowledge of physiopathology is important in order to resolve frequent complications.

In conclusion:

Global care=ICU care (hypothermia)

- Haemodynamic
- Metabolic: natremia, glycaemia, DI
- Ventilation

Organ care

- Improved function

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TOPIC 4 - Unit 1

Organ viability

ORGAN DONATION

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INTRODUCTION

When evaluating organ viability, it is necessary to compile as much information as possible about the current function of the organ as it relates to the general condition of the donor, their medical history, cause of death, medical evolution following critical admission, and management of the potential donor.

Viability criteria are directly related to possible outcomes of the organ.

There are no standard acceptance criteria due to the existence of different policies that may influence the acceptance of a specific organ such as:

- type and medical condition of recipient;
- organ allocation criteria;
- transplant team experience with standard or expanded criteria organs;
- legal framework of the country.

In order to objectively evaluate the clinical viability of a specific organ for transplant, both global and organ-specific viability criteria must be considered.

1. SECTION 1: GLOBAL EVALUATION

General organ viability criteria are applicable to the evaluation of all organs. There are some clinical criteria that may compromise one organ but are irrelevant for another. Global evaluation represents the standard starting point for every clinical evaluation.

Donor teams and transplant coordinators should balance parameters for investment versus outcome.

Acceptance criteria are based on two factors: donor-recipient compatibility and quality. Standardized protocols, excluding factors that can negatively influence transplant outcomes, should be based on extensive experience and the exchange of best practices between teams.

Transplantation results are influenced by several factors:

» Donor quality (comorbidity factors and donor management)

» Quality of organ recovery (surgical and technical aspects)

» Medical condition of the recipient

» Transplant quality and follow-up (surgical/medical)

1.1 Absolute contraindications

Overly restrictive criteria will exacerbate the problem of chronic organ scarcity.

An optimal system is one in which the transplant procurement manager, organ donor coordinator or transplant coordinator, in collaboration with the different transplant teams, decides on the clinical usability of the potential organ. In order to maximize the donor pool and avoid primary triage of potential donors, absolute exclusion criteria should be limited to a minimum:

» positive human immunodeficiency virus (see Section 1);

» multi-organ failure in an acute, irreversible phase with loss of organ function;

» acute untreated systemic infection (see Section 1);

» active malignant tumour that has not been curatively treated (see Section 1);

» prion diseases (e.g., Creutzfeldt-Jakob disease).

All the other cases should be considered potential organ donors and, therefore, referred.

To validate a donor, certain information is necessary.

1.2 Necessary information

It is important to obtain a broad picture of general and organ-specific viability criteria -based on clear, thorough, clinical evaluation tools- to ensure that the different transplant teams receive the information they require to objectively accept an organ.

Important information to collect:

» past medical history (from family physician): previous hospitalization, habitual treatments;

» recent travels, sexual partners with viral infection, drug addiction, frequent changes of sexual partners during the past six months, imprisonment during the past three months;

» in the ICU (from intensivist): clinical examination (tumour, nodes, tattoos, piercing, melanoma), lab tests, bacteriological results, treatments administered;

» during surgery: clinical examination of thoracic and abdominal cavity.

KEY IDEA

The information required to qualify a donor can be collected from several sources.

1.3 Infections / Virus

CMV / EBV

Organs can be accepted. Suitable prophylaxis or follow-up should be initiated with recipients in cases where there is a mismatch.

Hepatitis A virus

Organs can be accepted except in the case of acute HAV-infection in the donor.

Hepatitis B,C virus

See Tables 1 and 2.

Hepatitis D virus

Usually not accepted.

Herpes viruses (EBV and CMV excluded)

Organs can be accepted, except in the case of acute herpes viraemia in the donor.

HIV

Organs are usually not accepted but may be offered to select HIV-infected recipients (D+/R+) under a specifically designed experimental protocols. See Table 3.

HTLV

Anti-HTLV-1/2 screening should be attempted for donors coming from geographic regions where there is a high prevalence. D+/R+ could be considered.

KEY IDEA

Infection

Transplantation of organs from donors with certain infections may be considered, with an acceptable risk. The combination between each donor and recipient must be assessed individually.

Figure 1 shows the basic screening for viral infections [2].

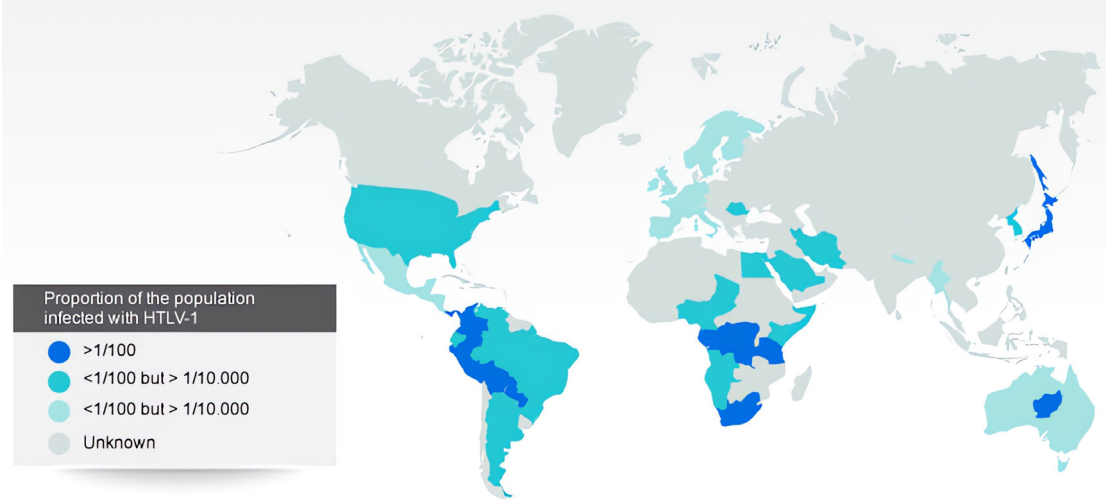

Figure 1. Proportion of the population infected with HTLV-1.

Table 1. Summary of potential risks of organs used for transplantation from hepatitis B-infected donors according to their screening results

Hepatitis B tests	Conclusion	Liver: Possible recipients/ consider transplant	Non-hepatic organs: Possible recipients/consider transplant
HbsAg+ Anti-HBc – Anti-HBc-IgM – Anti-HBs #	HBV viraemia		
HbsAg- Anti-HBc + Anti-HBc-IgM + Anti-HBs -	HBV viraemia Cannot be ruled out	HBV transmission: vital cases or infected recipients (with HBV-PRO*)	HBV transmission: vital cases or infected recipients (with HBV-PRO*)
HbsAg+ Anti-HBc + Anti-HBc-IgM – Anti-HBs #	Chronic HBV viraemia		
HbsAg- Anti-HBc + Anti-HBc-IgM – Anti-HBs +	Hepatocyte infected, usually no viraemia	HBV transmission: vital cases, infected or vaccinated recipients (with HBV-PRO*)	Transmission unlikely: vaccinated or infected recipients. May also be used in other recipients (without HBV-PRO*) and with life-long monitoring

+ = reactive, - nonreactive, # = result irrelevant for further conclusions.

*HBV-PRO = Anti-viral treatment and HBIG, in addition to life-long monitoring by serology and NAT (required).

Only in donors with anti-HBc reactivity should anti-HBs be determined (in addition to anti-HBc-IgM if HbsAg tests are used with a limited lower detection threshold).

Table 2. Summary of potential risks of organs used for transplantation from hepatitis C-infected donors according to their screening results

Hepatitis C tests	Conclusion	Liver: Possible recipients/ consider transplant	Non-hepatic organs: Possible recipients/consider transplant
Anti-HCV + HCV-NAT -	HCV viraemia cannot be ruled out**	HCV transmission: vital cases or viraemic recipients (with HCV-PRO)*	HCV transmission: vital cases or viraemic recipients (with HCV-PRO)*
Anti-HCV # HCV-NAT +	HCV viraemia		

+ = reactive, - nonreactive, # = result irrelevant for further conclusions.

*HBV-PRO = Anti-viral treatment (if possible), in addition to life-long monitoring by serology and NAT (required).

**HCV viraemia may be temporarily below detection threshold of HCV-NAT.

This causes a non-reactive result.

HCV-NAT is only recommended for donors with an elevated risk of HCV-infection.

Table 3. Recovery

Before organ recovery or implantation (1 to 3 hours)	As soon as possible (not necessarily before organ recovery)	Retrospectively, if indicated at the recipient transplant centre
» Anti-HIV ½ (inclusive of HIV-1-p24-Ag) » HbsAg and anti-HBc » Anti-HCV	» Anti-CMV » Anti-EBV-VCA-IgG » Anti-*Treponema pallidum* » Anti-*Toxoplasmosis*	i.e., additional tests for HSV 1 and 2 or VZV in cases of seronegative recipients

1.4 Bacteria

Organs with active bacterial infections should not be used unless adequate antibiotic therapy has been initiated in the donor and, subsequently, in the graft recipient.

Pulmonary infections: Organs, including lungs, may be used after adequate and effective antibiotic therapy for pulmonary infections.

Any suspected urinary tract infection in donors should be confirmed by urine culture and adequate antibiotic treatment administered to the donor and/or recipient.

Disseminated tuberculosis is a contraindication to organ donation. Organs (except for lungs) from donors with a history of tuberculosis may be used if successful treatment has been carried out for at least 3 to 6 months.

1.5 Fungal infections

Disseminated fungal infections must be eradicated before any organ is considered for use. Pulmonary fungal infection/contamination represents a particular problem that must be investigated and properly treated.

1.6 Parasites

Active parasitic disease in the donor is a contraindication to organ donation. The possibility of parasitic infections should be considered in donors from endemic areas [2].

KEY IDEA

Active bacterial infection is not an absolute contraindication if diagnosed and appropriate treatment begins at least several hours before recovery.

1.7 Risk of transmission of neoplastic diseases

The risk of tumour transmission through organ transplantation is rare. However, due to its serious consequences a careful evaluation of potential donors should be performed to avoid the inadvertent transmission of neoplastic disease.

Donors diagnosed with the following neoplasms are widely accepted for organ donation:

- Low-grade skin tumours with low metastatic capacity, such as basal cell and squamous spindle cell carcinoma
- *In situ* carcinomas
- Primary CNS tumours that rarely metastasise outside the CNS, capsulated papillary and minimally invasive follicular thyroid carcinoma (pT1a)
- Prostate carcinoma with a Gleason score ≤6
- Low malignancy grade kidney tumours <2.5 to 4 cm, Fuhrman grade I-II

Central nervous system tumours can be classified in 3 groups. Group I (meninges, peripheral nerves) is not a contraindication to organ donation.

Refer to updated classification [1] and discuss each case with the transplant teams and oncologist.

KEY IDEA

If there is doubt about whether a risk of transmission exists for the recipient, the transplant coordinator must discuss the case with a specialist.

1.8 Risk of transmission of other diseases

Poisoning

In case of poisoning, careful attention must be paid to the diagnosis of brain death and the impact of toxicity on organ function. Poisoning is not a formal contraindication to donation.

Congenital diseases

This type of disease is not a formal contraindication but requires precise diagnosis and consultation with a specialist. However, liver-related congenital diseases can contraindicate donation.

2. SECTION 2: ABDOMINAL ORGANS

Organ viability for abdominal organs

In addition to the general exclusion criteria applicable to all organs, this section reviews the specific criteria for abdominal organs.

The most liberal approach is seen in the liver, whereas the strictest criteria apply to intestinal viability. The balance between a life-saving transplant versus a quality-of-life transplant for the recipient is the main motivation behind this approach.

To shape the most accurate organ acceptance policy, evaluation requires information such as:

- General criteria
- Lab test criteria
- Organ imaging (standard radiography, US, CT scan)
- Macroscopic evaluation: this point is strongly influenced by the experience of the recovery team
- Specific considerations for each abdominal organ:
  - Kidney
  - Liver
  - Pancreas
  - Intestine

2.1 Kidney

The concurrence of several relative criteria could constitute an absolute exclusion criterion.

2.1.1 Absolute exclusion criteria

- Chronic renal insufficiency that means chronic and irreversible structural damage
- Malignant kidney tumour

2.1.2 Relative exclusion criteria

- Age over 70 years
- Arterial hypertension >10 years, without adequate treatment
- Diabetes mellitus types I and II

» Acute tubular necrosis

» Suboptimal and prolonged preservation

» Hepatitis B or C-positive patients (in many hospitals this is not contraindication criteria)

» Technically damaged kidneys (encapsulated, vessel damage, ureter damage)

2.1.3 Lab tests

Serum creatinine and urea, microscopic urinalysis for glucose and protein, urine output /24 h and last hour.

2.1.4 Imaging

US or CT.

2.1.5 Macroscopic evaluation

» Hypoplastic kidneys with severe arteriosclerosis of the renal artery

» Polycystic kidneys (Figure 2)

» Diffuse calcifications along the entire renal artery

» Suspicious lesions suggestive of malignant tumour

» Marbled kidney after flush (bad organ preservation)

KEY IDEA

In case of doubt, a biopsy should be performed to assess organ viability. In some countries this is mandatory.

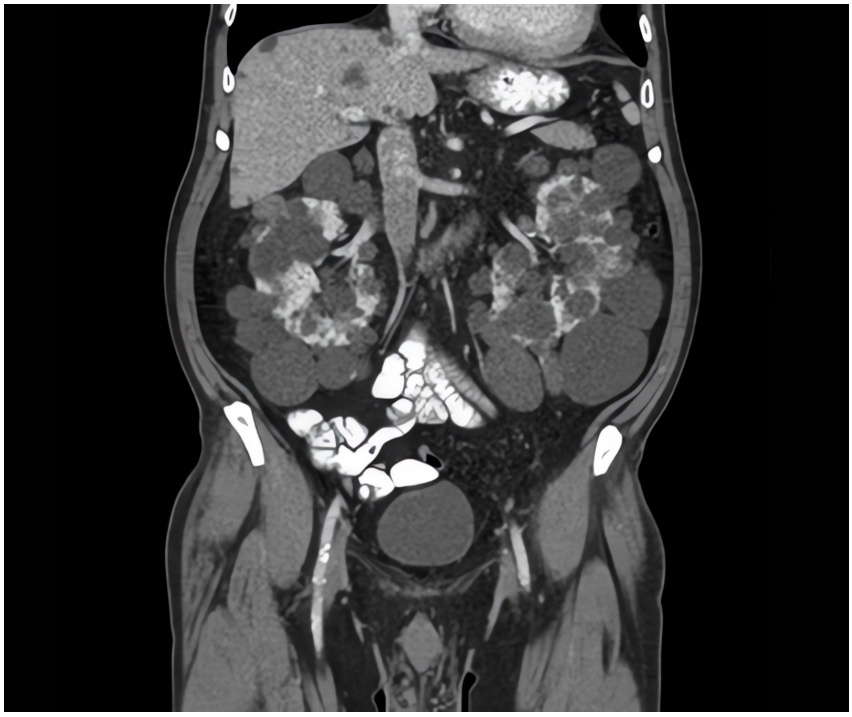

Figure 2. CT Scan.

2.2 Liver

Although the liver is possibly the most resistant abdominal organ, it also has specific exclusion criteria. Age is not a contraindication and often donors with an extended age (up to 90 years of age) are seen as suitable liver donors, whereas this type of donor's kidney function and quality are often poor. In these cases, absolute attention is paid to the combination of risk factors that could influence the outcome.

2.2.1 Absolute exclusion criteria

- Malignant liver tumour
- Hepatic failure
- Acute hepatitis (see Section 1)
- Steatohepatitis with steatosis above 60% micro/macro-vesicular
- Multiple lesions based on severe trauma

2.2.2 Relative exclusion criteria

- Ischaemic damage or long warm ischaemia time
- Steatohepatitis with steatosis between 30 and 60%
- Acute hepatitis (serology and biopsy may be necessary)
- Prolonged cold ischaemia >14 hours

2.2.3 Lab tests

- SGOT/SGPT, gamma-glutamyl transferase (GGT), bilirubin (total and direct), alkaline phosphate
- INR/PT/aPTT (donor clotting parameters)
- Sodium, lipases, amylases

Severe hypernatremia (>160 mmol/l) can cause primary non-function after transplant when not corrected. Correction before recovery can decrease such a risk [3].

Elevated enzymes following a period of ischaemia (CPR, hypotensive period) should be evaluated at different time points. These abnormalities can be reversible and once the liver has recovered it becomes suitable for donation.

In case of any elevated parameters without an immediate possible cause, they should always be checked by an abdominal ultrasound or CT in order to evaluate the liver parenchyma, particularly in the case of abdominal trauma, obesity or alcohol abuse.

2.2.4 Imaging

US or CT scan.

2.2.5 Macroscopic evaluation

- Colour, consistency, surface aspect
- Sharp edges
- Percentage of steatosis (frozen section to determine % of steatosis)

» Trauma

» Tumour

» Anatomical variances

Macroscopic observation and histological analysis (liver biopsy) are crucial for the final acceptance of a liver graft (Figure 3).

KEY IDEA

Macroscopic analysis is very important for the liver.

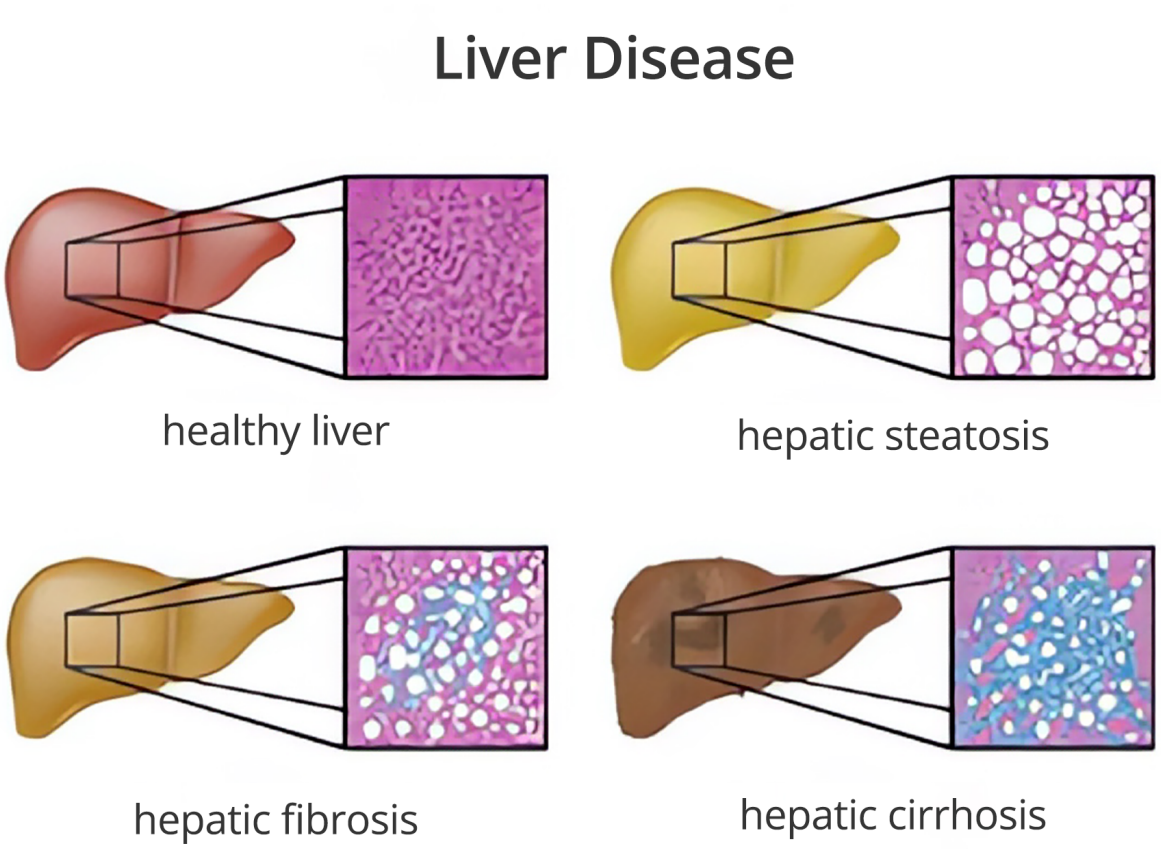

Figure 3. Liver disease.

2.3 Pancreas

As pancreas transplantation is a procedure which aims at improving the recipient's quality of life, strict criteria are applicable (hypotension, catecholamine, etc.)

Therefore, macroscopic evaluation is the best way to ultimately determine whether a pancreas is suitable or not.

Guidance for a final decision can always be supported by ultrasound or CT scan of the abdomen.

2.3.1 Absolute contraindications

- Malignant tumour of the pancreas
- Pancreatitis
- Haemodynamic instability
- Age >55 years, BMI >39
- Admission >10 days
- Chronic alcohol abuse
- Prolonged cold ischaemia >12 hours

2.3.2 Imaging

US or CT scan.

2.3.3 Macroscopic evaluation

- Absence of oedema
- Absence of contusion and/or subcapsular haematoma
- Soft
- No lipomatosis

2.4 Intestine

Until improvements in long-term outcomes, intestinal transplantation had been controversial. This means that for this type of transplant, strict criteria remain absolutely necessary in order to guarantee the optimal outcome for recipients.

2.4.1 Acceptance criteria

- Donor age <50 years BMI <27
- No previous or recent history of abdominal trauma (surgery, bowel disease, no CPR in the past 48 hours)
- Admission <5 days
- Normal kidney and pancreas function, normal oxygenation
- No cold ischaemia

2.4.2 Lab tests

The clinical parameters and biochemical analyses are similar to those for the evaluation of the liver and pancreas.

2.4.3 Macroscopic evaluation

Macroscopic evaluation and recovery should be performed by the team responsible for the transplant surgery. These procedures are rare and not standard, which makes recovery an essential step. Short cold ischaemia times and optimal time coordination of the procedure are pivotal to achieving success.

3. SECTION 3: THORACIC ORGANS

Thoracic organ criteria

The approach to follow differs depending on the type of thoracic organ. This is due, on the one hand, to recent developments, and on the other, to favourable outcomes. The most liberal approach is seen in lungs, whereas the strictest criteria are for combined heart-lung en bloc.

Thoracic organ transplantations are all life-saving interventions, with the most dramatic impact on patients waiting for a lung transplant. Recent developments and optimization of heart-assist devices have made the viability of heart donors more liberal as the backup possibility of a temporary assist device or bridge to retransplantation exists.

3.1 Lungs

Potential lung donors are still an underused group within organ donors. The approaches are strict and remained unchanged for years as the viability criteria for lungs were standardized from the beginning of lung transplantation. However, there has been a dramatic improvement of lung transplantation outcomes which has made the use of more extended lung criteria possible. A comparison of different countries and organ allocation organizations shows a percentage of lung donors that ranges dramatically from 10% to 50% in some centres. It is often the case that the absence of a lung transplant programme has a negative impact on the percentage of lungs available. The PaO_2/FiO_2 ratio is not sufficient criteria for the acceptance or rejection of lungs.

3.1.1 Absolute contraindications

- Malignant lung tumour
- Age >70 years
- Functional damage (fibrosis, emphysema, asbestosis)
- Multiple contusions in both lungs

3.1.2 Relative contraindications

- Over 55 years of age, in combination with tobacco abuse
- PaO_2 lower than 200 mmHg
- Infection
- Lung oedema

» Ventilation period >3 weeks

» Prolonged cold ischaemia >8 hours

3.1.3 Lung evaluation

» Blood gas on normo-ventilation

» Blood gas on 100% FiO_2 and PEEP 5 (debatable because this can induce atelectasis)

» Calculate percentage of shunting between the 2 values

» Blood gas after tracheal aspiration, recruitment manoeuvres

» Compare both standardized values

When evaluating lungs for transplant, a standardized lung evaluation protocol should be followed. Lungs are frequently declined on one-time evaluation data, which may explain the low percentage of lungs available for transplant. The clinical parameters for lungs are basic, which means that the protocol to correctly evaluate blood gases becomes essential. Besides a clean chest X-ray, a standardized approach should be followed in collaboration with the transplant team.

If an improvement is seen, lungs are likely to be suitable for transplant. At the time of surgery, a second evaluation can be performed *in situ*. Blood gas analysis must be performed in the operating room not only after transportation but also after donor stabilization.

KEY IDEA

One measurement of the PaO_2/FiO_2 ratio is not sufficient to accept or reject lungs. Donor management can improve lung function.

3.2 Heart

Although the general exclusion criteria applicable to every organ are also used for the heart, a more liberal approach to this organ has been seen in recent years. Moreover, due to the improved medical treatment of heart failure, indications for heart transplantations have decreased. In common with other organs, apart from clinical and biochemical analyses, the macroscopic appearance of the heart is an essential consideration.

3.2.1 Absolute contraindications

» Cardiomyopathy

» Congenital heart disease

» Ischaemic heart disease

» Valvular heart disease

3.2.2 Relative contraindications

» Coronary artery disease risk factors (arterial hypertension, age >60 years, diabetes mellitus, obesity, hyperlipidaemia)

» Extensive catecholamine use

» Extensive hypernatremia (not corrected)

» Prolonged cold ischaemia (>5 hours)

3.2.3 Clinical evaluation

The clinical evaluation parameters are based on a history of hypotension in combination with possible CPR and laboratory analysis of parameters suggestive of possible damage to the heart.

3.2.4 Lab tests

» Sodium

» CPK and CK-MB fraction

» Troponin and BNP (brain natriuretic peptide)

» Blood gases

» 12-lead ECG

3.2.5 Echocardiography

Ejection fraction, valvular appearance, contractility. Coronary angiography can be considered if a higher risk profile for coronary artery disease exists, although it can be difficult to perform due to donor instability, transport time and availability of the technique in the hospital. Cardiac CT scans have currently not been validated in this indication.

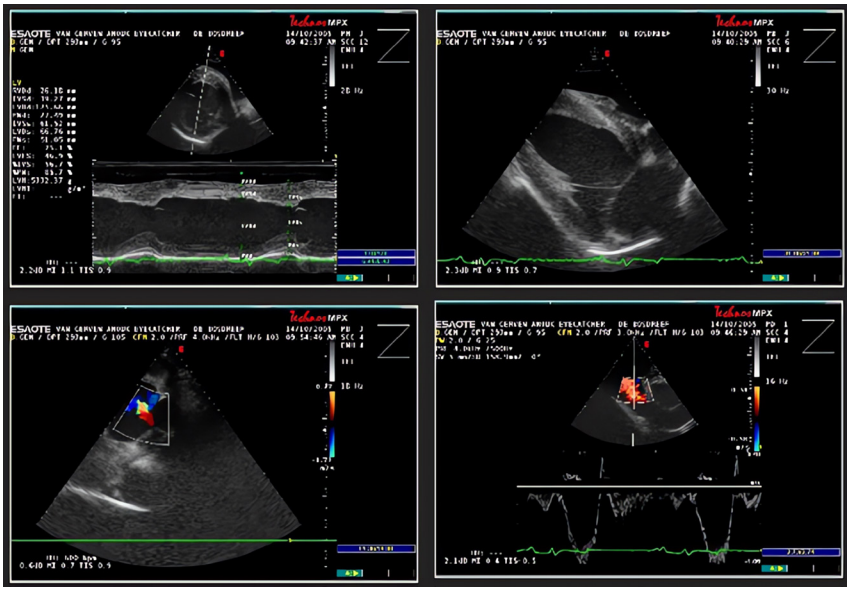

Figure 4: Echocardiography.

3.2.6 Macroscopic evaluation

If heart function is clinically optimal after a thorough diagnostic evaluation, macroscopic evaluation is the best approach:

- Hemopericardium or pericardial fluid
- Contractility
- Arteriosclerosis of the coronary branches

4. SECTION 4: EXPANDED CRITERIA DONORS (ECD)

Towards the end of the 1990s, the term "marginal donors" began to appear in reference to donors who did not meet the classic screening criteria, for reasons of age or the presence of concomitant diseases [4].

One of the first papers evaluating these donors, published in the mid-1980s, recognized that the results of organ transplants from elderly donors were the same as those from younger donors. These cases demonstrated that with better recovery techniques, donor maintenance and immunosuppressive treatment, donor acceptance criteria could be expanded.

However, the term "marginal" immediately generated conflict, as it seemed to imply that the results were inferior, or second class, calling into question the benefit. The term "expanded criteria donors" (ECD) was coined to specifically differentiate these criteria from classic acceptance criteria.

4.1 Definitions

The difficulty of analysing these types of donors arises from the fact that they include many different categories: all types of DCD donors ("controlled" DCD donors, whose cardiac arrest was anticipated in the operating theatre after the removal of mechanical ventilation, as distinct from "uncontrolled" DCD donors, whose cardiac arrest occurred in or out of the hospital setting), elderly donors, donors with infections, or with concomitant diseases. It is accepted that the use of DCD donors is one way of increasing the donor pool with good results.

Another consideration is that for ECD, universally accepted criteria apply to kidneys but not to liver, lung, heart or pancreas transplants.

An accepted policy for ECD in the case of kidney transplantation was established in the USA in 2002 (Ref. 5). A kidney ECD is over the age of 60, or over 50 years who complies with two of the following criteria:

- Arterial hypertension
- Cause of death cerebrovascular accident
- Creatinine over 1.5

However, age is not always the only criterion used in ECD.

4.2 Results

In 1994, the number of donors in the USA who met these criteria was 651 compared to 4,090 standard criteria donors. In 2003, ECD represented 1,169 *vs.* 4,329 SCD. In 2004, there were 1,341 ECD kidneys, which was 21% of all renal donors.

There is no unanimous agreement in the published literature on the use of this type of donor, as can be seen below.

Some studies report good results with the use of kidneys from ECD [6]. The studies show similar results with ECD and standard donors, highlighting that due to the use of ECD alone, the number of renal transplants doubled in one year [7]. The same authors subsequently found that a better selection of recipients, avoiding recipients with a high immunological risk, improves the results obtained [8].

However, other articles question the use of kidneys from ECD. Ojo [9] stressed the worse results obtained and suggested avoiding the use of ECD kidneys in recipients under the age of 40 and in African Americans with a mean waiting list period of less than 1,350 days (Figure 5).

What appears to be clear is that ECD kidney transplantation offers advantages and benefits, and undoubtedly the best results are obtained with improved selection and definition of the groups who will receive the transplant [10].

There is no such consensus on ECD for other organ types, but the use of livers from donors over the age of 65 is becoming more common, which maintains the donor pool. In the case of lung transplants, certain criteria are already being studied [10]. One optimization has enabled ECD lung transplants, thus increasing the number of grafts transplanted without any difference in the recipients [11].

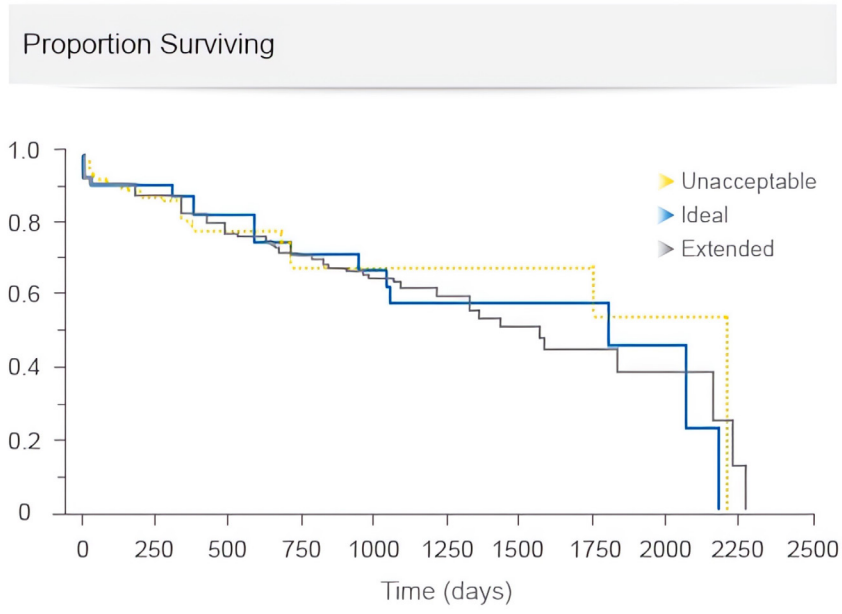

Figure 5. Lung donor.

4.3 Balancing risk and benefit

When applying organ viability criteria, it is essential to avoid the loss of potential organs that can be used for transplantation. Criteria that are too strict should not be applied, and therefore standardization of acceptance criteria is necessary. Macroscopic evaluation guarantees the best approach.

To maximize the donor pool, standardized training on evaluating organs is a crucial area.

The major factor for acceptance of an organ is the clinical situation of the recipient who will receive the graft. Therefore, an organ may be unsuitable for one particular patient, but may be perfectly suitable for another. The gold standard is to maximize independent investigation into the organ type as soon as a donor enters the extended criteria profile. This will be the best and safest way for clinical transplantation teams to properly evaluate acceptance of an organ for transplant.

We now see a more liberal approach, which includes extended criteria donors or DCD donors, meaning that there is a need for standardized analyses of clinical parameters, and protocols to evaluate viability criteria.

4.4 Perfusion machine

There is an increasing need for greater preservation techniques (machine perfusion) in order to create a safety window for organs which require further evaluation ex vivo. In particular, kidneys originating from donors with relative contraindications or ECD could be indicated for this type of preservation since the recovery of kidneys with ischaemic lesions can be successful.

In 2009, Moers et al. demonstrated that hypothermic machine perfusion versus cold storage was associated with a reduced risk of delayed graft function and improved graft survival in the first year after transplantation [12].

Future improvements in machine perfusion may allow the monitoring and improvement of organs before their transplantation.

Figure 6. Perfusion machine.

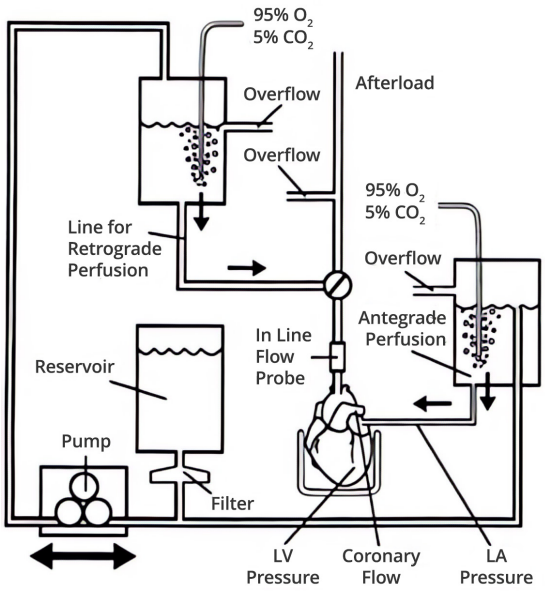

Figure 7. Perfusion.

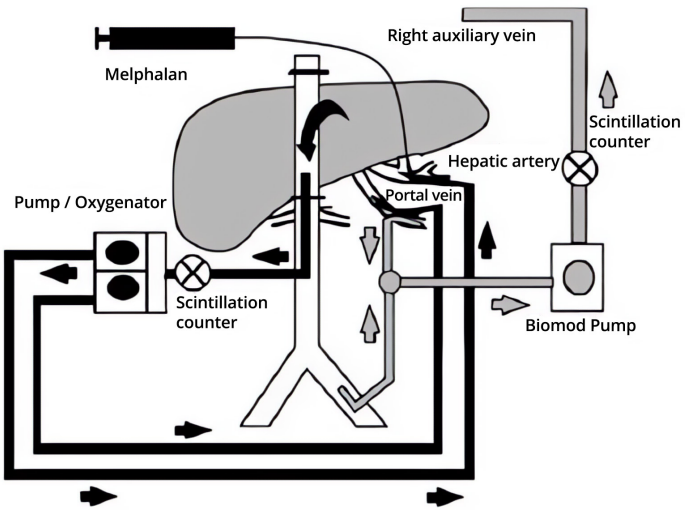

Figure 8. Perfusion.

CONCLUSIONS

» One way to increase the number of donors when dealing with an aging population is ECD, although it is not free of ethical debates [13].

» Evaluation of both organ and donor viability are crucial for recipients. The information required for this type of evaluation must be collected from all available sources.

» There is always a balance between risk and benefit.

» Apart from the global evaluation of an organ, there must be a detailed evaluation of each organ.

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TOPIC 5 - Unit 1

Breaking bad news

ORGAN DONATION

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Breaking bad news is a complex task that causes anxiety and discomfort for the giver and leaves an indelible memory on the mind of the person who receives it.

Healthcare professionals frequently have to be the bearers of bad news and have rarely received training for this task. In addition, transplant coordinators constantly deal with people who have lost a loved one. Transplant coordinators not only help families understand difficult concepts, such as brain death, but also have the task of making the request for donation.

A skilful and careful approach can minimize the emotional damage for the family in their acute grief. Sound knowledge of specific communication tools can help professionals to successfully manage this difficult task.

The ability to discuss donation, support the family, provide information and sensitively assess biological risk factors are also challenges that the transplant coordinator faces. The TC is a healthcare professional who acts not only as an advocate for the donor and their family, but also for the potential recipients.

INTRODUCTION

This unit discusses the concept of bad news, which goes far beyond a mere negative piece of information. We will see that for a better outcome of an interview where bad news is imparted, the TC needs not only good communication skills but also a structured interview. This unit recommends some steps that will allow the person who receives the bad news to be prepared, understand the information conveyed and reduce the emotional impact the bad news may have on them.

Finally, there is a brief review of some emotional support techniques aimed at helping the recipient to accept, confront and reduce the damage that bad news causes. In addition, when it comes to communicating the death of a potential donor, it is essential for the bearer to help initiate a process of physiological, rather than pathological, grief so that the family is be able to take decisions concerning organ donation for transplantation.

1. SECTION 1: BREAKING BAD NEWS – METHOD OF COMMUNICATING BAD NEWS

Bad news is information which has serious adverse effects on an individual's view of the future. Factors that can influence this perception are associated with the news itself, the degree of family support, in addition to individual and social factors like education, culture, religious beliefs or even financial position (Figure 1) [1,2].

The common denominator is that bad news consists of messages that have the potential to shatter hopes and dreams, and lead to dramatic changes in the lives and lifestyles of recipients. Several factors influence reactions to such news [3].

1.1 Factors associated with the news itself

How expected, unexpected or sudden the news is, and the potential degree of disability it will cause (an illness with a life-threatening prognosis, the associated life expectancy, etc.).

1.2 Family support

This is one of the keys to alleviating the fear of abandonment and will help to adjust to the new situation.

1.3 Individual factors

These are the most difficult to analyse, as they are undoubtedly the least controllable and involve aspects such as each person's coping mechanisms, previous personal experiences, interpretation of reality, and factors inherent to personality.

1.4 Social factors

Education, culture, religious beliefs and financial position can determine the way different individuals react to the same news. For example, religious beliefs can modify the significance death, since for some people it is the end and for others, it represents a beginning. Societies stigmatize certain illnesses, such as tuberculosis, AIDS, and until relatively recently, cancer.

Society's deep-rooted work ethic, considering individuals as productive elements, will affect their value in that society in the event of a disability. A person's financial position may ease or make their adjustment to a new situation more difficult.

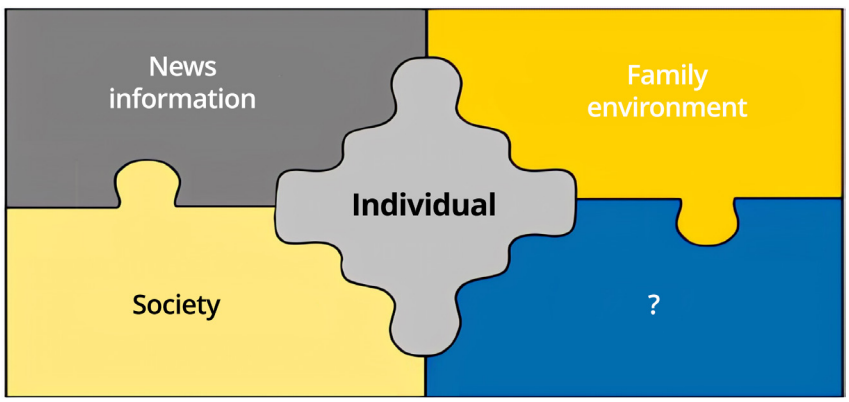

Figure 1. Influential factors 1.

1.5 Coping with bad news

Breaking bad news is a communicative task and therefore involves interaction between individuals, which makes both the progress and outcome unpredictable. The outcome of communicating the news of a death will thus depend on various factors such as:

1.5.1 Factors related to the communicator

Factors such as the manner in which the communicator assesses the news, their judgments, fears, experience, communication skills, or their training in methods of breaking bad news have an impact on how the bad news is presented.

Other factors associated with the person who actually gives the news, such as their own interpretation of the event or their degree of anxiety and fears at the time of confronting the task can substantially modify the process. Studies report that 42% of physicians experience stress after conveying bad news, and the effects may last anywhere between several hours to more than three days [4].

The way in which bad news is delivered and how the TC responds to the reactions and emotions caused in the recipient are also essential considerations. Studies suggest that a number of factors can affect the physician's ability to impart bad news, among which are burnout and fatigue, personal difficulties, behavioural beliefs, subjective attitudes and previous clinical experience.

The coping strategies of the recipients of bad news, the social support they are receiving, and their cultural circumstances can be difficult to identify.

Coping with bad news is a dynamic process that changes over time. People need to manage the initial emotional shock of a diagnosis, assimilate the information, construct an understanding of the new situation and the limitations it imposes upon them, and formulate ways to cope with it. Some other, less helpful, coping strategies include hoping and praying that the condition will disappear spontaneously, denial, obsessively focussing on minute details of the disorder or seeking a scapegoat.

It is important for healthcare professionals to be able to understand and differentiate between normal reactions and physical diseases, as well as detecting psychiatric problems if and when they arise.

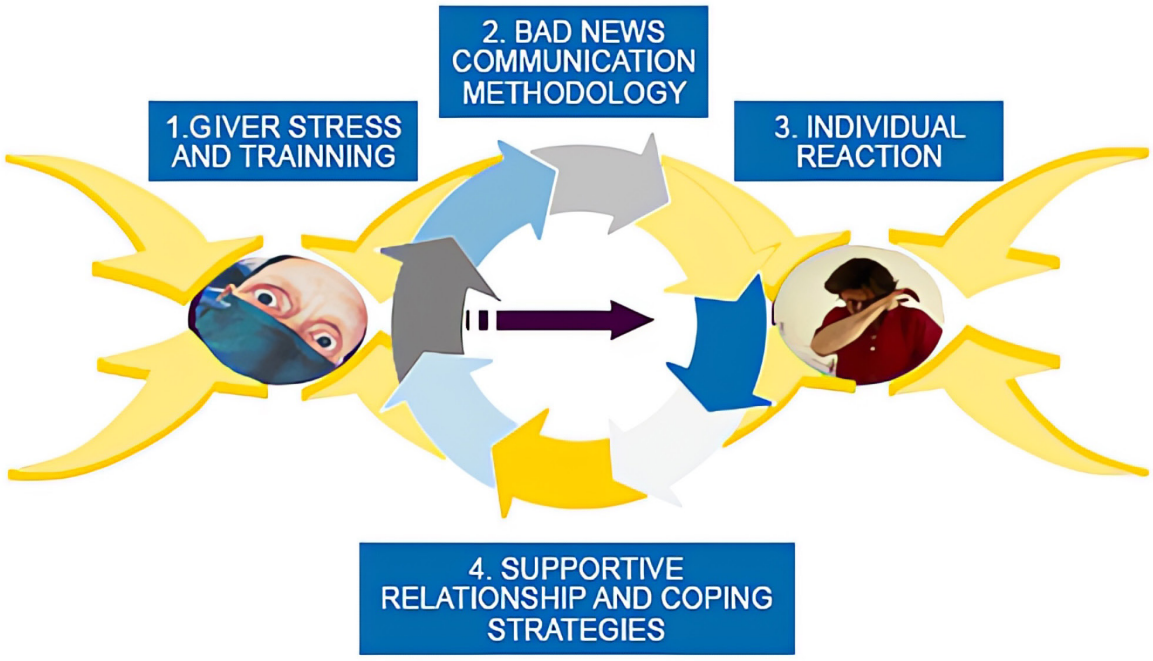

Figure 2. Influential factors 2.

1.6 Method of communicating bad news

The skills of the professional who delivers the bad news and the timing of such a conversation may have a significant impact on consent rates.

Following a method based on a series of stages, which are worked through consecutively, allows the recipient of the news to dictate the pace, and this seems to be the best approach when breaking bad news. It also allows an efficient response to the recipients' needs [5,6]. This procedure can not only improve the recipient's assimilation of bad news, but also decrease the stress level of the deliverer when tackling this difficult task.

However, this method used for imparting bad news is not intended to be restrictive and rigid. It is a useful, flexible way to structure the conversation in order to reach the objectives that have been established. Thus, each professional needs to develop and identify their own style, adapting the proposed method accordingly [7].

Step 1. Preparation

This consists of collecting all of the necessary information and preparing oneself before starting the interview. To do so, review the chart and talk to the healthcare professionals in charge, doctors and nurses, to identify the cause of death and learn about the patient's evolution since admission and from the onset of the illness. Finally, it is important to know who visited the patient, the nature of their relationship and who the decision-maker is.

This preliminary phase also involves deciding where the news will be given, who will be present at the interview and when the right moment is.

Where to deliver the news

Privacy, space and comfort must be ensured. Preparation may be required, but even in the worst circumstances, in the poorest conditions, it is still essential to facilitate the privacy required to proceed. We have to avoid physical barriers between the person communicating the news and the patient and/or relatives, ensure any supplies that may be needed (tissues, water, drinks, telephone) but avoid unnecessary furniture or medical equipment. Ensure that there will be no interruptions and schedule an adequate amount of time for the interview.

Who will receive the news

Decide who the news will be given to and ascertain how many family members will be present.

Although certain priorities exist, based on the degree of family relationship, it is also important to consider and include people who have played an important part in the deceased's life and decision-making processes.

It is important to undertake thorough mental and emotional preparation for delivering the news. This preparation includes rehearsing how to deliver the news, writing down key words and phrases to use or avoid, conducting a self-analysis concerning feelings and fears (fear of judging and being judged, of empathizing with their pain, of the unknown, etc.), in addition to any prejudices towards the family or their environment. When delivering bad news, it is essential to avoid judgmental attitudes.

Step 2. Perception

The objective of this step is to find out, by using open questions, what the family already knows and to explore their capacity to understand. The family must be ready to receive bad news, so they have to be brought to that point, starting from their knowledge of the situation.

We may discover that relatives lack information that we believed they had received, or they may have been badly informed. On certain occasions, the recipients of bad news may not admit to having been informed in order to check whether the information delivered previously is accurate and congruent, and on other occasions, this attitude forms part of denial as a defence mechanism.

Try to ask open questions:

> *"I'd like to make sure that you have understood what I have just told you. Why don't you tell me what have you have understood so far?*
>
> *"What did my colleagues tell you about the situation?"*

You may also use the narrative or summarizing technique which enables going over the whole story such as:

> *"Let me make sure that we are all on the same page, that you have understood all the information so far. Your son arrived at the emergency room 3 days ago because of a traffic accident and..."*

Step 3. Invitation

The objective of this step is to ascertain how much detail the family wants to know and to prepare to adapt to the family's demand for information. Unfortunately, in the case of death, the announcement cannot be delayed. But even in this event, details concerning the mechanism which led to death can be provided according to demand.

Whereas for some people the news of death itself suffices, for others it is not enough because they may want to understand what brain death is and how it differs from death induced by cardiac arrest. In such cases, all the required information needs to be provided.

For good, effective collaboration with the recipient of bad news, a great amount of information is usually required since the plans to be made or the decisions to be taken are more complex. This is precisely the case in the family interview for organ donation, when relatives have to understand death and make decisions about organ donation.

Step 4. Communication

It is important to begin by using phrases which start preparing the family to receive bad news such as "I'm sorry to tell you..." or "I'm afraid I don't have good news...," which act as warning shots. Be sensitive, warm, sincere, respectful, clear and concise.

We must understand the rate at which each recipient comprehends the news and check whether they understand it. Immediately after receiving bad news, the recipient tends to pay less attention to what is being said. This is why it is recommended to respect periods of silence and to summarize the information given in short and simple messages [8].

Table 1. Summary

When interacting with grieving families remember to:
Be aware of the fears and worries of the family
Avoid confrontation (reflection of emotions)
Provide privacy and information
Communicate bad news clearly, honestly and sensitively
Provide freedom to show emotions
Establish cooperation between doctors, nurses and other healthcare workers
Establish empathy
Allow thinking time and time to ask questions

Step 5. Responding to emotions

After news has been communicated, a phase of emotional turmoil begins. This is the start of the grieving process, and perhaps the most difficult moment to deal with due to the imminent necessity that arises to respond to the emotions generated.

In this phase, we must establish a relationship of empathy with the family and so help the initiation of a supportive relationship.

Step 6: Planning

The final stage is planning, also known as a care plan, strategy or summary. If the family has a clear plan for the near future, it is less likely that they will be anxious or confused. Moreover, making a plan, explaining it and guaranteeing prompt return of the body is very useful, for example: "In two hours we'll transfer your relative to the operating theatre where they'll remove the organs; then, later, the body will be returned so that you can arrange the funeral."

Throughout the planning stage we have ensure transmission of three concepts:

- every possible effort will be made to help;
- the person is not going to be abandoned;
- we will continue to help with decision-making.

1.7 The communication

At times, coping strategies may fail, and/or other factors may contribute to the development of a depression or another psychiatric disorder. It is important for healthcare professionals to be able to understand and differentiate normal reactions from physical disease, and to detect psychiatric problems if and when they arise.

Other factors will depend on the manner in which news is delivered, i.e., on the method used. Hence, how bad news is delivered and how we respond to the reactions and emotions caused in the recipient are essential considerations. Studies suggest that a number of factors can affect the physician's ability to impart bad news including burnout and fatigue, personal difficulties, behavioural beliefs, subjective attitudes and prior clinical experience.

The communication of brain death in the case of a potential organ donor involves additional difficulties [2]. The situation frequently implies an unexpected death, since in principle, the potential donor is healthy, did not suffer from any serious chronic illnesses such as cancer (usually contraindicated for donation), and is not of an age corresponding with his/her life expectancy [3].

Section 2 discusses the supportive relationship in greater depth.

KEY IDEA

Thayre and Hadfield suggest that "losses may take many forms: a loved one's death; a devastating diagnosis which shatters hopes, dreams, aspirations; disability; impairment; or poor prognosis confirming or confronting the recipient's worst fears."

1.8 The outcome

Bad news is information which has a serious adverse effect on an individual's view of the future [4]. Factors that can influence this perception are associated with the news itself, the degree of family support, individual and social factors like education, culture, religious beliefs, or even financial position [5].

The outcome of communicating the news of a death will thus depend on various factors such as:

Factors related to the communicator

For instance, the manner in which the communicator assesses the news, their judgments and fears, their experience, communication skills, and any training taken on methods for breaking bad news.

Factors concerning recipient evaluation

The recipient's coping strategies, social support and cultural aspects, which are difficult to ascertain.

2. SECTION 2: COMMUNICATION SKILLS AND SUPPORTIVE RELATIONSHIP

Accepting loss, experiencing pain and adjusting to a new life are the main tasks in immediate phase of grief.

Healthcare workers may help the family with their grieving process by establishing a supportive relationship that allows relatives the family to understand and accept death, identify and recognize their feelings, reduce the intensity of emotions, verbalize problems, look for resources, make their own decisions and count on the unconditional support of medical staff [9].

The supportive relationship is based on Person-Centred Therapy (PCT), developed by Carl Rogers, who holds that the therapist's primary effectiveness is through the therapeutic relationship. The therapist must show empathy, genuineness and unconditional positive regard.

2.1 Empathy

Empathy allows us to understand others even though we do not share the same feelings. When healthcare workers have the ability to understand relatives' reactions and put themselves in their position, family members feel understood, rather than evaluated or judged. Empathic understanding is the basic attitude for active listening and reflection of emotions.

2.2 Warm respect

This implies the approval of, and an unconditional positive regard for, the family. It is the acceptance of the individual as a separate person, without passing any judgment on their feelings, actions or attitudes.

2.3 Genuineness, congruence

In face-to-face communication, the family may feel afraid to confide, which is why realness and genuineness are essential attitudes to gain the trust of relatives.

KEY IDEA

Shock is usually the first reaction, which is followed by anger, fear and often a profound sense of sadness.

2.4 Communication skills

A supportive communication approach may help both family and health professionals to deal with a difficult situation. The method of communicating effectively encompasses several aspects such as active listening, language, non-verbal communication and the ability to identify and respond to emotional reactions.

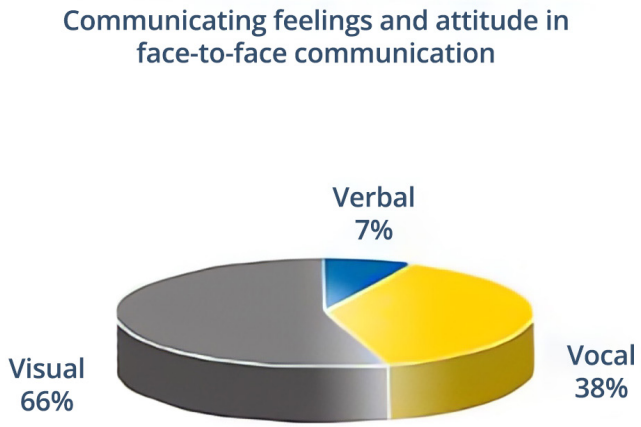

Figure 3. Believability.

2.5 Verbal communication skills

Verbal communication skills can be used to establish the right supportive relationship. Such skills include:

- Employ narrative and summarizing techniques: they allow focus on the subject, avoid digression and going over the whole story from admission. Use phrases which start preparing the family to receive bad news (i.e., *"I'm sorry to have to bring bad news...," "I regret to tell you..."*).
- Metaphors and examples may aid comprehension of brain death (e.g.: a cut flower looks alive, but it will fade...).
- Use coherent, reasoned, simple and concise language.
- Formulate open questions: maintain the recipient's attention and give them time to think of answers. Ask "what, how, where, when" questions rather than closed "yes/no" questions.
- Avoid technical/medical language.
- Use neutral vocabulary.
- Use reiterative phrases, clarifications, interpretations: make the family aware we understand what they mean.
- Paraphrase: repeat the message received but in different words. The listener does not necessarily need to agree with the speaker, but it shows the family that the message transmitted was understood.

Table 2. Examples of empathic, exploratory, and validating responses

Empathic statements	Exploratory queries	Validating responses
"I can see how upsetting this is to you."	*"What do you mean?"*	*"I can understand how you felt/ feel that way."*
"I can tell you wereń t expecting to hear this."	*"Tell me more about..."*	*"I guess anyone might have that same reaction."*
"I know this is not good news for you."	*"Could you explain what you mean?"*	*"You were perfectly correct to think that way."*
"Í m sorry to have to tell you this."	*"You said ... frightened you?"*	*"Yes, your understanding of the reason for the tests is very good."*
"I'm finding this very difficult too."	*"Could you tell me what yoú re worried about?"*	*"It appears that yoú ve thought things through very well."*
"I was also hoping for a better result."	*"Now, you said you were concerned about your children. Tell me more."*	*"Many other patients have had a similar experience."*

2.6 Non-verbal communication skills

The supportive use of non-verbal communication is based on:

- An appropriate setting: a comfortable, private place is recommended to respect the family's privacy. Barriers must be removed to ensure efficient communication.
- Use of clear diction, proper intonation, a soft and warm tone of voice.
- Functional silence, low reactions, pauses of four to five seconds show respect, express interest and attention. (We accompany the family in their silence but make them aware of our presence, availability and openness to what they want to say).
- Eye contact: should be maintained most of the time; however, we should consider cultures where this might be a sensitive issue.
- Physical position: we have to position ourselves close to the relatives, in a circle, without barriers, adopting a position of proximity and a posture of approach.
- Assent: assent by nodding, raising eyebrows or making hand gestures to communicate interest, engagement and attention.
- Physical contact: can be used to console, show warmth and tenderness. We must be sensitive to family withdrawal and avoid physical contact with angry relatives or in situations when contact is not culturally appropriate.

2.7 Active listening

Active listening is a structured way of listening, which requires the listener to repeat what they hear to the speaker by re-stating or paraphrasing what they have heard to confirm and improve mutual understanding.

The process is successful when the feedback given shows understanding of meaning. Thus, the listener checks with the speaker to make sure that the message transmitted has been correctly understood. Active listening avoids misunderstandings, encourages people to open up, resolves conflicts and builds trust.

To practice active listening, prepare yourself and adopt a positive attitude:

- Be other-directed; focus on the person communicating. Stop all non-relevant activities beforehand.
- Listen with your ears, eyes and other senses.
- Mentally review what you already know about the subject and avoid distractions.
- Recognize any emotional state, eliminate negative emotions
- Set aside your prejudices and opinions. You are there to learn what the speaker has to say.
- Use and be aware of non-verbal communication by the speakers (Remember to use an open posture to show involvement and encourage the speaker).
- Be involved: actively respond to questions and directions.

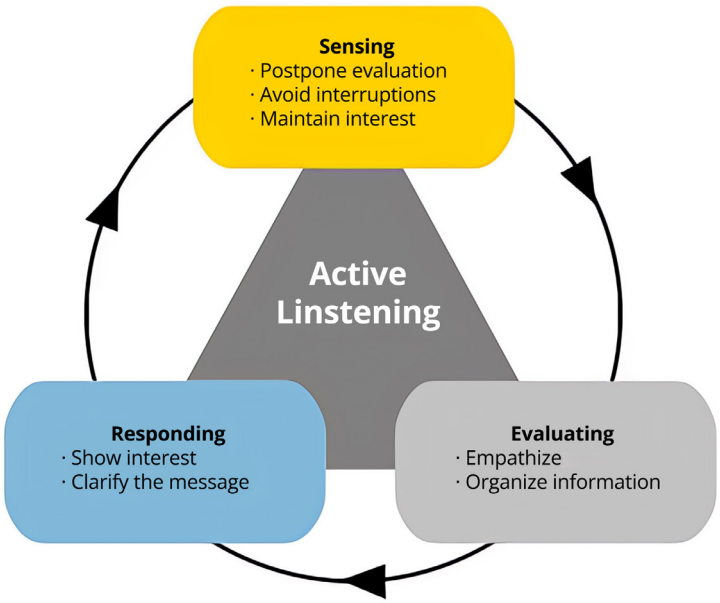

Figure 4. Active listening.

2.8 Reflection of emotions

In emotionally charged communications, the listener should be aware of feelings. Rather than merely repeating what the speaker has said, the active listener will describe the underlying emotion. Reflection of emotions helps to clarify, express and handle feelings:

» Identify the emotion and name it.

» Encourage its open expression and finish with a leading question: *"You seem to feel very angry, is that right?"*

» Express the correct intensity of the emotion and help to reduce it.

To practice reflecting emotions:

Step 1

Observe and listen actively.

Step 2

Listen to yourself:

» Be aware of your own emotions.

» Neutralize them if they are negative.

Step 3

Reflect emotions:

» Show the family that you are listening and that you care.

» Allow relatives to examine their own emotions.

» Name the emotion they are feeling.

» Let the family confirm or correct your interpretation of their feelings.

Step 4

Normalize the emotion: all feelings are normal.

Acknowledge their right to feel the way they do, and that this feeling will help start the healing process and consolidate the therapeutic relationship.

2.9. Interacting with the grieving family

The manner in which families are informed about the death of a loved one has a lifelong impact on survivors.

The behaviours that families perceive as most comforting and helpful are:

- a caring attitude
- clarity of message
- privacy
- ability to answer questions
- empathy

DID YOU KNOW...?

Healthcare professionals are in a unique position to help people through the turning points in their lives which arise at times of loss.

A supportive relationship should be established with the family in order to reduce the potential damage caused by death, ease the suffering and provide emotional support, facilitating the expression of emotions.

The contribution of healthcare workers to grieving families should:

- give information in a clear, honest and direct manner;
- avoid euphemisms such as: *"You have lost your child."*;
- identify and accept feelings and behaviours;
- help relatives have a realistic approach of the loss;
- offer and facilitate the possibility of bidding farewell;
- ease the suffering and provide emotional assistance;
- identify external support available;
- support relatives to make decisions on their own so they can discover skills to cope with the crisis.

Table 3. Interacting

When interacting with grieving families remember to:
Be aware of the family's fears and worries
Avoid confrontation (reflection of emotions)
Provide privacy and information
Communicate bad news clearly, honestly and sensitively
Provide freedom to show emotions
Establish cooperation between doctors, nurses and other health care workers
Establish empathy
Grant time to think or to ask questions

3. SECTION 3: DEATH AS BAD NEWS IN THE CONTEXT OF A POTENTIAL ORGAN DONOR

Communicating bad news and the family interview for organ donation have specific characteristics depending on the type of donor.

Brain death donors (DBD) involve the difficulty of the relatives understanding the concept of brain death itself.

Controlled donation after circulatory death (c-DCD) requires a complex conversation about futility, end of life and the withdrawal of life sustaining therapy (LST).

In the case of uncontrolled donation after circulatory death (u-DCD), the major difficulty relatives face is related to the short time between the event that led to death and the moment when decisions have to be made and organ retrieval. Another consideration is the challenges of different scenarios such as the emergency department, the intensive care unit or even the operating room.

3.1 Characteristics of communication for brain death donors

KEY IDEA

Comprehension and understanding of the concept of brain death.

When communicating death due to neurological criteria it is very important to make it clear that the patient has died, and that brain death equals death. To use euphemisms or terms like *"brainstem death"* can be confusing because this concept is not generally known by society.

We must emphasize, and may need to explain, the differences between death and a coma. Brain death is irreversible and means that there is no blood flow or electrical activity. We must prepare the family to understand that apparent vital signs like rhythm, pulse, breathing movements and body temperature are artificially maintained. The patient does not have spontaneous breathing, the brain does not regulate any body function, and there is no chance of recovery. This situation constitutes the death of the person.

3.2 Characteristics of the communication of death in controlled donation after circulatory determination of death (c-DCD)

KEY IDEAS

- » End of life conversations.
- » Understanding and accepting medical futility and withdrawal of life-sustaining therapies.

Donation after death by circulatory criteria, unlike brain death, is usually an understandable concept for the family because they observe an inanimate, cold body that does not have a pulse or breathing.

In the case of controlled DCD donors (also called Maastricht classification III donors), organ retrieval is performed after the withdrawal of life-sustaining treatment techniques, which leads to asystole and certification of death. This moment can be planned to occur in the intensive care unit or the operating room. The key points of this type of family interview will be the conversation about end of life and the withdrawal of life-sustaining therapies. We must help relatives to understand medical futility: there is no therapeutic possibility of providing a reasonable chance of survival; any treatment is useless or ineffective; no treatment can fulfil the patient's goals or will be successful at enhancing either quality of life or medical utility [1].

Differences in perceptions of what constitutes futile treatment have created many challenges between the family members of patients and healthcare professionals regarding the continuation or discontinuation of treatment. Conversations may consider a patient's values and preferences, but futility is determined by the medical team, based on medical evidence and well-established prognosis.

Controlled-DCD also raises the issue of the family's presence at the moment of withdrawal of the LST that will lead to the declaration of death. We should act as facilitators of what might be the most helpful in each case. For some relatives, witnessing the moment of death can help them to assimilate and accept death, while for others, it may be too stressful, and they would prefer to bid farewell to their loved one before this moment. Our role is to inform and accompany them in their decisions.

3.3 Characteristics of the communication of death in uncontrolled donation after circulatory determination of death (u-DCD)

KEY IDEAS

- » Ethical concerns surround the decision to move the body to a hospital after unsuccessful resuscitation manoeuvres with the intention of evaluating the possibility of organ donation if the family have not been consulted.
- » Doubts exist regarding the decision to initiate organ preservation techniques without having spoken to relatives or knowing the wishes of the deceased.
- » Informing the family about a sudden and unexpected death.

In the case of u-DCD there is no difficulty understanding that death has occurred since relatives have often witnessed the sudden event of loss of consciousness and circulatory arrest. However, relatives do face the difficulty of coping with a sudden and unexpected death.

The patients in these cases are usually young, given the fact that the current criteria for u-DCD is under 60 years. In this context, healthcare professionals working with this type of donor have not usually had the opportunity to meet the family previously, and so have not had the opportunity to talk about the patient's preferences, or to establish a bond of trust with the relatives as occurs in the event of DBD or c-DCD.

Moreover, enormous pressure exists because of the time restrictions involved with a successful donation. There must be less than 150 minutes between the moment of cardiac arrest and the initiation of organ preservation techniques, and less than four hours to organ retrieval.

The family interview usually takes place after the initiation of organ preservation techniques have started. On the family's arrival at the hospital, the body is usually in the emergency department or the operating room. The doctors in charge declare death and the transplant coordinators raises the subject of a possible organ donation, explaining the fact that preservation techniques have begun.

In certain circumstances the possibility exists of broaching the subject of organ donation at the place where the cardiac arrest happened. The out-of-hospital medical team decides that resuscitation manoeuvres are unsuccessful, usually after more than 30 minutes. At that point, if the patient meets u-DCD criteria, circumstances allow it, and the medical team is trained, they propose continuing resuscitation manoeuvres and transferring the patient to a hospital, where the diagnosis of death will be established, and the process of organ donation will begin.

In all cases, however, the information given must be guided by accuracy and authenticity and be adapted to the family's rhythm of understanding. Moreover, this process will also depend on the experience of the healthcare professionals involved, and must be guided by standard procedures, including any requests for information from relatives.

CONCLUSIONS

Breaking bad news is a communicative task and thus subject to interaction between individuals, which makes its course and outcome unpredictable.

Following a method based on a series of stages allows the recipient of news to set the pace.

Healthcare workers can help the relations with their grieving process by establishing a supportive relationship that allows the family to understand and accept death, identify and recognize feelings, reduce the intensity of emotions, verbalize problems, look for resources and make their own decisions.

The communication of bad news and the family interview for organ donation have some particularities depending on the type of donor.

Effective communication makes use of basic attitudes such as empathy, warmth, respect, authenticity, congruence, verbal and nonverbal communication skills, active listening and reflection of emotions.

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TOPIC 5 - Unit 2

Requesting an organ

ORGAN DONATION

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INTRODUCTION

Improving family consent rates requires the commitment of expert clinicians in donation who are well prepared and focussed on successful outcomes [1]. In order to achieve success when approaching the family for a donation, the transplant coordinator must be able to communicate effectively and sensitively when dealing with bereaved families. The coordinator must be supportive of the family's emotional needs and also be effective in gaining consent for donation [2].

1. SECTION 1: MAKING THE REQUEST AND DEALING WITH REFUSAL

1.1 When is the right time to discuss donation with the family?

The request for donation should not come at the same time as the diagnosis of brain death is delivered or when explaining futility and the withdrawal of life sustaining therapies (WLST) to the family. In both donation routes, donation after brain death (DBD) and donation after circulatory death (DCD), whether controlled (c-DCD) or uncontrolled (u-DCD), the timing of when to move on to the next step can be crucial for the outcome of the family discussion about donation.

Well established research demonstrates that when a separation or "decoupling" exists between notification and acceptance of death and the request for donation, there is an improved rate of consent [3]. One such study describes increased consent rates of 68% if the timing of the request was considered appropriate, whereas consent was only 18% if timing was thought poor [4].

1.2 Is there a difference between requesting a DBD or a DCD donation?

There are particular characteristics relating to when to approach the family and the type of information you provide, based on the type of death. Regardless of whether death was diagnosed by neurological criteria or circulatory criteria, in the ICU or in the emergency department, the request for donation should follow the same pattern of supporting the family in their grief. The request should also provide positive information about donation in order for the family to reach the right decision both for their relative and for themselves.

The table below describes the flow of determination of death and the request for donation in the different scenarios:

Table 1. Flow of the determination of death and the request for donation in donation after brain death (DBD) and donation after circulatory death (DCD)

Donation after brain death (DBD)	Donation after circulatory death (DCD)	
Intensive care unit	**CONTROLLED** Intensive care Unit (c-DCD)	**UNCONTROLLED** Emergency Department (u-DCD)
Patient diagnosed with catastrophic brain injury Brain death is suspected	Patient for whom any treatment is considered futile Decision to withdraw life-sustaining therapies (WLST) is made	Patient has suffered a cardiac arrest in or out of the hospital
Diagnosis of brain death is made	In-hospital cardiac arrest is anticipated Diagnosis of death by circulatory criteria is made	Diagnosis of death by circulatory criteria is made after unsuccessful advanced life support manoeuvres

Treating doctors talk to family to notify death of the patient	Treating doctors discuss futility, WLST and end of life care with the family	Treating doctors talk to family to notify death of the patient
Separation in time between notification of death and discussion about donation	Separation in time between discussions regarding futility and donation	Separation in time between notification of death and discussion about donation
Family re-convened for discussion about possibility of donation with transplant coordinator	Family re-convened for discussion about possibility of donation with the transplant coordinator after death has occurred	Family re-convened for discussion about possibility of donation with transplant coordinator
Family re-convened for discussion about possibility of donation with transplant coordinator	Family re-convened for discussion about possibility of donation with the transplant coordinator after death has occurred	Family re-convened for discussion about possibility of donation with transplant coordinator
Family supported and information provided about the possibility of donation and the process of retrieval.	Family advised of process of circulatory death after WLST, declaration of death and time frames. Family supported and information provided about the possibility of donation and retrieval	Family supported and information about the possibility of donation and the process of retrieval. Information provided about preservation manoeuvres (cannulation and extracorporeal circulation) often already initiated at the moment of the interview
Family agreement for donation after clinical and legal criteria of brain death established (If no consent – end of life care continues)	Family agreement for donation after circulatory arrest (If no consent – end of life care continues)	Family agreement for donation after circulatory arrest (If no consent – preservation manoeuvres are withdrawn or not initiated, and funeral process begins)
Family supported – offered a break and biological risk assessment performed	Family supported – offered a break and biological risk assessment performed	Family supported – offered a break and biological risk assessment performed

KEY CONCEPT

The right time to discuss donation is when the family members have understood and accepted brain death or the withdrawal of life sustaining therapies.

1.3 Reasons for requesting donation

As health professionals, we have to know the reasons that justify our presence in a request for donation and remember that we act as an advocate for both the donor and the recipients. Our justifications include:

1.3.1 Solidarity (with society as a whole)

Solidarity refers to the agreement of the community that organ donation saves lives and recipients benefit from organ transplants.

1.3.2 Reciprocity

Reciprocity refers to the practice of exchanging something with others for mutual benefit. In the context of organ donation, it refers to the notion that if you were willing to receive an organ transplant, you would be willing to give one.

1.3.3 Usefulness

Death is often described as a waste of a life, but the outcome of donation after death could be helpful for others and for the family. Some people consider donation as a way of continuing life or prolonging the lives of others.

1.3.4 Providing information about the benefits of donation

It is important that we provide positive information about donation to the family in a way that is respectful and honest without being coercive. Some authors report that the "amount" of positive information which is given by the health care team when discussing donation can influence consent rates [12].

1.3.5 Why do families say YES to donation?

Understanding why some families say YES to organ donation is just as important as knowing why others say NO.

Solidarity and reciprocity, as well as the usefulness of donation in saving lives are strong indicators of the general perception in society as a whole. The table below shows some of the reasons expressed by families and illustrates the most common reasons why people agree to donation on behalf of their relative.

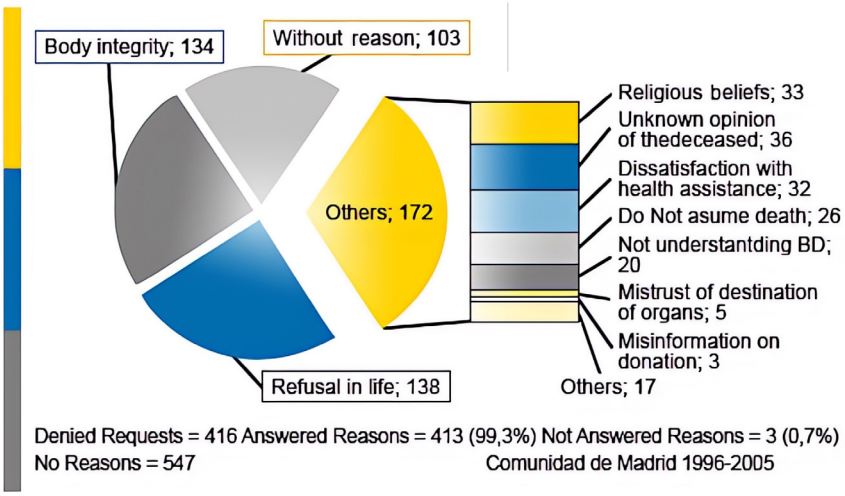


Figure 1. Why do people donate?

Families often look for a 'meaning' to their tragic loss and donation can provide comfort in their grief. However, making the decision that is right for both the donor and the family is a very important consideration. As health professionals, it is our duty to never harm a family by discussing donation with them. If we have provided appropriate information respectfully and at the right time, then sometimes, a NO is the right decision for the family.

For those families who agree to donation, there is strong evidence to suggest that they are comfortable with their decision [13].

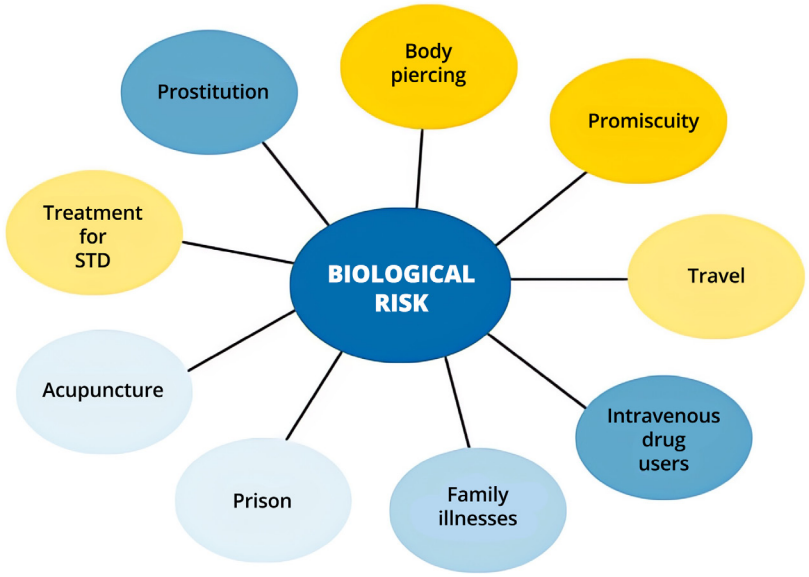


Figure 2. Level of comfort with the decision to donate.

1.4 Key steps to the family interview

1.4.1 Preparation and planning

Before meeting the family to discuss donation, the planning meeting between the treating team and the transplant coordinator should cover the following key points:

- Advice from the treating team: discussion with treating doctor, bedside nurse, and social worker to compile as much information as possible about the potential donor and the family.
- Clinical picture of the potential donor: review of the medical chart, reason for admission, pathology, current status and any known risk behaviours.
- Outcomes of previous family meetings: any perceived barriers to the conversation, for example, a different language, known religious/cultural beliefs, or any family dynamics such as family disagreements.
- Family dynamics and background: discussion with the treating doctor, bedside nurse, and social worker to compile as much information as possible about the potential donor and the family.
- Register status: if there is a local or national donor register, is the patient a registered donor?
- Identification of roles and introductions: discussion with the treating doctor about how you will be introduced to the family and how you will open the discussion.

1.4.2 The environment for the family interview

Ensure that:

- you have a quiet, private, room;

» you have enough chairs for all members of the family and yourself;

» you will not be interrupted by staff, your mobile phone, etc.;

» you have tissues and water available for the family;

» you are seated in a way that cannot be perceived as confrontational by the family, for example, not directly in front of them but to one side;

» you do not block the doorway in case a family member needs to leave abruptly.

1.4.3 Structuring the interview

The interview should be structured in such a way that it flows naturally for the family and the transplant coordinator. When meeting the family, it is important to develop a relationship of trust.

The request process should comprise the following considerations in a sequential manner:

» Determine the family's understanding of brain death (or planned withdrawal of life sustaining therapies).

» Explain your role of providing information and support.

» Discuss the opportunity for donation with positive information about the benefits of organ and tissue donation - how it can help others.

» Consider the deceased person's wishes during their lifetime.

» Provide small amounts of information in plain language.

» Allow the opportunity and time for questions, family reactions and emotions.

» Acknowledge any concerns and address them.

» Provide adequate information about the donation process according to the family's needs.

» Inform about the timeframes involved in the process so the family can plan accordingly.

» Enquire about potential biological risk.

» Summarize the interview and communicate the next steps.

» Support the family and their decision.

» Thank them.

KEY CONCEPT

The quality of care and how you communicate with families can have an impact on their decisions and how they remember their donation experience. For bereaved families, often it is not what you say but how you say it that will have most impact on them [5].

1.5 Understanding why families refuse donation and considerations when dealing a refusal

The most frequent cause of loss of organs and tissues for transplantation is the refusal of relatives. Increasing of the number of organs available for transplant depends in part on the ability to reduce the number of refusals.

During the interview, relatives may give us many reasons against donation. We must always be prepared to understand these reasons and to accept that the relatives -or even the potential organ donor themselves- can and may refuse donation. On occasions, however, the refusal may be due to a lack of understanding, misconceptions or a fear of making decisions. It is precisely in these circumstances that we can provide better help to the relatives.

We must also consider and prepare for the condition of the families at the time of the donation request. Among others, such conditions include the family's stamina, their ability to deal with complex information, the timing of the request or prolonging the dying process, all of which are factors that affect consent rates [14].

Training interviewers in strategies that might change the attitude of relatives who refuse consent for donation, and supporting the relatives in their grieving process as smoothly as possible are elements that help people to adapt to the idea of donation. The way we can achieve this is by:

» supporting the family to make decisions;

» timing - separating discussions about death and donation;

» providing positive information about donation in a way that the family can understand;

» fulfilling the last wishes of the deceased person.

1.6 Common reasons why families refuse donation

The magnitude of the problem of refusal has led to numerous studies, conducted in an attempt to ascertain what common factors determine refusals and the reasons behind them [6,7].

Some reasons include:

» not understanding brain death;

» fear of disfigurement and loss of integrity of the body;

» not knowing the deceased person's beliefs about donation;

» presumed refusal in life;

» dissatisfaction with the health care system;

» family refusal without reason;

» religious objections;

» assertive refusal.

KEY IDEA

During the interview, relatives may give us many reasons against donation. We must always be prepared to understand these reasons and accept that relatives, or even the potential organ donor, can and may refuse donation. However, on occasions, a refusal may be due to a lack of understanding, misconception or fear of making decisions. It is precisely in these situations that we can provide better help to relatives.

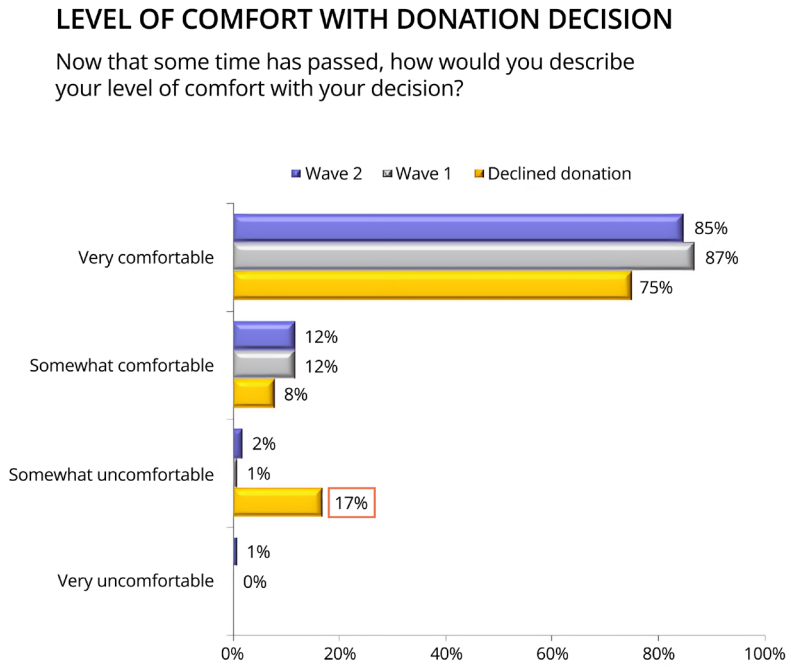


Figure 3. Reasons for refusal.

Base: Total sample, less non-response
Consented to donation: Wave 2 (n=317); Wave 1 (n=185)
Declined donation: Wave 2 (n=12)

1.6.1 Not understanding brain death

As previously mentioned, it is fundamental that relatives understand the concept of brain death before a request for donation is made. It is recommendable to ask questions that ascertain exactly what they have seen or heard that makes them think their relative is still alive and address that issue.

- » Use metaphors to explain the concept of brain death.
- » Explain the difference between brain death and coma, using clear, simple language without medical terms.
- » Offer the possibility of reviewing the brain death test or the patient's scans (this should be done together with the treating doctor).
- » Give the family some time to adjust to the information and understand that death has occurred before moving on to discussing donation.

Table 2. Language

The language of organ donation	
» Refer to the patient by name	» NOT *"body"* or *"cadaver"*
» Organ removal or organ retrieval	» NOT *"harvest"*
» Mechanical ventilation	» NOT *"life support"*
Family-focussed language	» Discussing organ donation » The opportunity for donation » Family agreement to donation

1.6.2 Fear of disfigurement and loss of integrity of the body

Fear of body disfigurement is a common reason for refusal which can be addressed.

A family might express their concerns by suggesting that the patient should not *"have anything more done"* to them or that the family believes that the patient has *"already been through too much"*. They may even simply tell you that they are concerned about disfigurement and want to maintain their image of their loved one the way he or she is now.

We recommend:

- taking time to inform the family that you can guarantee the external appearance will remain unchanged after the retrieval process and that it is our responsibility to restore their loved-one's appearance;
- comparing the retrieval process to a surgical procedure;
- allowing the family to provide familiar clothing.

Sometimes the family may have fears relating to the social image of the deceased person, expressing ideas such as, *"We don't want the neighbours to find out about it"*. In such cases, we should give advice such as:

- there will be no external signs or scars;
- we can guarantee that the privacy of the decision will be respected and confirm that their donation decision will remain confidential.

Finally, the family may express a fear that the deceased person may feel pain. In these circumstances, we should normalise their concerns, suggesting that this is a common consideration for families, but assure them that the deceased person will not feel pain because they have already died.

KEY IDEA

Avoid mentioning specific organs and tissues in order to avoid the idea of an *"experience of dismemberment"*, which might be very upsetting for the family.

1.6.3 Not knowing what the deceased believed about donation

Sometimes refusal is not definite, but the family do not know what their relative's wishes were as they had never discussed it. This is a common response from families.

Firstly, we can normalise their responses by explaining that not everyone has discussed their views with their families, but we would like to rely on the family to make this decision because they knew the person in life. We should support the family to interpret the deceased person's opinions according to the values they expressed in life. We can provide arguments of generosity and reciprocity.

However, the relatives may be afraid to make decisions. Our support should be directed at reminding them that not deciding is the equivalent to saying, *"No"* to donation.

Consider that not knowing the deceased person's wishes might mean that they would have wanted to donate.

By default, people choose to help others and show a positive attitude towards donation. It is important for them to be sure that in the future they will not regret the decision they make today.

We suggest the following:

> *"If [patient's name] did not make [his/her] wishes known to you, it is your decision as [his/her] family to decide whether this is something [he/she] would have wanted – to help others after death".*

DID YOU KNOW ...?

Studies report that the sex of the deceased person, the cause of death, knowing the transplant recipients, or the number of people present at the interview are not factors that affected refusal.

1.6.4 Presumed refusal in life and refusal without reason

Presumed refusal in life

Although we must accept the deceased person's right to refuse donation, we also have to be sure that this belief was reasonable and reliable. We should ask about the circumstances under which this decision was made (e.g., after seeing something negative on television or in the media) and find out what the deceased person actually expressed in life. Ask the family to tell you about any conversations they had on the subject and how the potential donor felt at the time. Most people learn about donation and transplantation from the media and information obtained this way may often be very misleading.

Family refusal without reason

This is a very difficult situation to combat, however, we should try to discover who is supportive of donation and encourage them in a positive way by repeating or reinforcing any positive statements they make.

In the case of families who are against donation, we should address their concerns and support the inclusion of their concerns in the natural flow of conversation. An open discussion exploring such concerns may help with any misconceptions about donation.

It is important to tell the family that whatever their decision, it will be respected.

KEY IDEA

'Universalising' or 'normalising' the family's statements can make them feel that they are not alone in how they feel.

1.6.5 Dissatisfaction with the health care

When the refusal stems from the idea that something went wrong with the medical care or the progression of the disease, we recommend first acknowledging the family's complaints and avoiding attempts at justification of what happened. We should try to separate the concept of donation from the context of their complaint.

It is important to differentiate donation from the perceived treatment, and to distinguish our work from the origin of the complaint. We recommend acknowledging possible failures of the health system, avoiding attempts to justify what happened, and not defending actions or professionals that we do not know.

We must support the family and help them understand that organ donation would not interfere with any claim or later action if they make a legal complaint.

Sometimes refusal stems from perceived dissatisfaction with the care given to the family themselves while their relative was in hospital. It is important to gain an understanding from the family about the context in which they felt they were not treated appropriately. This aspect is usually beyond the control of the transplant coordinator. However, we should thank the family for sharing their feelings and opinions with us and assure them that we will transfer their concerns to the staff. This information should then be communicated to the staff in the ICU so that they can improve their practices in the future.

1.6.6 Religious objections

Refusal based on religious objections may sometimes simply be a misunderstanding. However, the family's concerns must be acknowledged, and we must reassure them we understand the importance of their beliefs to them.

Regarding religious objections, it is necessary ascertain that relatives know the real attitude of their religion towards donation as most western religions favour organ donation. We can provide supporting documents and contact religious leaders or find spiritual advisors on their behalf.

It is advisable to know how to contact religious leaders of the most common religions and denominations in your city. For less common religions, we can refer to the published guidelines that explain their views about donation.

We must accept the legitimacy of the family's views and offer the opportunity to consult their own religious leader or representative, whatever the religion may be.

DID YOU KNOW ...?

Most religions support organ and tissue donation.

1.6.7 Assertive refusal

This type of refusal is complicated, and it is often difficult to give information about donation to the family in this situation. These refusals usually come from family members with a high socio-economic level and the refusal is expressed with self-control and politeness. Try talking to the family, employ arguments that stress social solidarity and ask them if they know anyone on a transplant waiting list. Contextualise donation within the concepts of generosity and reciprocity. Offer the family the opportunity to ask questions.

However, remember that we must always remain non-judgemental, empathise and preserve our supportive relationship with the family. Always let the family know that their decision will be respected, whatever they decide.

1.7 Preparing the environment for the family interview

We must always remember that an ICU is very foreign environment for the family.

You will need to:

- identify a place that conveys warmth, comfort and privacy with adequate supplies for the family, such as water, tissues and a telephone;
- the interview room should be free of unnecessary furniture or medical equipment;
- ensure that you will not be interrupted – if necessary, place a sign on the door to deter any accidental visitors;

» identify how many family members will be present for the interview and have enough chairs;

» avoid non-immediate family members, unless the family requests them for support;

» consider who you will ask to be in the room with you for the interview, for instance, the social worker or bedside nurse, as it may be reassuring for the family to have someone that they already know;

» schedule adequate time for the interview - it is impossible to determine how long you will need to spend with the family, so it is important that you allow enough time. The family should feel that your only purpose at this time is to care for them and consider their needs.

DID YOU KNOW...?

Studies in the USA show that a private location for the discussion about organ donation improves consent rates [3].

1.7 Preparing yourself for the family interview

The family interview should be an event planned between the health care professionals and the transplant coordinator. The transplant coordinator needs to address several points that require preparation before meeting with the family.

Become familiar with the patient's medical and social history because all the details provided can help to obtain a better picture of the situation.

Information that can be provided by the healthcare team responsible for treatment includes:

» the reason for ICU admission and the sequence of events of the care;

» any medical or surgical procedures or known risk behaviours;

» how death was diagnosed and the family's understanding and response to the news about the death (or impending withdrawal of cardiorespiratory support in the case of a donation after circulatory death);

» the family dynamics and possible issues between family members (from the social worker or bedside nurse);

» any cultural, religious or language barriers that may exist.

KEY IDEA

If you have a local organ donation register or driver license database, it needs to be accessed and checked for either a written objection or consent before meeting with the family.

1.8 Introducing yourself to the family

The family has a first impression of the TC at the first family meeting. Aspects of an appropriate introduction to the family may include:

- a warm, respectful greeting and offer of condolences - refer to the deceased person and family members by name;
- physical contact by way of handshake (be mindful of cultural differences)
- acknowledgement of their loss;
- positioning yourself close to the family to indicate interest and the ability to provide visual contact to indicate your attentiveness (again be mindful of cultural differences);
- a delicate smile can show empathy;
- refer to the deceased person by name - this can personalise the relationship;
- invite the relatives to make themselves comfortable;
- take into account the family's needs and logistics (e.g., check that everyone is present by asking, *"Are we expecting anyone else today?"*);
- clarify your function and role: make it clear to the family who you are, and that your role is to facilitate their understanding of the information they have received so far and provide them with information about end-of-life care decisions.

KEY IDEA

Organize your thoughts and how you will deliver the information before you meet the family. This will help build your confidence and ability to speak to the family with ease.

Summary

The request for donation should always be a planned event that involves the skills necessary to adequately prepare the family interview.

The main points to consider when planning the family interview are:

- preparation, ensuring we have as much information as possible regarding the deceased person and their family;
- preparation of the environment for privacy and comfort;
- professional introduction to the family and definition of our role;
- separating the conversation about brain death from the request for donation
- identifying the deceased person's wishes;
- sound knowledge of the reasons for requesting donation;
- providing information and support to the family;
- summarising the interview with the family and making a plan.

DID YOU KNOW ...?

Although the law in Spain is a model of presumed consent, the Spanish transplant model favours consultation with the family, considering that to proceed in any other way could provoke reactions of rejection which would have negative repercussions on the smooth working of the transplant system [6,7].

Summary

Understanding why families refuse donation is an important part of the TC's profile and training. Being confident, compassionate and knowledgeable about donation will help us develop arguments to support the family's decision-making and support them to take a decision which upholds the deceased person's wishes. With good communication skills and knowledge of how to engage the family and identify their concerns, we have a greater opportunity of the family agreeing to donation.

The easiest decisions to reverse are those where the wishes of the deceased person were unknown, where there is a lack of understanding of brain death, or there are concerns about disfigurement of the body.

On the other hand, we must also have the necessary resources to be able to confront problems that may arise as a matter of course, such as responding to suspicions about possible financial or commercial motives for requesting the organs, making a donation conditional on there being a specific recipient for the transplant, or asking for direct information about the transplant recipients, etc.

As long as donation is an option, society must be well informed, with the creation of social necessity and awareness of donation that are maintained by means of conscious strategies.

KEY IDEA

- Donation is a therapeutic option for relatives
- It is a duty for health care workers
- Pain comes from death, not donation

2. SECTION 2: ASSESSING POSSIBLE BIOLOGICAL RISKS FOR TRANSPLANTATION BASED ON INTERVIEWING RELATIVES

2.1 Introduction

Although it is impossible to completely remove the risk of disease transmission through solid organ transplantation, there are a number of ways the transplant coordinator can reduce that risk. These include:

- physical examination of the donor to identify any previous or current clinical signs of surgery, or high-risk behaviours (needle track marks/tattoos);
- laboratory screening of the donor. Currently, legal recommendations for serological screening in the guidelines for organ and tissue donation allow us to rule out the presence of known transmissible diseases and enhance the quality of donor organs;

» medical and social history of the donor (behavioural risk) provided by the family or a significant other person, who may have a more comprehensive knowledge of the deceased person. In addition to the request for organ and tissue donation, the interview with the relatives is a way of obtaining useful information to help predict the presence of biological risk factors, possibly related to the presence of infectious agents, that could compromise the transplant recipient's life.

This section discusses how to address the interview with the family to assess biological risk.

2.2 Advising the family about biological assessment

Conducting a proper clinical and epidemiological history is an important method for ruling out donors who are carriers of infectious processes that might be in the window period (HIV, HBV, HCV). It can also be used to rule out the existence of any diseases transmissible through prions (Creutzfeldt-Jakob disease). A recent travel history should also be sought to identify risk of any transmissible diseases that are endemic in certain countries.

After the family have agreed to donation, the transplant coordinator must sensitively advise the family that they will also need to answer some questions related to the medical and social history of their deceased relative. The TC should tell the family that this could take around 30 minutes. In some situations, depending on the fragility and condition of the family, you may need to offer them a break to attend to personal needs before providing this information.

EXAMPLE

A statement such to the following may help the family understand why these questions are necessary.

> *"Some people should not donate organs and tissues because of the possibility of transmitting a disease, like cancer or HIV, to others through transplantation. We need to evaluate the risk of disease transmission so we can provide safe organs and tissues for transplant. We do this by testing [name of the donor]'s blood and also by asking you some questions about [his/her] past medical and lifestyle history.*
>
> *Some of the questions are sensitive and personal in nature and are similar to the questions that are asked at a blood bank if you want to donate blood.*
>
> *Please answer the questions as honestly as you can."*

2.3 Before and during the interview

Before the interview

1. Try to get as much information as possible from all available sources.
2. Review the hospital medical chart thoroughly.
3. Search for previous laboratory tests.
4. If possible, contact general practitioners or clinics.
5. Talk to the ICU medical and nursing team, in addition to the social worker (if they have contact with the family.

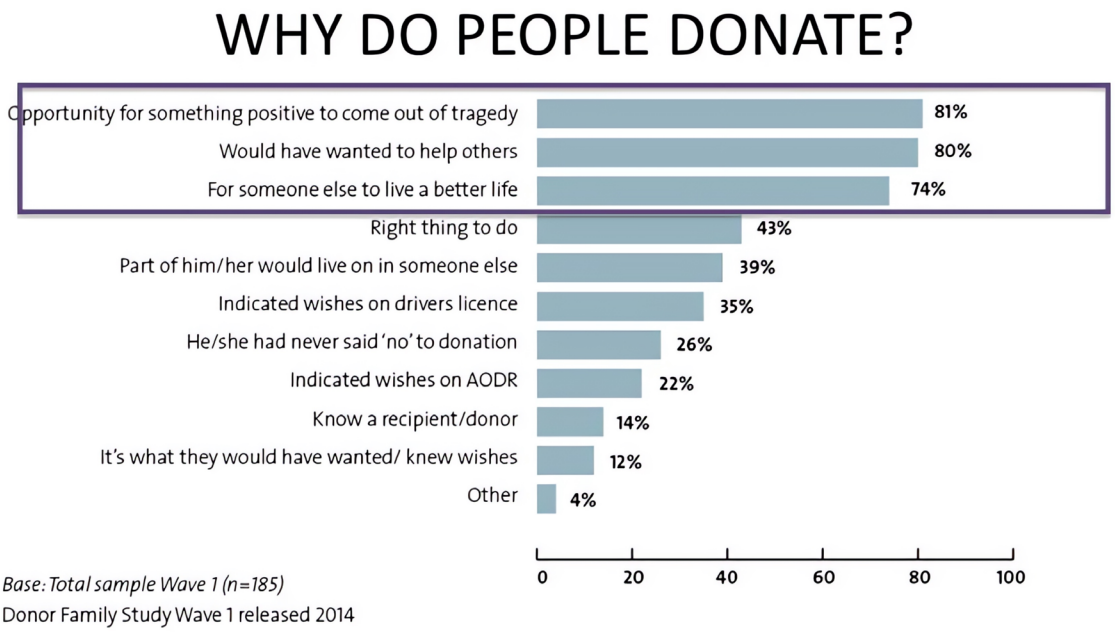
During the interview

6. Choose someone close to the donor, who knew the donor's lifestyle the best - try to obtain the information from this person.
7. Explain the reason why you need the information. It is a matter of safety and quality. Explain that this is a routine procedure.
8. Start with less awkward or more comfortable questions.
9. Continue with the protocol and explain the more sensitive questions. Do not forget that these questions touch on the most private life of the deceased person, that you are talking to people who were very close to the donor, and that they are in the grieving process.
10. Be sensitive - postpone the interview if you feel the participants are very uncomfortable; take your time.
11. Offer the participants further information if any unexpected results are found.
12. Thank them for their cooperation.

2.4 International standards of assessing biological risk

International standards suggest that in order to evaluate and determine the suitability to donate organs and tissues, the family should be asked about certain details of a donor's medical history and behavioural risk [8,11]:

- medical history
- previous infections
- vaccinations
- occupational risks
- exposure (travel history)
- transfusions with blood or blood products
- contacts with persons with an HIV, HBV, or HCV infection or other transmissible diseases
- tattooing, ear piercing, or body piercing
- use of illicit drugs, sexual behaviour, incarceration
- contact with bats, stray dogs, or rodents (including pets)



Source: National Study of Family Experience of Organ and Tissue Donation Wave 1 – 2010 and 2011 (September 2014)
Prepared by Proof Research Pty Ltd for the Organ and Tissue Authority

Figure 4. Biological risks.

2.5 Serological testing

Donor-derived infectious diseases transmitted through organ transplantation may include viruses (e.g., CMV, EBV, HIV, hepatitis B, hepatitis C), bacteria, fungi and other transmittable agents. It is possible to screen for a limited number of organisms and, while some infections can be treated in the donor and/or recipient, transmitted infections – particularly when unexpected – can result in significant recipient morbidity and mortality [15].

Enhanced testing, such as nucleic acid testing (NAT) can reduce the window period for some blood-borne viruses.

Table 3. Length of window period for selected blood-borne viruses under different testing methods

Pathogen	Standard serology	Enhanced serology (4th generation of combined antibody-antigen tests)	Nucleic acid testing
» HIV	» 17-22 days	» **~7-16 days**	» **5-6 days**
» HCV	» ~70 days	» **~40-50 days**	» **3-5 days**
» HBV	» 35-44 days	» **Not applicable**	» **20-22 days**

Based on Gen Probe TMA for HIV and HCV, and Roche Gobas MPX for HBV

(Extracted from The Transplantation Society of Australia and New Zealand – Infectious Disease Transmission in Solid Organ Transplantation: Donor Evaluation, Recipient Risk & Outcomes of Transmission. S.L. White 2018) [16]

The different techniques used to detect the markers of infection have high sensitivity, and specificity, as well as positive and negative predictive values. However, in certain circumstances, the possibility exists of finding ourselves faced with false negatives, whether due to a recent infection (we are in the window period) or because the serological determination was carried out on diluted blood samples.

In a deceased donor (non-heart beating) – tissue donor

The products of tissue degradation, secondary to haemolysis, which occur after death, can interfere with the serological screening values and be the cause of false positives. In order to avoid invalidating the donation it is recommended that blood samples are obtained as soon as possible after death.

In a brain dead / circulatory death donor (heart beating donor) – organ donor

Conversely, for the potential donor who is on mechanical ventilator support, blood transfusion, infusion of colloids or crystalloids can be routine elements of care and treatment. As a consequence, haemodilution may occur and the serological screening could result in false negatives (by reducing the titration of markers below the sensitivity of the techniques). In cases where haemodilution is suspected recognised methods such as plasma dilution-infusion/transfusion calculation, must be used to determine whether the haemodilution has been sufficient to dilute the sample. If a sample is diluted, it is recommended that testing be carried out on samples taken before the infusions or transfusions.

In living organ donors

A serological screen must first be carried out three months before donation, and again immediately prior to donation. At the same time, it would also be advisable to conduct a health education programme with the potential donor in order to avoid activities which carry biological risk of infection by HIV, HBV and HCV.

2.6 Serology testing

Common screening tests for organ donors include:

- HIV antibody
- HBV serology, including HBsAg, HBV core antibody and surface antibody, and hepatitis delta virus antigen and/or antibody in HBsAg-positive donors
- HCV antibody
- Nontreponemal and treponemal testing (RPR + TPHA or TPPA or FTA antibodies)
- HTLV-I/II antibody (currently less common given assay performance)
- *Toxoplasma* antibody (notably for heart donors)
- Cytomegalovirus antibody
- EBV antibody panel (EBV capsid antigen, with or without early antigen and nuclear antigen antibody levels)
- Herpes simplex virus antibody
- Varicella zoster virus antibody
- Blood and urine cultures [14]

Despite the rigorous testing available to us, not all transmissible diseases can be identified before donation.

DID YOU KNOW...?

Did you know that many organ donation organisations may supplement these tests with additional assays based on their local epidemiology and/or use of nucleic acid- based assays? [14]

2.7 Summary

In addition to initiating the request for donation process, the interview with relatives is also the time to conduct a reassessment of the existing medical history. From the next of kin or the person who knew the donor best, we can investigate the presence or absence of determining factors and assess the possibility of the potential donor being a carrier of an infection which might contraindicate organ or tissue donation.

We assess the existence of activities which carry biological risk (acupuncture, body- piercings, tattoos, injection of illicit drugs), as well as ascertaining where and under what conditions such practices were carried out.

We ask about the existence of sexually promiscuous activities or prostitution, as well as recent time spent in prison. It is important to ascertain any specific treatment received recently for sexually transmitted diseases (syphilis, gonorrhoea), or recent travel to countries where infections that are contraindicated for donation (e.g., Chagas disease) are endemic, as well as the existence of any family illnesses with a high risk of prion transmission.

For this reason, we ask families or significant others to state in writing that, "to the best of their knowledge", the potential donor has not been in any of the situations mentioned in the medical and social history questions.

CONCLUSIONS

This unit highlights the professional expertise required by the transplant coordinator to effectively approach the family, request organ donation and understand the challenges a TC may face in developing a relationship of trust and empathy that will provide the information necessary for the family to agree to donation. We have discussed how to prepare for the interview, ready the environment, and consider when the best time to approach the family is.

We must also be knowledgeable about why families may refuse donation and be comfortable with the use of strategies which may be beneficial to encourage the family to consider another viewpoint without coercion.

The transplant coordinator has the professional duty to care for the donor, their family and the potential recipients of the donation; therefore, it is imperative that they should be trained and skilled in identifying any biological risks which could potentially harm the recipients.

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TOPIC 6 - Unit 1

Organ recovery and preservation

ORGAN DONATION

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The aim of this topic is to learn how the transplant procurement manager (TPM) needs to plan and organize the recovery of organs and tissue, have good knowledge of procedures and bench surgery, finish the recovery and ensure storage and transport. This topic will also further explain different mechanisms to preserve organs, along with the solutions and devices that may improve preservation and outcomes.

Organ allocation is conducted following policies that define allocation priorities. Whether the allocation scheme is centre-based or patient-based, the major focus is on saving lives and obtaining the best long-term post-transplantation outcome for the recipient, along with a continuous optimization of the system. The process of organ allocation must be fair, transparent and ensure that organs are allocated efficiently, with equitable access to transplantation.

INTRODUCTION

The process of donation and transplantation involves different important phases, one of which is organ recovery and preservation.

This unit consists of four different sections.

The first, organization of multiorgan recovery, deals with the logistic organization of a multiorgan recovery that involves several surgical teams, usually from different centres. To perform their function well a TPM needs to plan and organize the recovery of organs and tissue, have good knowledge of the procedure and bench surgery, finish the recovery and ensure storage and transportation.

The second section covers technical aspects and includes useful information on the surgical teams involved, phases of recovery surgery and cannulation techniques.

The third section, preservation, includes strategies used to minimize the adverse consequences of ischaemia-reperfusion injury for solid organs as well as the characteristics and formulation of flush solutions.

Pulsatile devices for preservation, the final section, provides information about organ preservation with pulsatile perfusion devices and analyses the differences between normothermic and hypothermic circulation.

1. SECTION 1: ORGANIZATION OF MULTIORGAN RECOVERY

This section focusses on the logistic organization of a multiorgan recovery as follows: how to contact the different surgical teams, the organ sharing office (OSO), TPM tasks, consecutive phases, how to store and transport organs.

The first section consists of seven subsections:

- Introduction
- Planning before the recovery
- Organizing the recovery
- The procedure
- Bench work
- Tissue removal and finishing the recovery
- Storage and transport
- Summary

1.1. Introduction

Organ recovery is a complex process that requires a high level of communication between the donor's hospital, the recipient hospital and the organ sharing office (OSO).

The TPM is in charge of organizing and supervising the multiorgan recovery at the procurement centre, as well as for coordinating the transport of the surgical teams from other hospitals with the support of the OSO. The TPM is also responsible for the collection of donor samples and biopsies, and any records or reports completed by the surgical team. It is the TPM who has to provide transplant surgeons via OSO, with the resources and reports on organ viability.

The four basic rules that apply to all surgical teams during recovery are:

- Coordination
- Cooperation
- Collaboration
- Communication

It is the task of the transplant coordinator to achieve a good relationship between the various surgical teams so as to optimize resources, reduce procedure times as much as possible, and achieve a relaxed and dynamic working atmosphere [1,2].

KEY CONCEPT

The TPM is the professional who unites and coordinates all the teams working on organ recovery.

1.2 Planning before the recovery

Once the donation has received consent, the TPM needs to obtain legal authorization when this is required, according to the cause of death. The coordinator will inform all teams about the donor's general characteristics, hemodynamic status, the organs and tissues to be removed, etc. This information will be transmitted to the OSO (where there is one) so the office can transmit the data to the various teams, allocate the organs and coordinate transport.

Once the organs and tissues have been accepted, the TPM, OSO and transplant teams will reach a consensus on the start time of the recovery, which will be communicated to all teams and units collaborating in the recovery: the ICU, surgeons, anaesthesia and nursing staff [3].

This schedule must be set according to parameters such as the donor's clinical stability, availability of an operating room (OR) and anaesthesia, recovery teams, and the time necessary time for their transportation [4].

The TPM receives the transplant teams, both those from the same hospital and the teams who come from other centres, who must be taken to and become acquainted with the new surgical area.

The protocol for receiving the teams and an awareness of the legal issues implied by the process are vital for an efficient working process, which will be detailed below.

1.3 Organizing the recovery

Multiorgan recovery is a sterile surgical procedure performed in the OR. Upon arriving at the surgical area, the OR nursing team will prepare the following elements, supervised by the TPM:

- surgical area;
- anaesthetic and vasoactive drugs;
- donor monitoring;
- ventilator and verification of its proper functioning;
- infusion pumps;
- surgical and laparotomy instruments;
- cannulation and perfusion materials: aspiration tubes of various calibres (10F -12F) for portal perfusion and specific cannulae of various calibres for the different perfusions of each organ;
- aspiration cannulae and balloon cannulae;
- light and heavy bags for packaging the recovered organs, as well as hard plastic containers, clothes, waterproof smocks, etc.;
- boots, bags, ice cubes and cooler boxes for organ preservation and transport
- expendable surgical materials.

The recovery teams from other hospitals should come equipped with all the materials required for recovery, but the hospital supplier must be prepared to provide anything that is necessary if required. All of the related information must be checked before the team's arrival.

Inspect the OR. This should be done with several teams working simultaneously. The TPM is the crucial link who coordinates the entire process.

KEY IDEA

Working together with the nursing staff is key to a successful process. Nurses play a very important role in our teams.

1.4 The procedure

The TPM will inform the anaesthesiologist and together they will transfer the donor to the OR on mechanical ventilation.

The TPM will welcome the surgical teams upon arrival, give them a brief explanation about the donor's current status, specify the key points of interest and any changes that have occurred during donor management, as well as any other data which may influence surgery.

The coordinator will ask the recovery teams to provide samples for study: nodes, spleen for immunology, the number and type of biopsies required to complete the donor study as well as the timing of the recovery according to the type of procedure performed (see Section 2).

The TPM checks with the nursing staff to make sure the perioperative tasks are completed as follows:

- preparation of surgical tables;
- donor placement on the surgical table and initiation of monitoring;
- review and preparation of vascular routes;
- skin preparation at the incision site (shaving if necessary). The donor is covered in accordance with the organs and tissues to be removed, donor status, and organ viability, leaving only the incision site available.

DID YOU KNOW?

It is very important to administer muscular relaxant drugs to avoid muscular reflexes in the deceased donor that may occur during transfer to the OR. Such reflexes could create confusion among family members or even staff.

1.5 Bench work

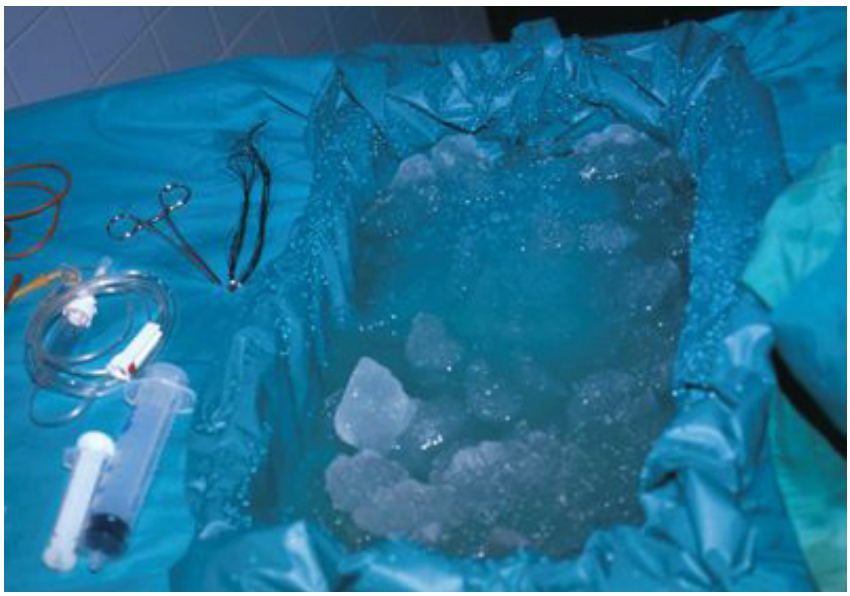
Once organs have been removed, they need to undergo a technical process called bench surgery. Each organ is completely dissected and revised, and all vessels to be anastomosed are prepared. Sometimes it is necessary to add a vascular graft, as is the case with the pancreas.

A container full of ice and cold saline solution is prepared on a sterile surgical table. After bench surgery, the organ is first packed in layers of sterile containers holding preservation solution and then placed in the cooler, which is full of a slushy icy mixture. Thus, any contact between ice and organs/tissues is avoided (Figure 1, 2, 3, 4).

Organs like the heart and lungs need a very short period of bench work. On the other hand, the liver, kidneys and pancreas require longer bench surgeries (Figure 5). The TPM must be familiar with the various lengths of times of these procedures in order to efficiently coordinate time and resources (Figure 6, 7).

In the liver, venous and arterial grafts are always performed, as there are recipients who need them.

Pancreas arterial inflow is always reconstructed with an arterial Y-shaped graft, including the common iliac artery and both internal and external iliac arteries (Figure 8, 9, 10, 11).



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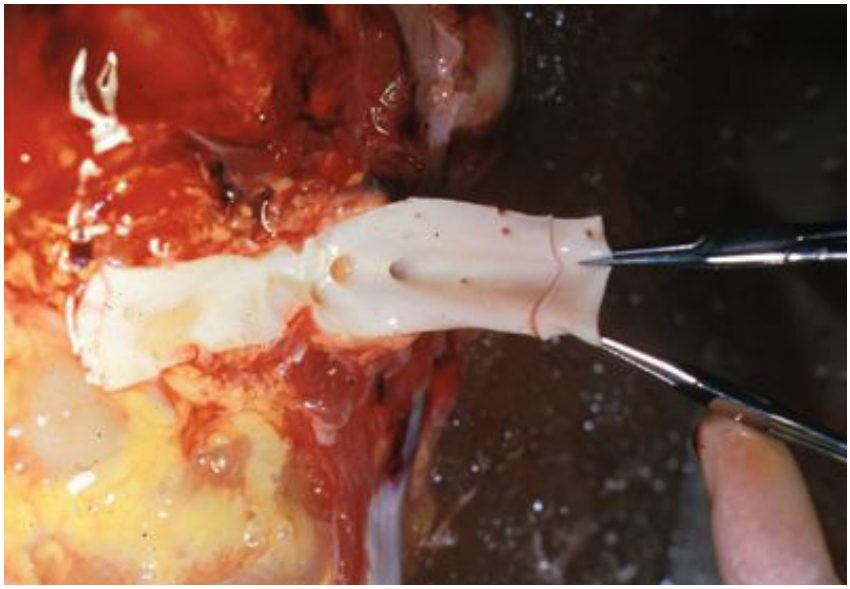

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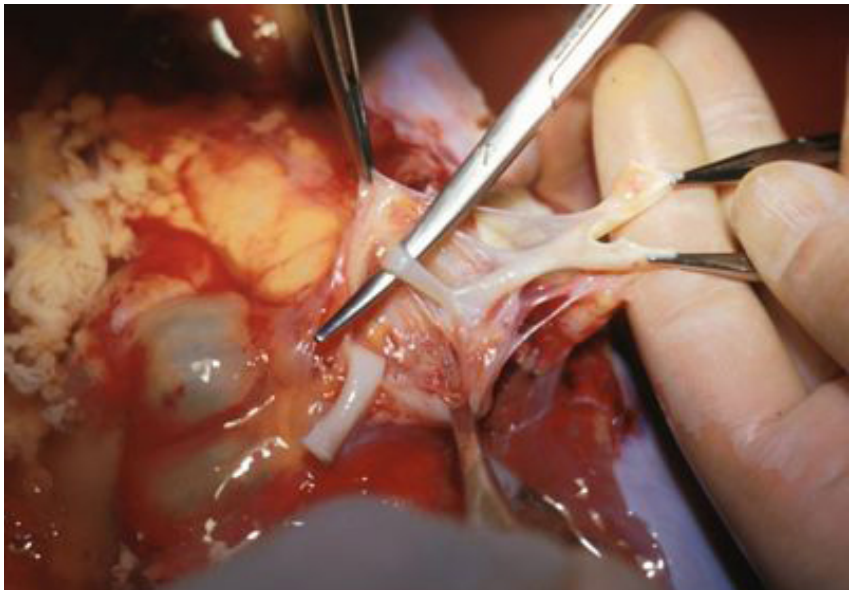

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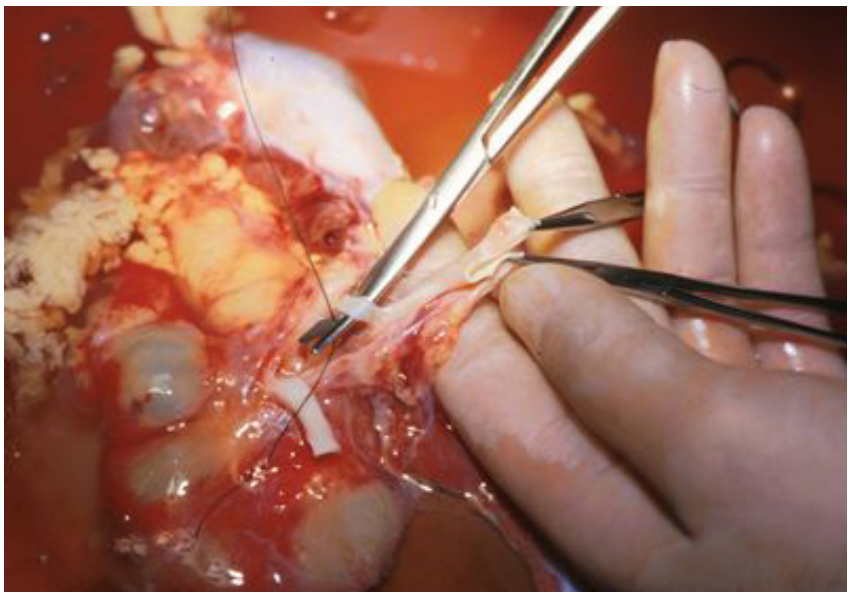

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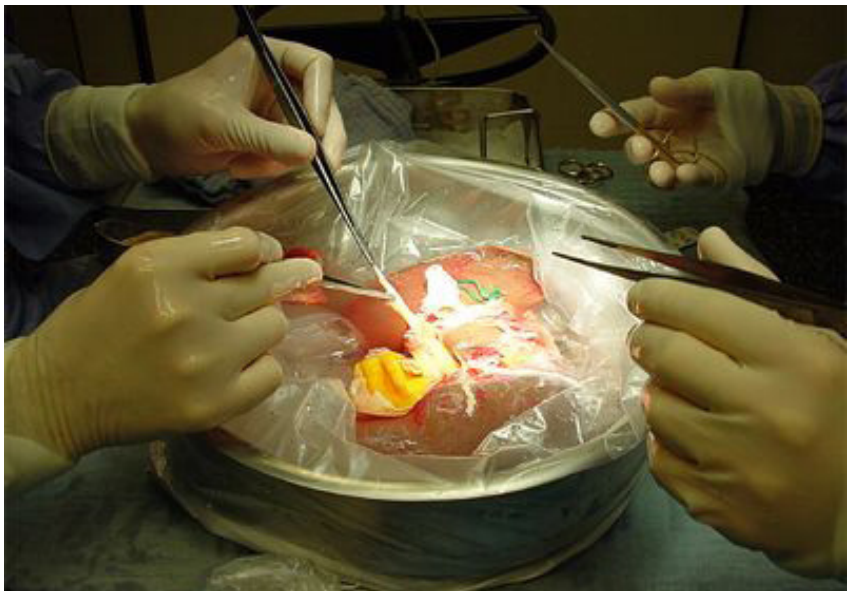

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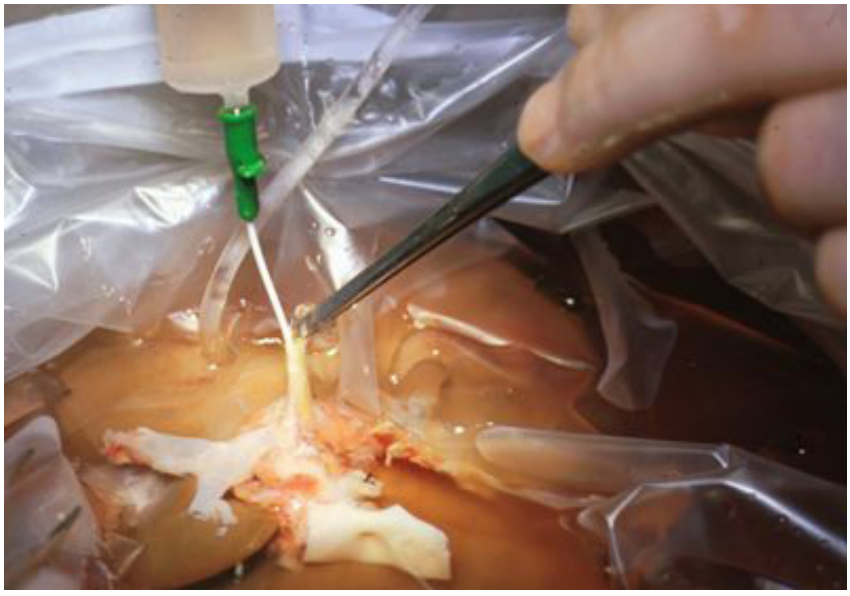

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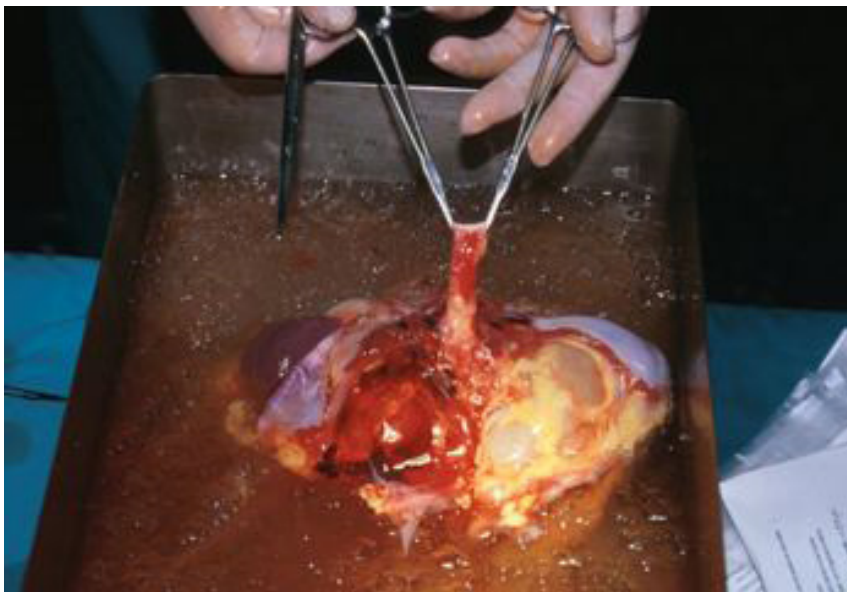

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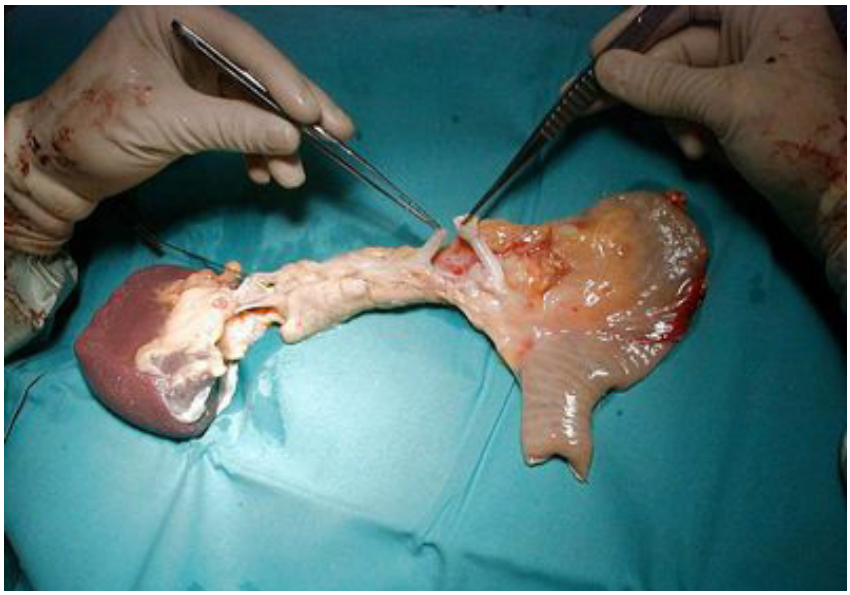

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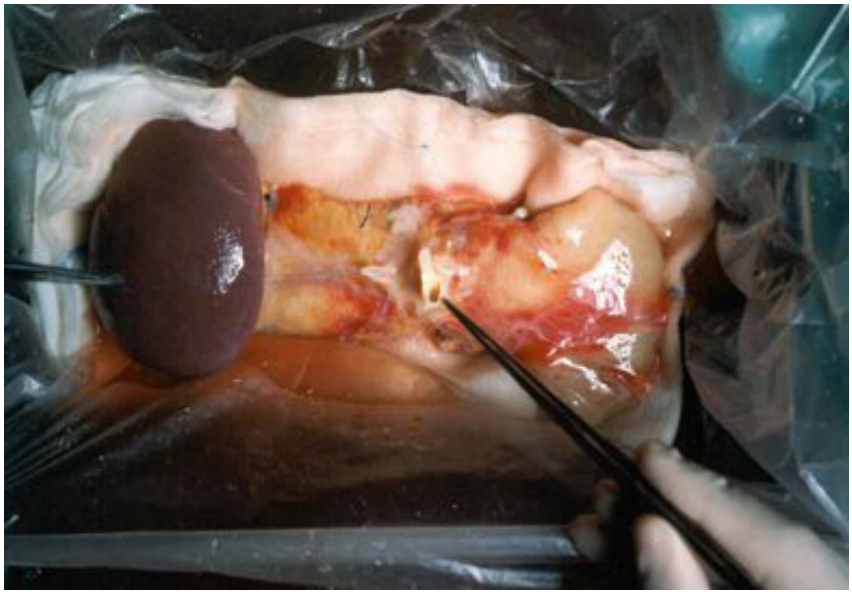

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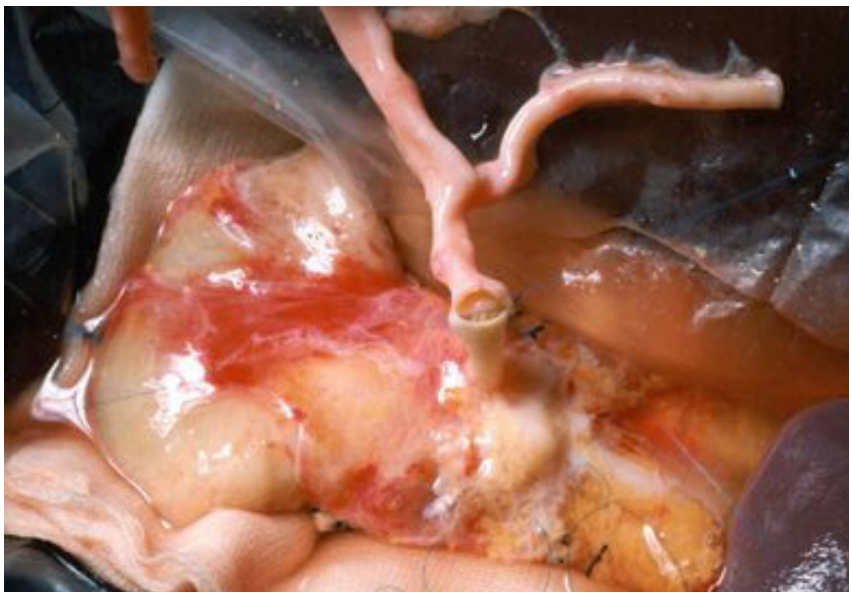

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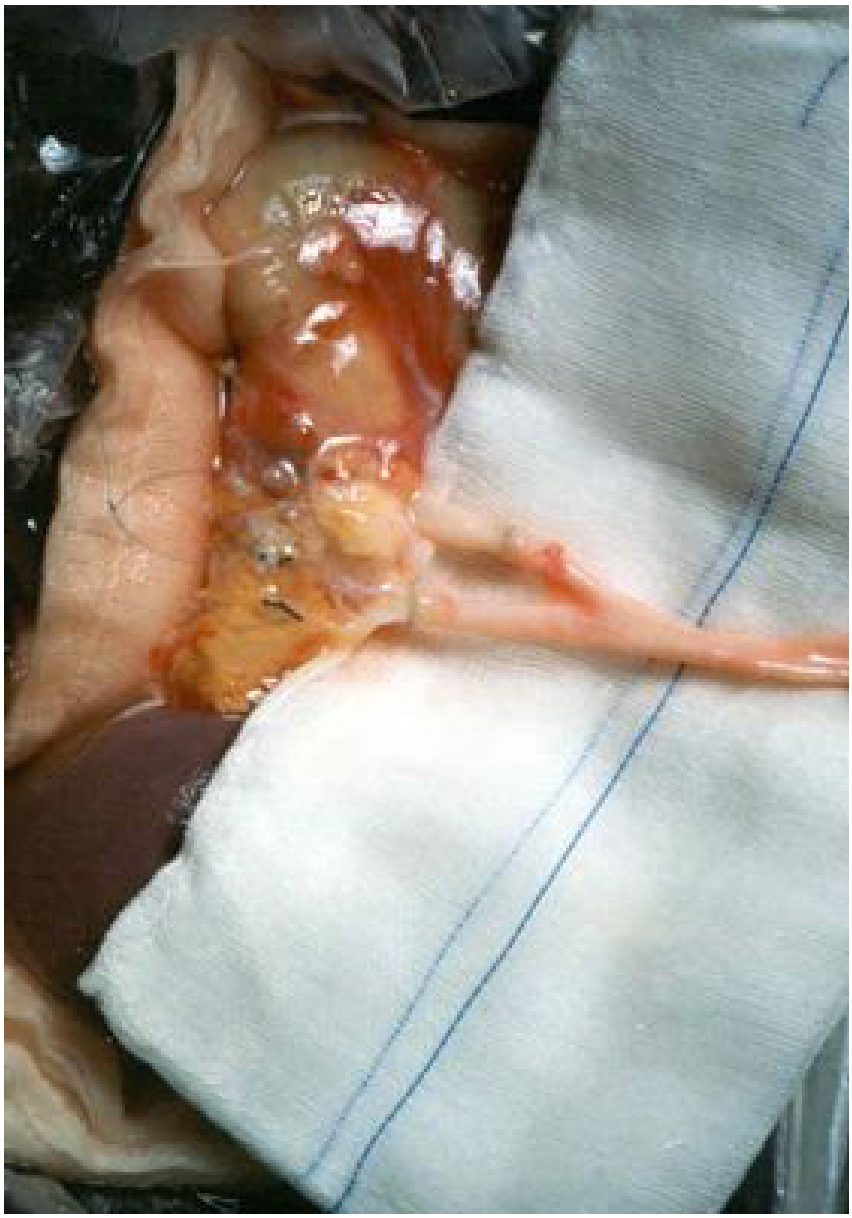


Figure 11.

1.6 Tissue removal and finishing the recovery

Once organ recovery has finished, the OR and donor are cleaned in order to continue with the procedure of tissue procurement:

- Corneas
- Vessels
- Bones
- Skin

Once all surgical incisions have been well sutured and covered with gauze dressings, the clean body is transferred to the morgue. The TPM must estimate the duration of recovery so that the family can organize the funeral.

Bearing in mind that multiorgan recovery requires the simultaneous surgical intervention of several teams, the TPM must have the required skills and abilities to efficiently and smoothly coordinate the whole process, both from a clinical and a human point of view, and to ensure that the donor is treated with respect, great care and dignity at all times.

The PM must also facilitate the return of each surgical team to their own hospital, in order to minimize cold ischaemia time.

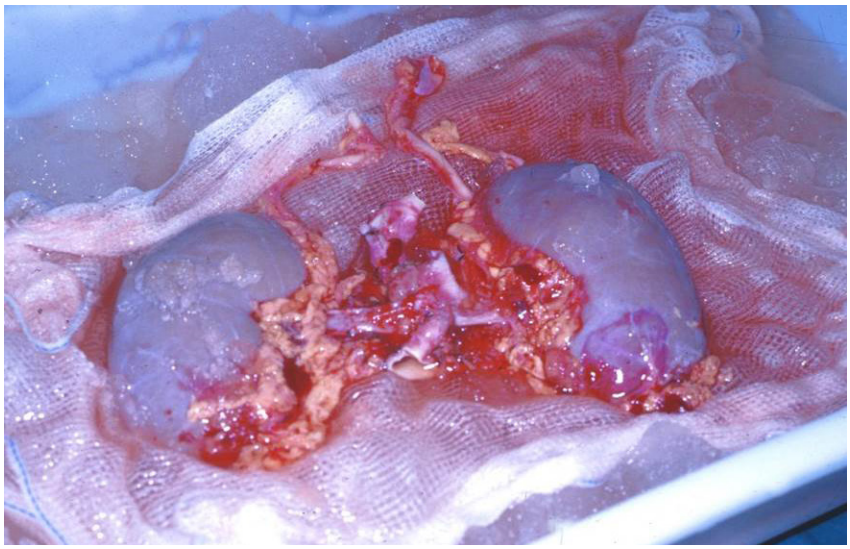
DID YOU KNOW?

For careful reconstruction of the body, various materials are used to substitute segments of large bones, like the femur (plastic tubes, etc.) and leave any visible areas unmarked so as to enable an open-coffin funeral.

1.7 Storage and transport

All organs are stored in 3 sterile containers. The organ is placed in the first self-sealing plastic bag or container with 1 litre of cold preservation liquid. When closing, the air needs to be removed from the bag. The first bag or container is placed inside two other sterile plastic bags, so that the organ has triple protection. Moreover, the third container protects the first two from possible breakage (Figure 12, 13, 14).

To prevent ice damage, further protection of the sterile bags can be assured with a soft cloth.



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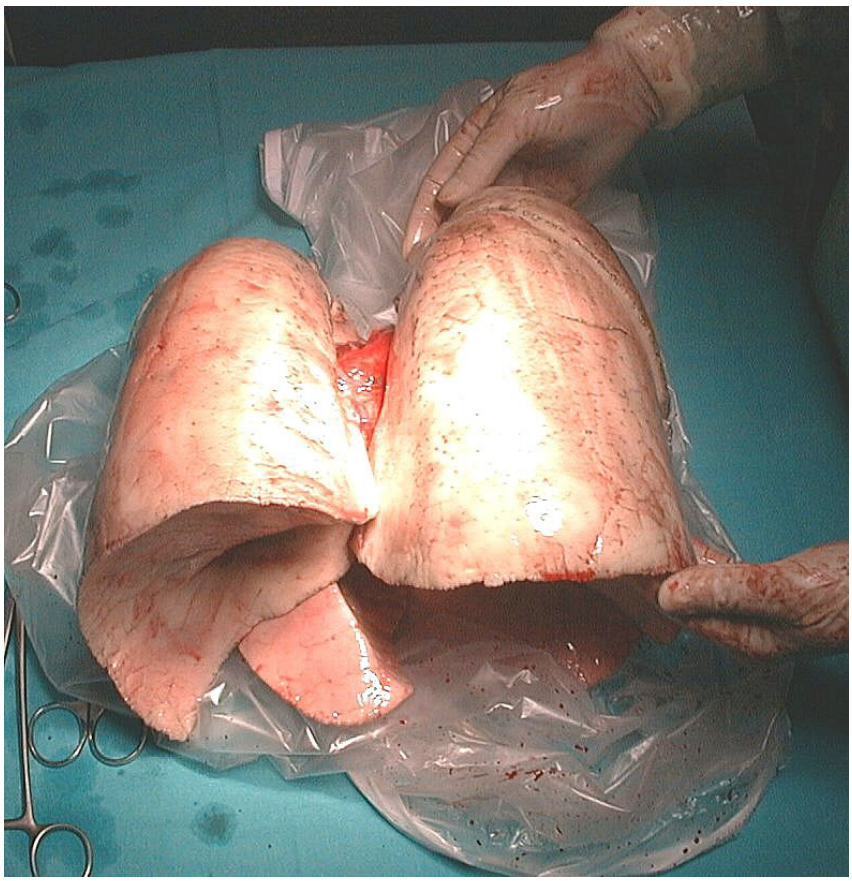


Figure 13.

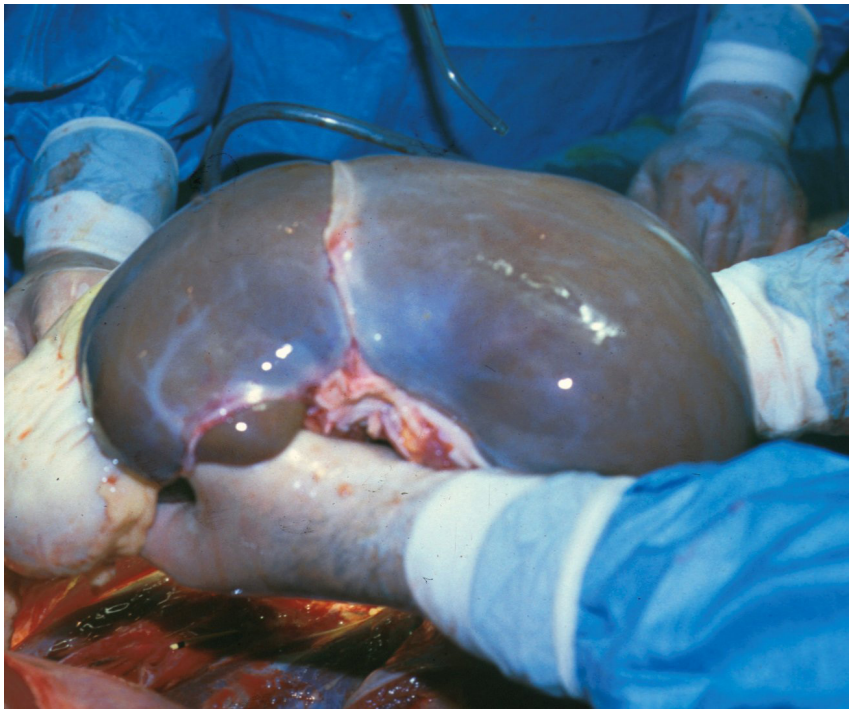


Figure 14.

DID YOU KNOW?

Sometimes organs are removed by the donor hospital team and sent to another centre. In such a case the organ travels alone. Depending on the country, different means of transport are used. In Spain, we usually take advantage of regular commercial flights.

Organs are transported in portable cooler boxes with water ice cubes to maintain the temperature at 4°C. It is not recommended to place ice inside the bags.

Confirm that the outer labelling of each cooler box is correct.

At a minimum, the label must include:

- Organ name
- Issuing hospital
- Receiving hospital
- Time of clamping
- Contact telephone
- Blood group

Ensure that all the necessary documentation is provided: the donor's clinical information and recovery report. Confirm that all the required analyses and biopsies have been processed [5-9].

Include all the necessary biological samples, adequately enclosed (nodes, spleen, biopsies).

1.8 Summary

Multiorgan recovery is a complex process which involves different surgical teams, usually from different hospitals. The TPM plays an important role during the entire process, uniting and coordinating all stakeholders [10]. The TPM is the professional who deals with the family, coordinates the medical staff involved in the organ recovery process, and ensures that the donor is treated with respect, great care and dignity at all times.

To summarize, the TPM is in charge of:

- Consent to donation
- Communication with OSO and/or surgical teams
- Organization of recovery process and transport of teams to and from their centres
- Donor transfer and OR preparation
- Recording all the necessary data and providing it to the teams
- Ensuring maximum care in body reconstruction

2. SECTION 2: TECHNICAL ASPECTS

The recovery process requires the collaboration of different surgical teams. TPMs take no active part in the surgery itself, but they must have a good knowledge of the procedure and be aware of the process at all times.

During surgery, organs are validated, and cold ischaemia time is recorded as a key element of the donation process. The TPM needs to record all the data provided by surgeons and adjust the logistics of the different groups accordingly.

Section 2 contains the following information:

- Surgical teams
- Phases of recovery surgery
- Phase 1: Inspection, dissection
- Phase 2: Cannulation
- Phase 3: Cross-clamping and perfusion
- Phase 4: Organ removal and preservation
- Two different techniques: Classic and quick cannulation technique
- Summary

2.1 Surgical teams

Several surgical teams are involved in a multiorgan recovery:

- Lung team
- Heart team
- Liver team
- Pancreas team
- Kidney team
- Tissue teams (cornea, bones, vascular segments, skin)

This requires a large number of people working in the OR. First, we will focus on solid organ recovery teams.

Three surgical teams (thoracic, cardiac and abdominal) will work simultaneously at two levels:

- Thoracic (heart and lung) (Figure 15)
- Abdominal (liver, pancreas and kidney)

At abdominal level, removal may be performed either by three different teams, each of them removing an organ (liver, pancreas and kidneys) (Figure 16), or by a single, well trained team. A single abdominal team is preferred as it facilitates the procedure, and saves a lot of effort, financial resources and time.

Thus, only three surgical procedures would be performed at the same time, two at thoracic level and one at abdominal level. In habitual practice, everybody begins at the same time, although sometimes one team may start first, making the incisions and dissection.

KEY IDEA

The abdominal team should be trained in en bloc recovery (liver, pancreas, and kidneys), in order to save effort and costs.

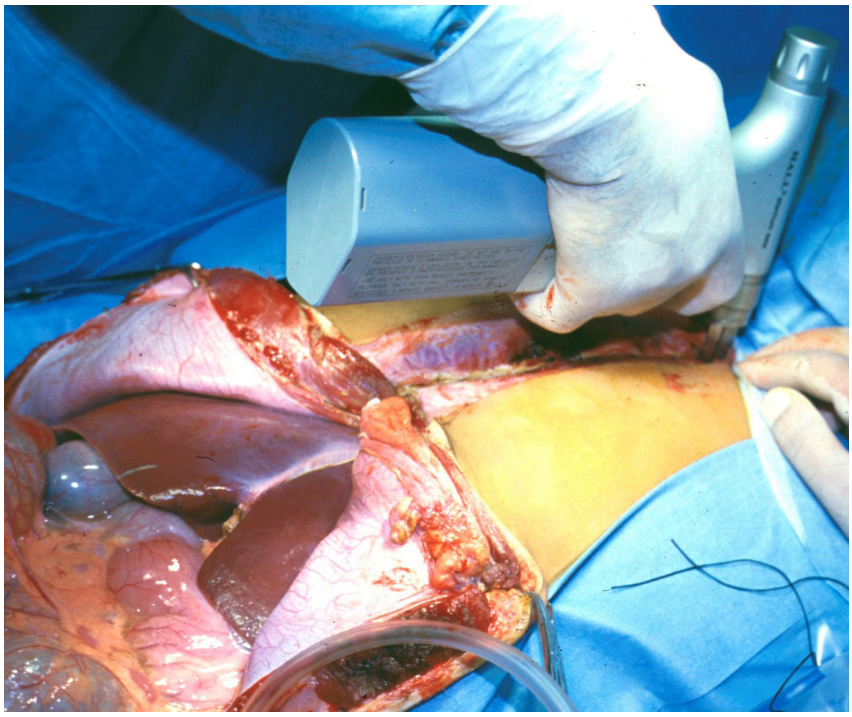


Figure 15.

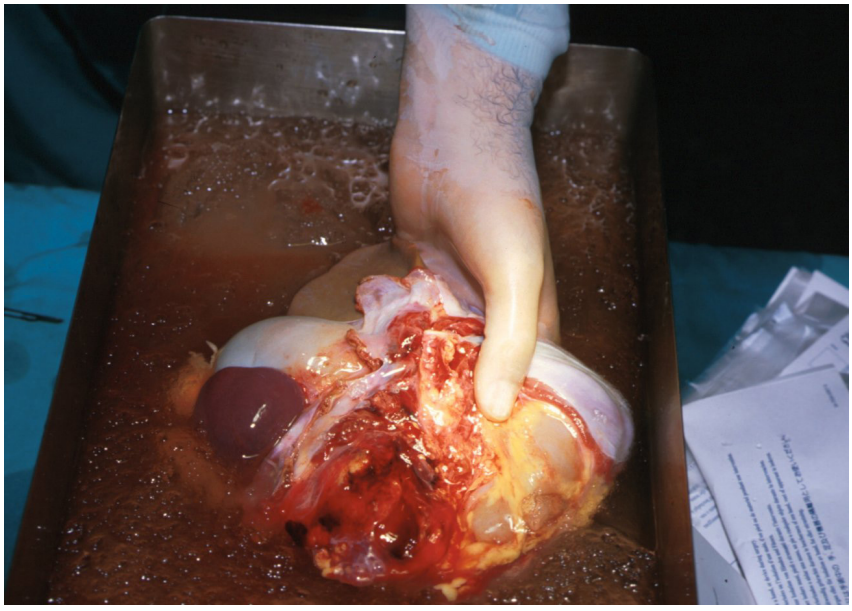


Figure 16.

2.2 Phases of recovery surgery

Multiorgan recovery is divided into four different phases:

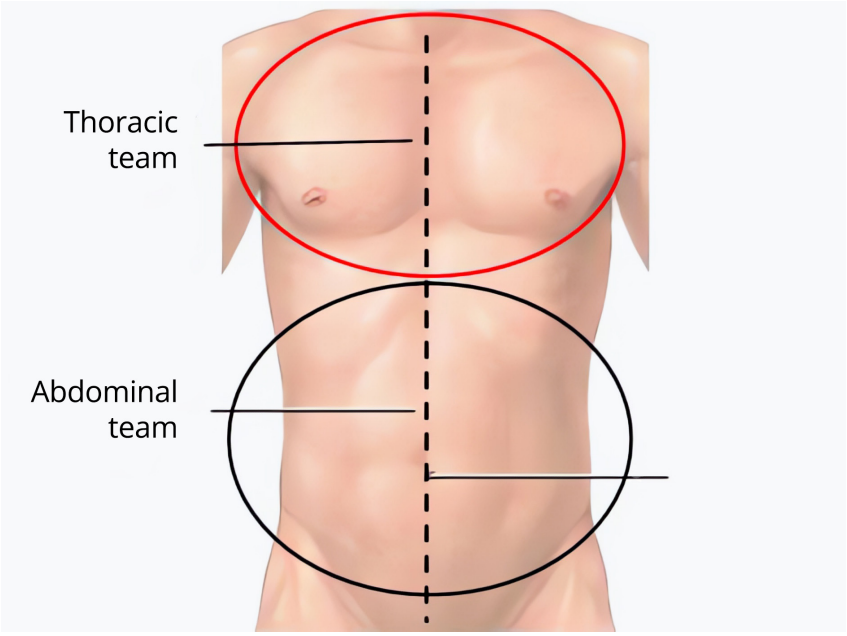
- Inspection-dissection
- Cannulation
- Cross-clamping and perfusion
- Organ removal and preservation

All of the phases are performed at the same time at both thoracic and abdominal levels. The TPM does not participate actively but must be present to record the essential information provided by the recovery teams.

The objective of the first phase is to evaluate the organs *in situ*, validate, and check for any possible contraindications (Figure 17, 18).

In the second phase, cannulas are placed to ensure the perfusion circuits of the different organs (Figure 19).

During the third phase, circuits are closed in order to perfuse only the different anatomical regions involving the organs which are to be removed. Cold ischaemia time begins with cross-clamping, performed simultaneously at both levels under the coordination of the thoracic and abdominal surgeons.



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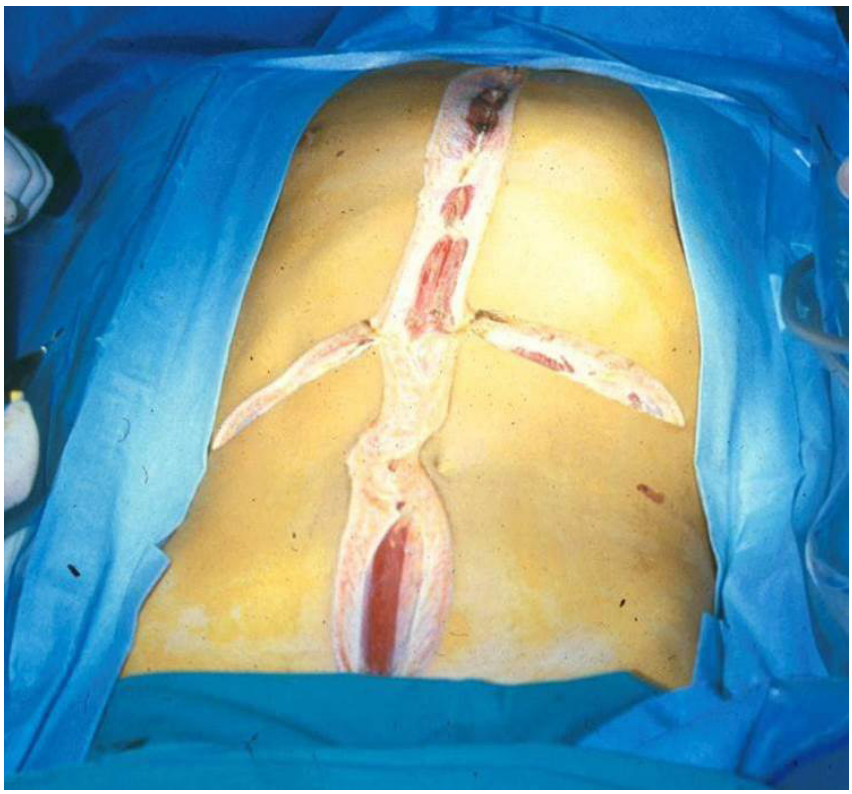

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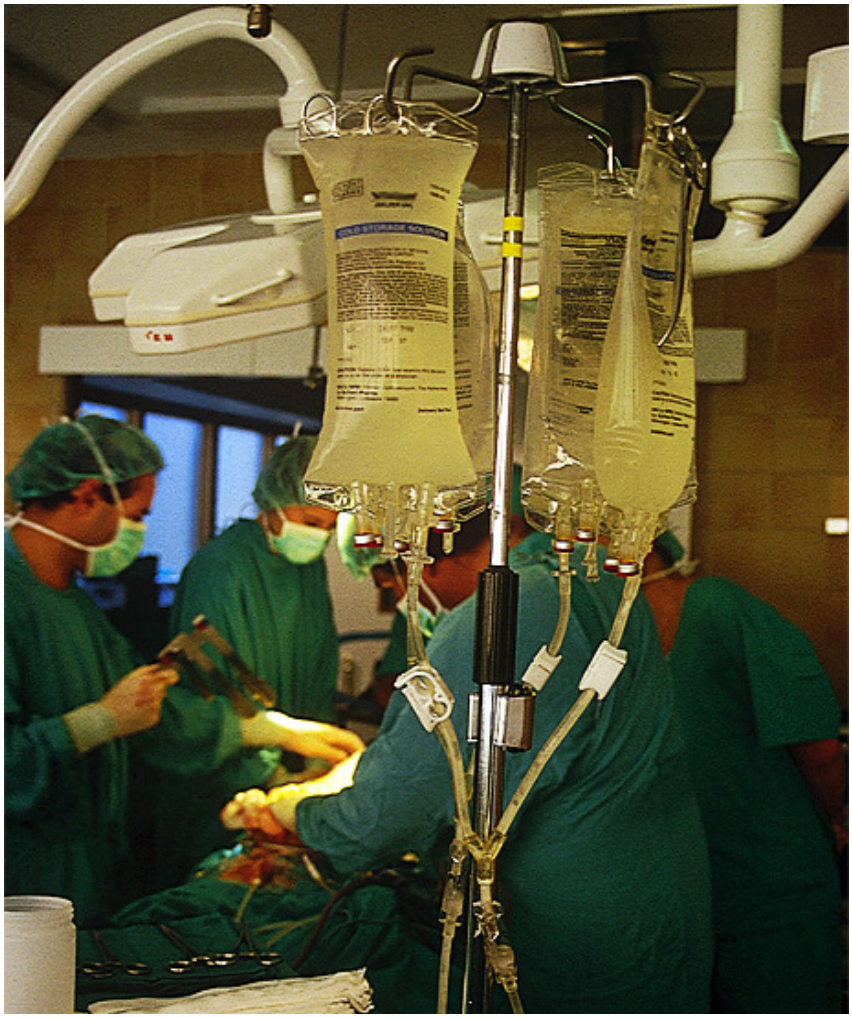


Figure 19.

The fourth phase consists of organ removal and storage for transport [11,12].

During this process anatomical circuits are created. Each circuit uses its own preservation solution.

KEY IDEA

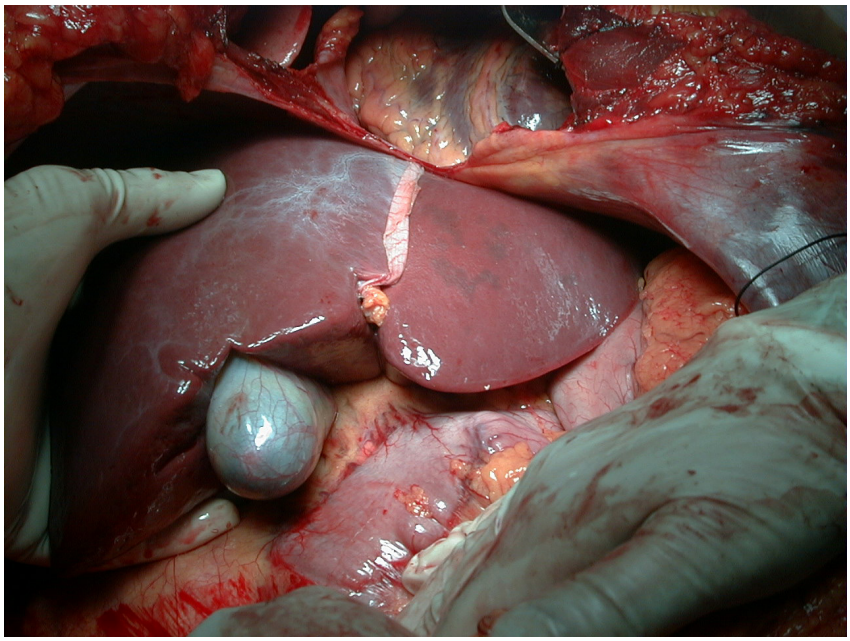
Comprehension of the different recovery phases is critical for the TPM. Despite passive participation during surgery, the TPM must be present to record all the essential information.

2.2.1 Phase 1: Inspection, dissection

Thoracic surgery is performed by two teams composed of cardiac and lung surgeons, whereas abdominal surgery may be performed by a single team (we will assume that abdominal organs are removed by a single team, which is the ideal situation).

A midline incision from the neck to pubis is performed. Usually, both teams work simultaneously during this phase. Organs and cavities are explored, checking whether they are suitable for transplant and ruling out contraindications like infections or tumours. This information is recorded by the TPM and delivered to the different transplant teams (Figure 20, 21).

Dissection: each organ is removed from the surrounding tissues, and all the necessary vessels are prepared for the next phase. Time of recovery at abdominal level needs to be considered as it may last longer than thoracic recovery, where dissection is quicker and easier [13-15]. Heart and lungs are only attached by large vessels and the trachea (Figure 22, 23) whereas complete dissection of the abdominal organs is more complex, especially when pancreas removal is performed.



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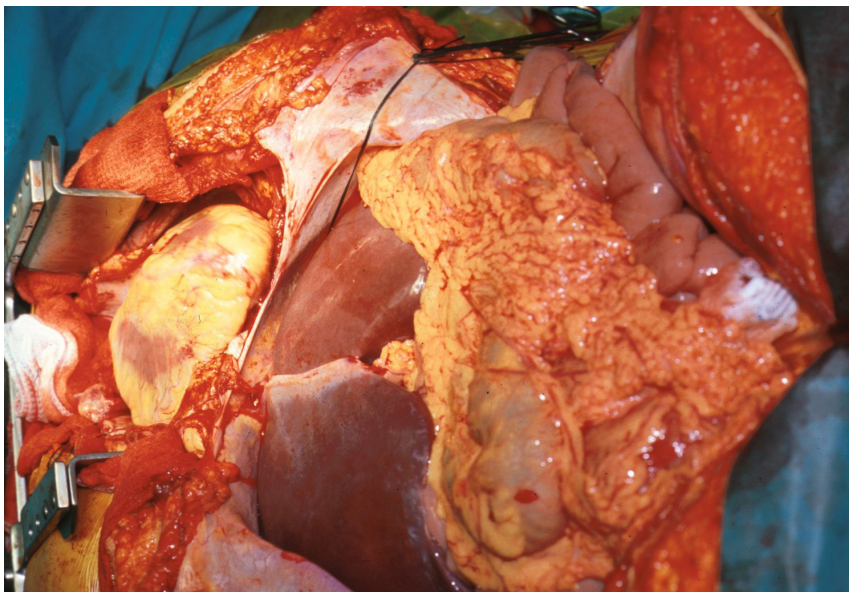

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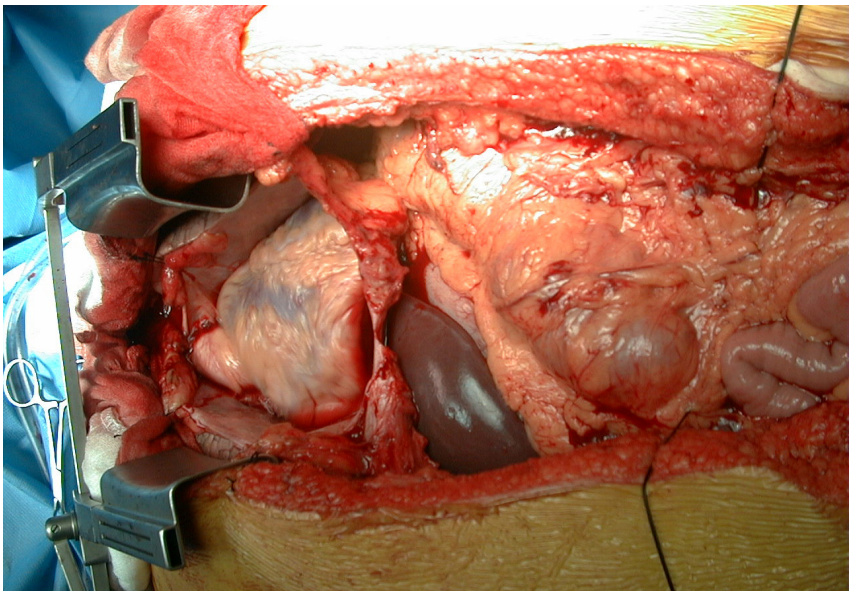

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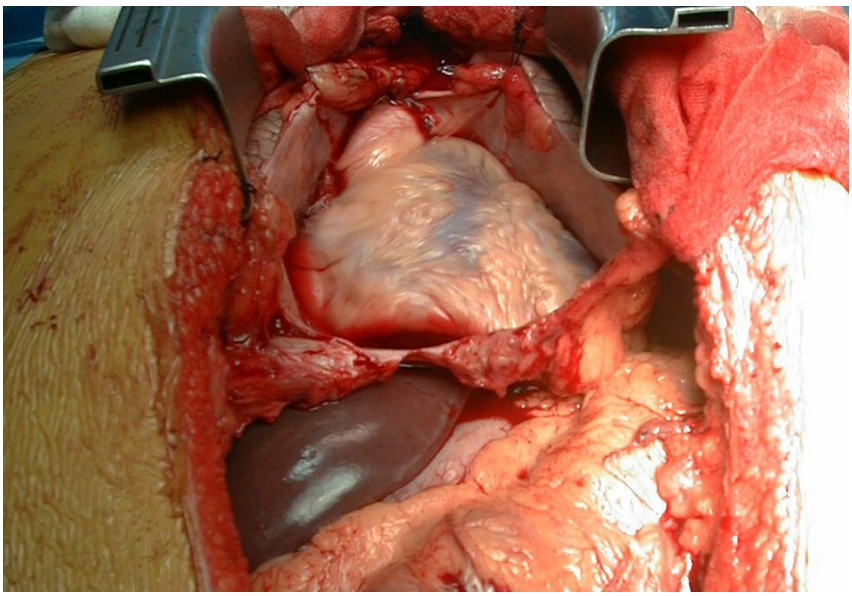


Figure 23.

2.2.2 Phase 2: Cannulation

Once organs have been dissected, perfusion circuits need to be created, as each organ or organ block requires different volumes of different preservation solutions.

FURTHER INFORMATION...

The best moment for heparinization is just before cannulation. We wait two minutes to allow the drug to reach all the organs, and then we can clamp.

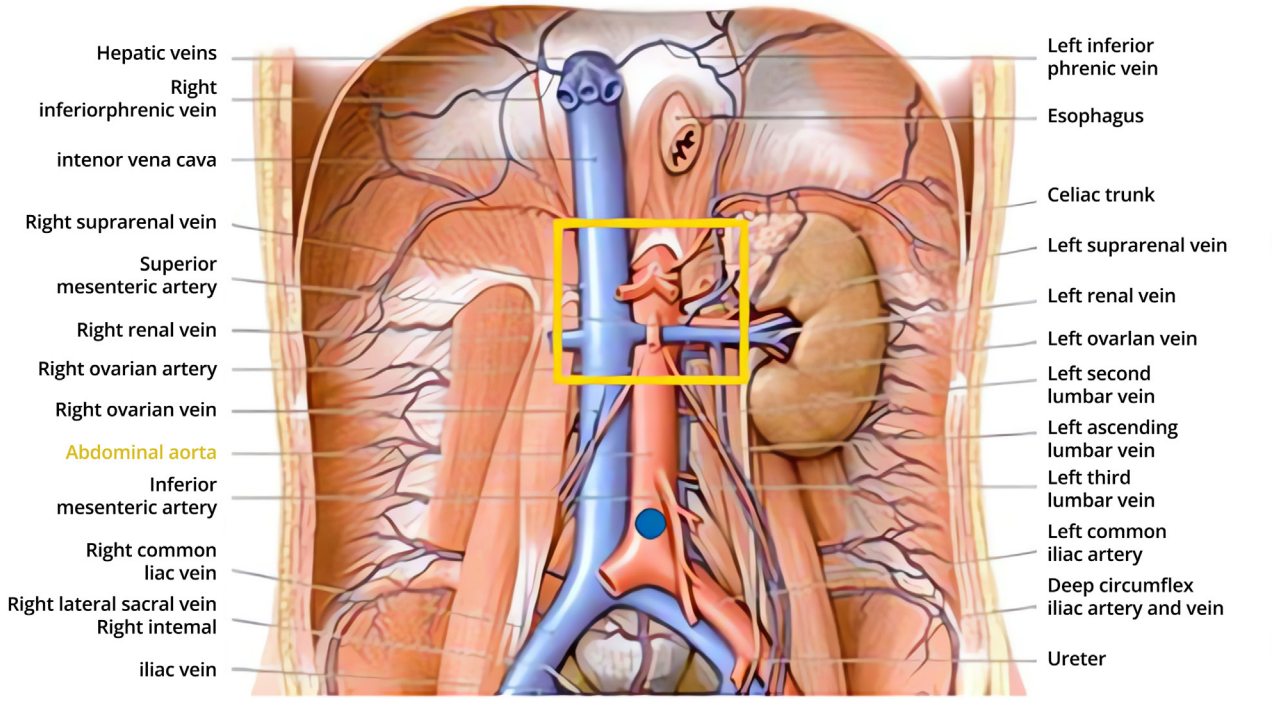
The objective of cannulation is to place the infusion lines and ensure organ perfusion. At abdominal level, two large vessels are used for liver, pancreas and kidneys. Preservation solution is flushed through renal, superior mesenteric arteries and the coeliac trunk (Figure 24), placing a cannula in the infrarenal aorta, and ligating both iliac arteries distally to avoid leakage (Figure 25).

The liver has a double supply from the hepatic artery and portal vein. A cannula is placed in the superior mesenteric vein for venous inflow (Figure 26, 27, 28). At thoracic level, a cannula is placed in the ascending aorta to perfuse the coronary arteries (Figure 29).

The lung is irrigated through a cannula inserted in the pulmonary artery (Figure 30), thus ensuring inflow for all circuits.

Cannulas are placed simultaneously by all teams.

Heparin is administered to avoid clot formation and achieve good perfusion [16,17].



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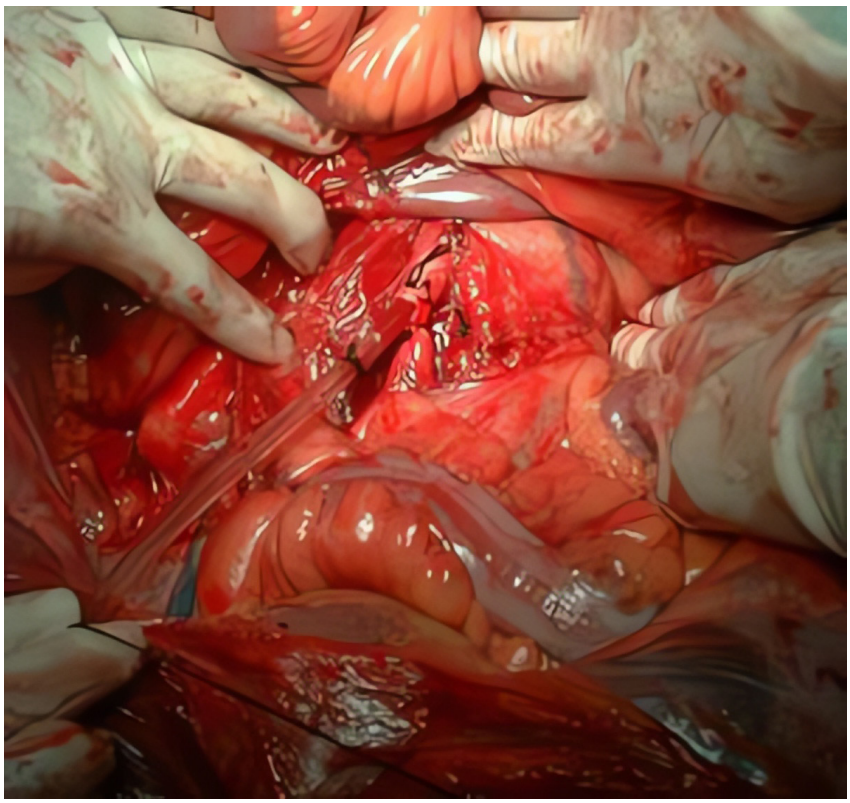

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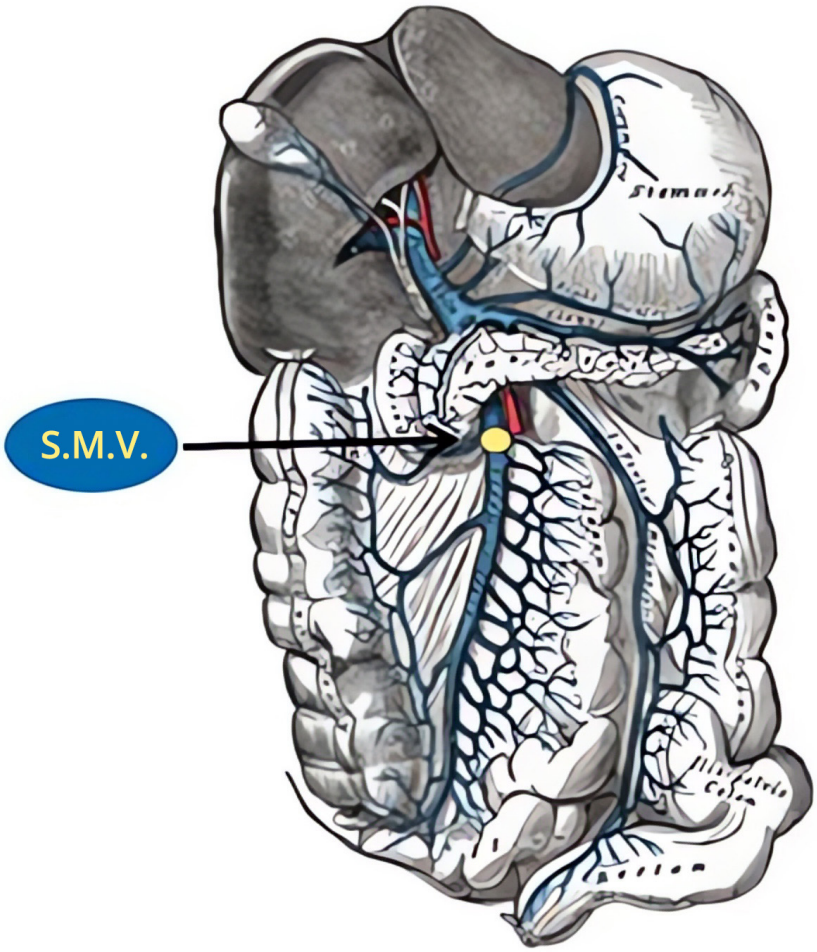

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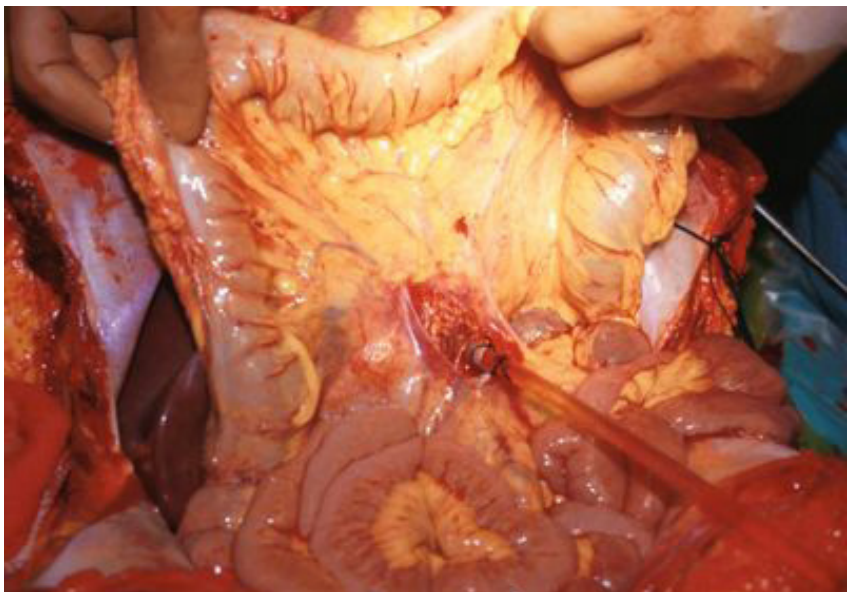

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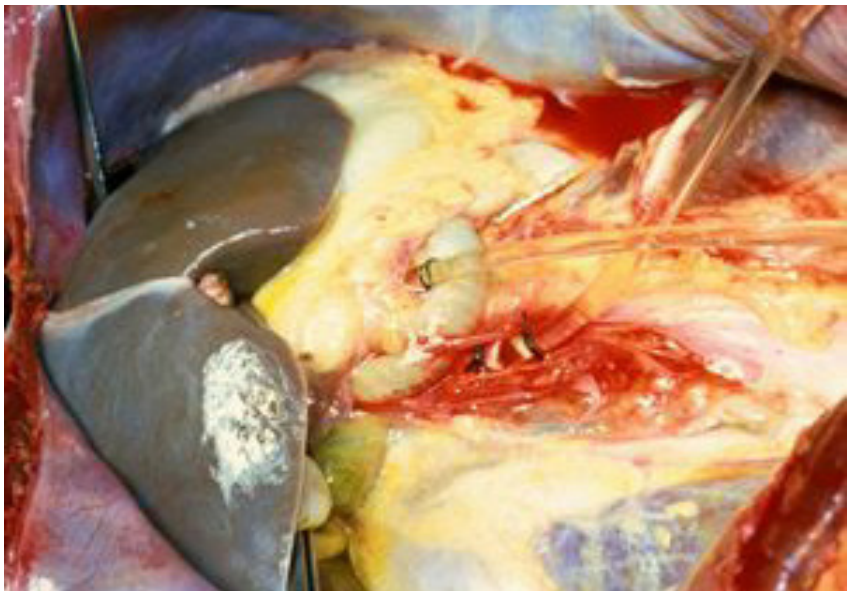

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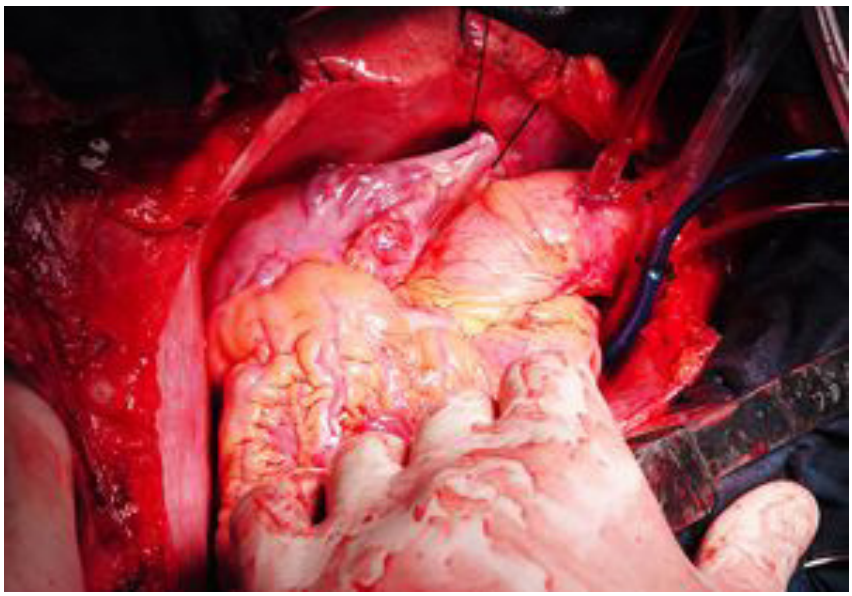

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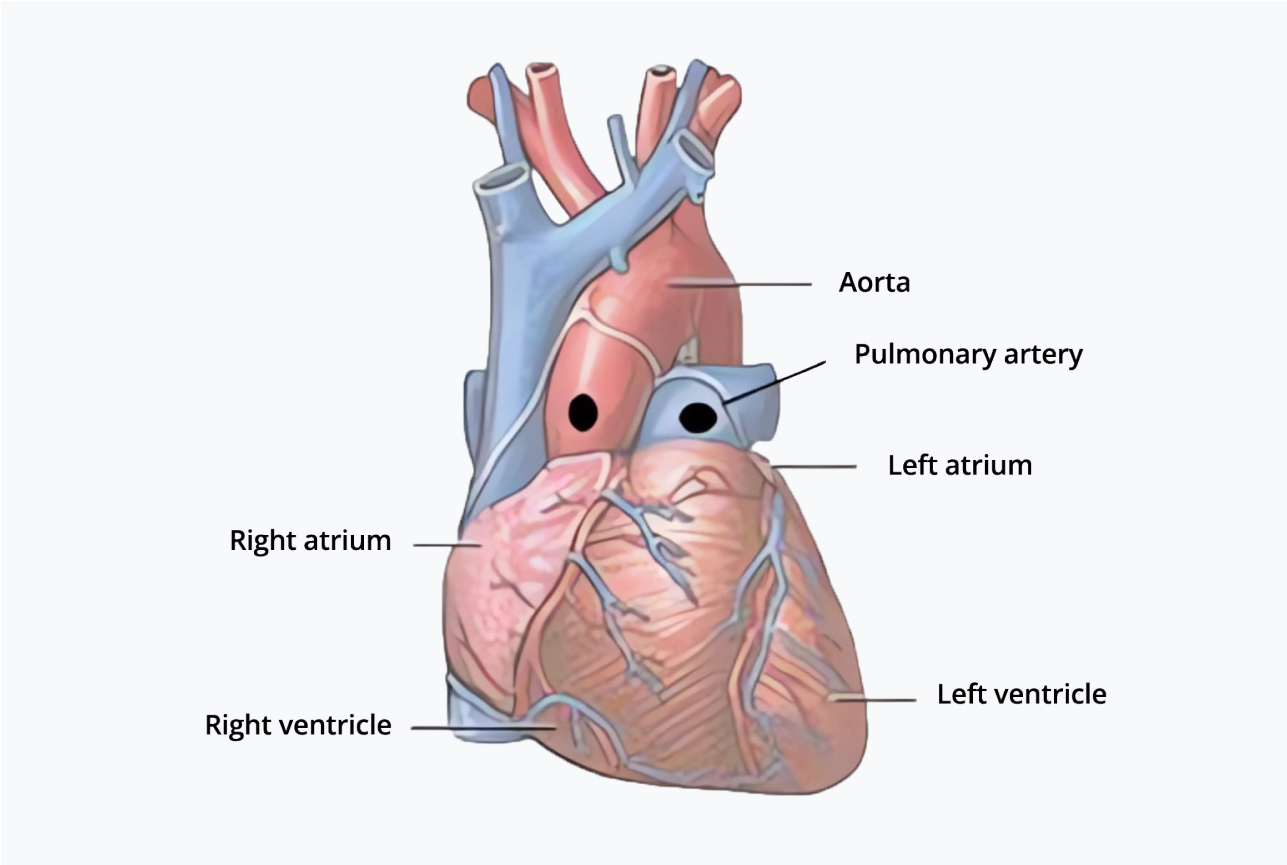


Figure 30.

KEY IDEA

With the cannulas placed, the heart continues flushing the organs, as circulation does not stop until we place the clamps. Ischaemia has not yet started.

2.2.3 Phase 3: Cross-clamping and perfusion

Once inflow lines have been placed, the circuits have to be closed to avoid the perfusion of segments we do not need and the mixture of preservation solutions.

Abdominal level: by clamping the aorta just above the coeliac trunk, the abdominal circuit is closed, and all abdominal organs are perfused.

Thoracic level: by clamping the ascending aorta just distal to the cannula, the cardiac circuit is closed, ensuring perfusion through the coronary arteries (Figure 31, 32). For the pulmonary circuit, clamping is not required.

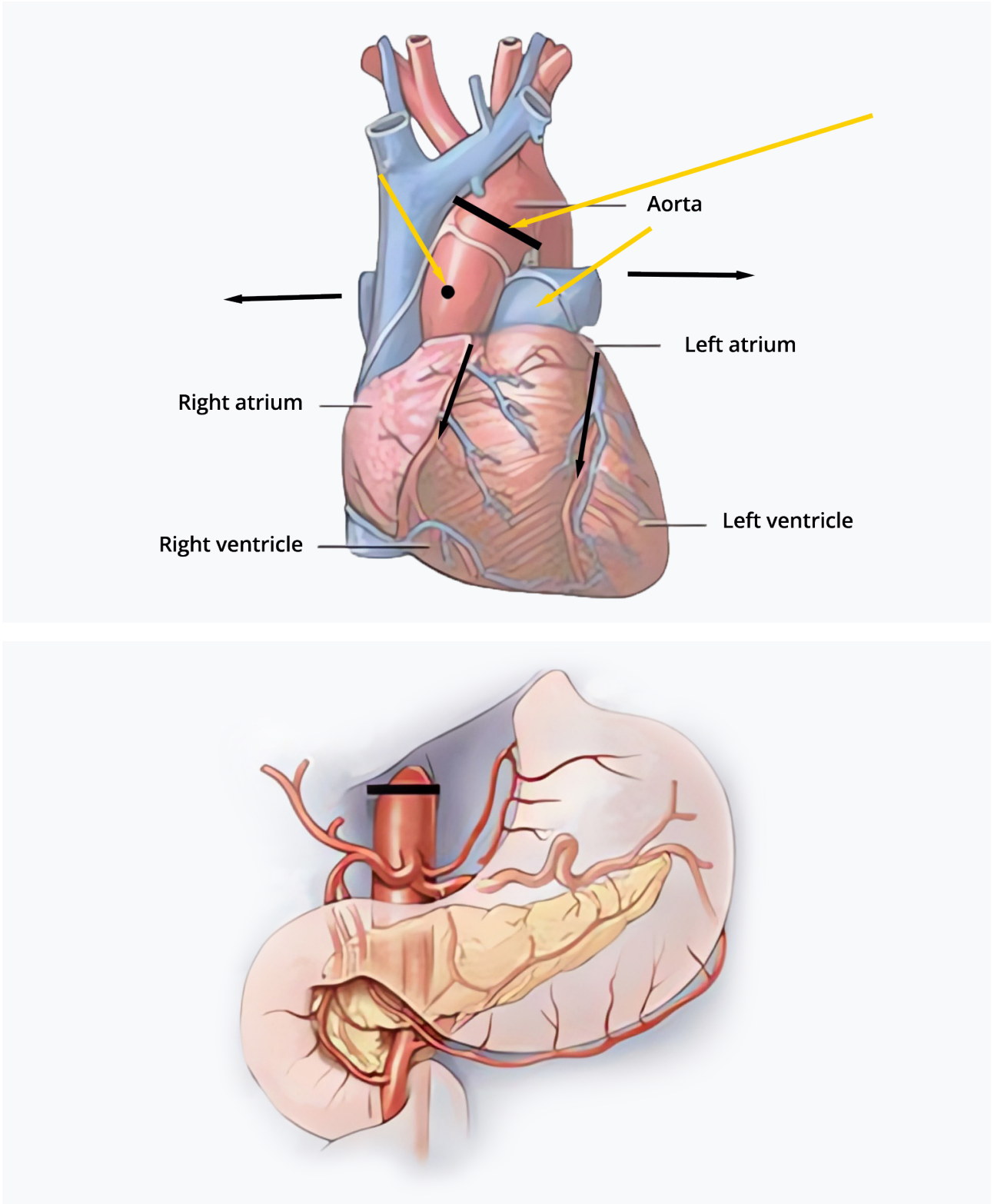
All teams cross-clamp at the same time. This is the moment when cold ischaemia time begins, and the TPM must record it.

Preservation solutions are opened (Figure 33) and flushed through the cannulas. Circuits have inflow, so we need an outflow to drain all the liquids (Figure 34).

To achieve a very good outflow for all circuits at the same time, the inferior vena cava is opened between the right atrium and suprahepatic veins. Another option for the abdominal circuit is to divide the infrarenal inferior vena cava (Figure 35, 36).

Cavities are filled with cold saline solution or crushed iced, according to the preferences of each team (Figure 37).

Cross-clamping and perfusion are performed almost simultaneously as surgeons clamp at the same time and immediately open perfusion lines. Thus, it may be considered that cold ischaemia time starts with cross- clamping. In fact, when cross-clamping is performed there is no circulation for 2 or 3 seconds until perfusion flushes through organs. It takes approximately 2 to 4 minutes to wash the blood out of organs and to cool them to 4°C, depending on each organ.



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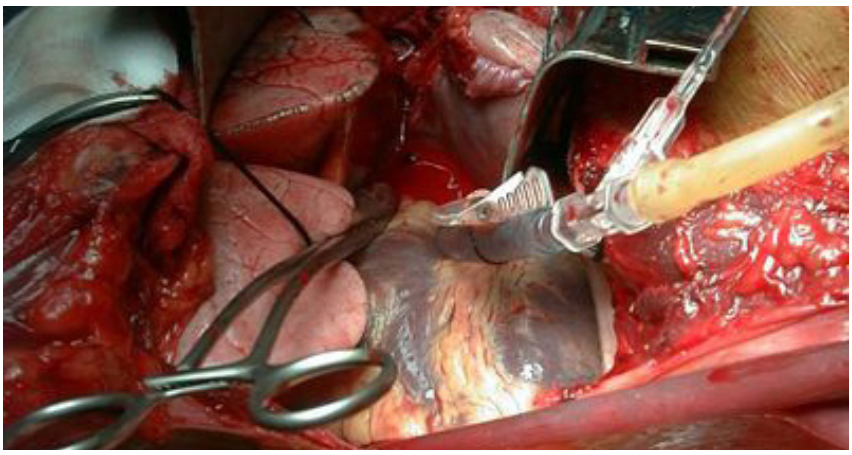

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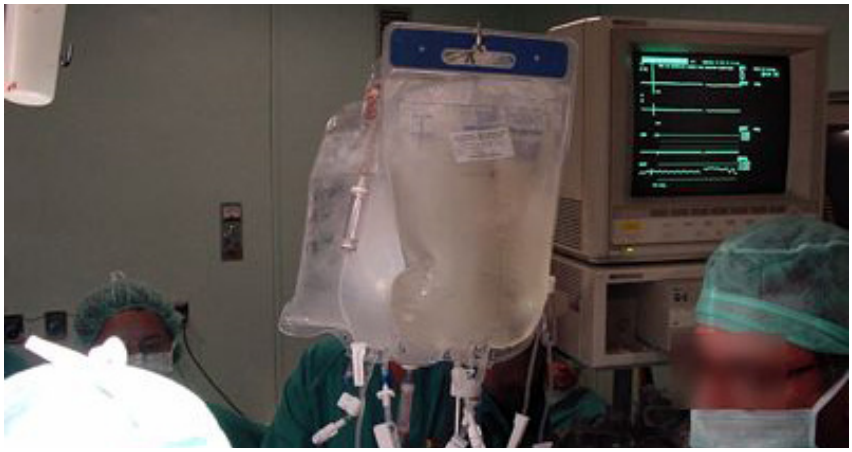

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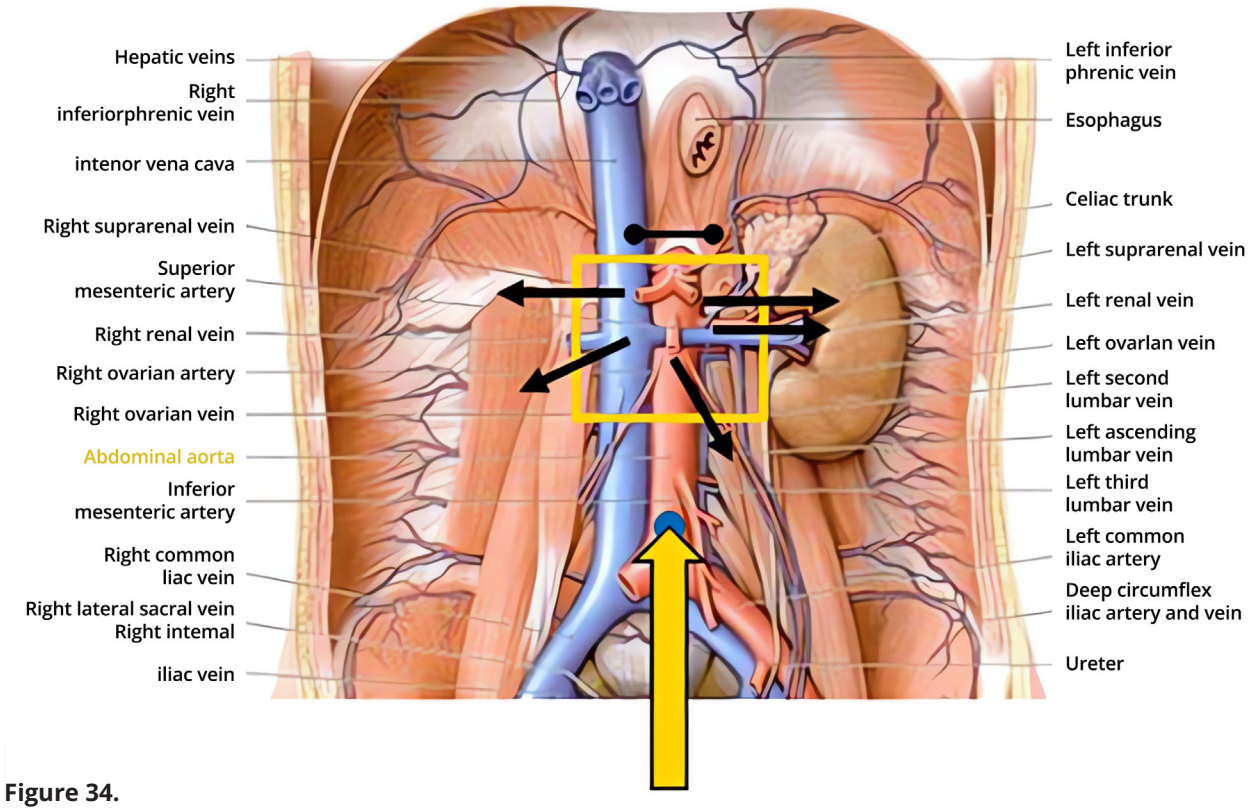

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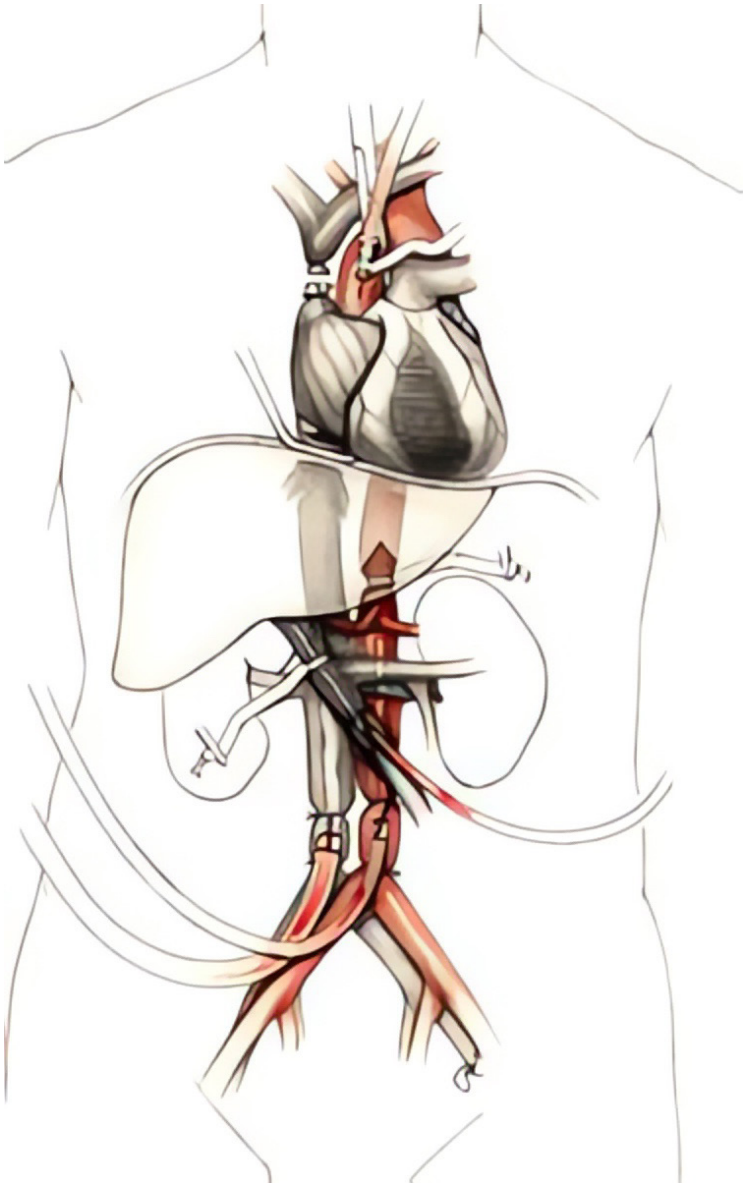

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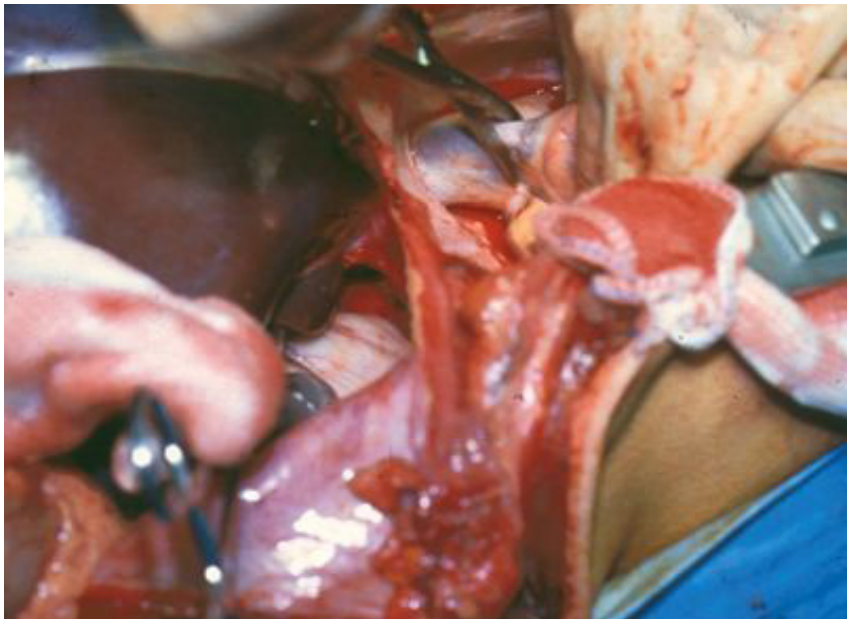

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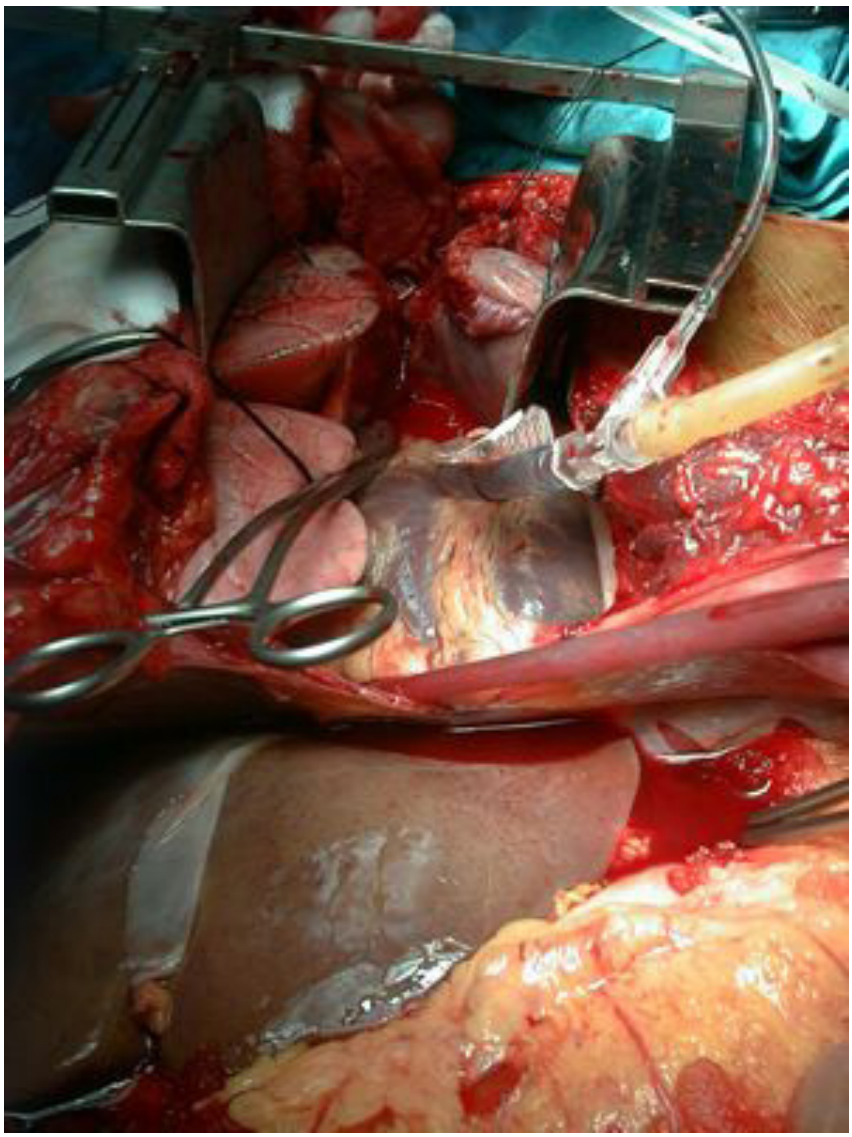


Figure 37.

2.2.4 Phase 4: Organ removal and preservation

Once perfusion ends, organs are removed in accordance with the different cold ischaemia times.

The heart comes first (4 hours), then lungs (4-6-hours), liver (around 12 hours), pancreas (14 hours) and kidneys (up to 24) (Figure 38).

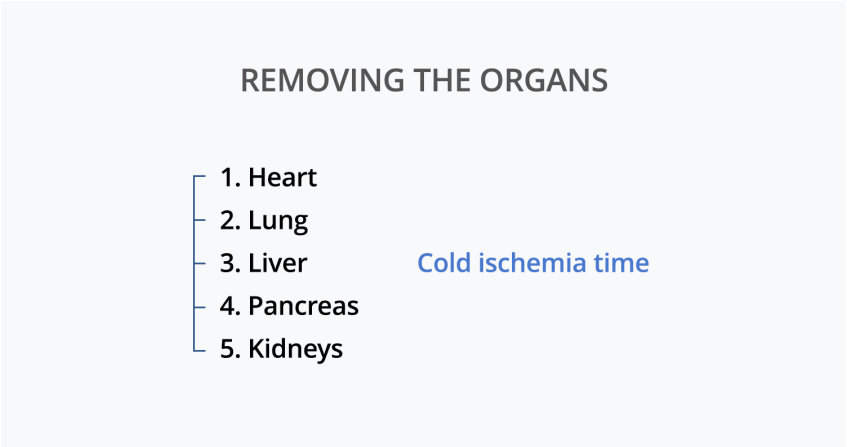
- **Key 1** - Thoracic and cardiac surgeons share the pulmonary veins.
- **Key 2** - The heart and liver share the inferior vena cava between the right atrium and suprahepatic veins.
- **Key 3** - The pancreas and liver share the splenic artery. The coeliac trunk goes with the liver, with a small portion of the splenic artery.
- **Key 4** - The liver and kidneys share the infrahepatic inferior vena cava.

Thus, the length of these vascular segments needs to be sufficient for sutures (Figure 39).

Organs are prepared for bench surgery (Figure 40). The more dissections performed on the deceased donor; the less the bench work required after organ removal.

After bench work, organs are prepared for transport (Figure 41,42). Lymph nodes or spleen are sent with every organ.

If vascular grafts are required with the organs, they are stored similarly. Once organ recovery ends, tissue recovery commences.



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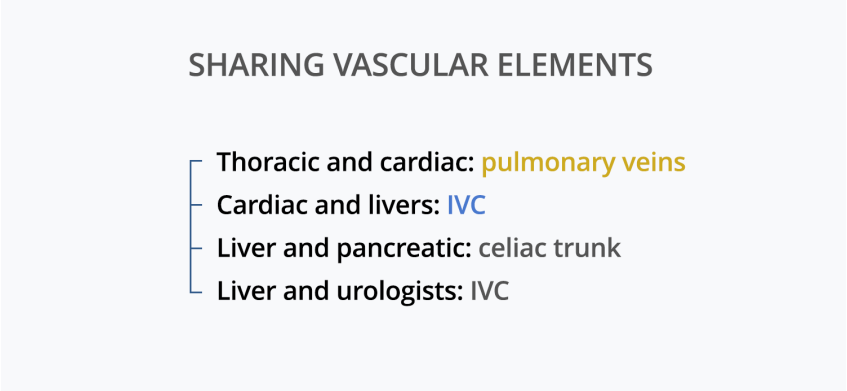

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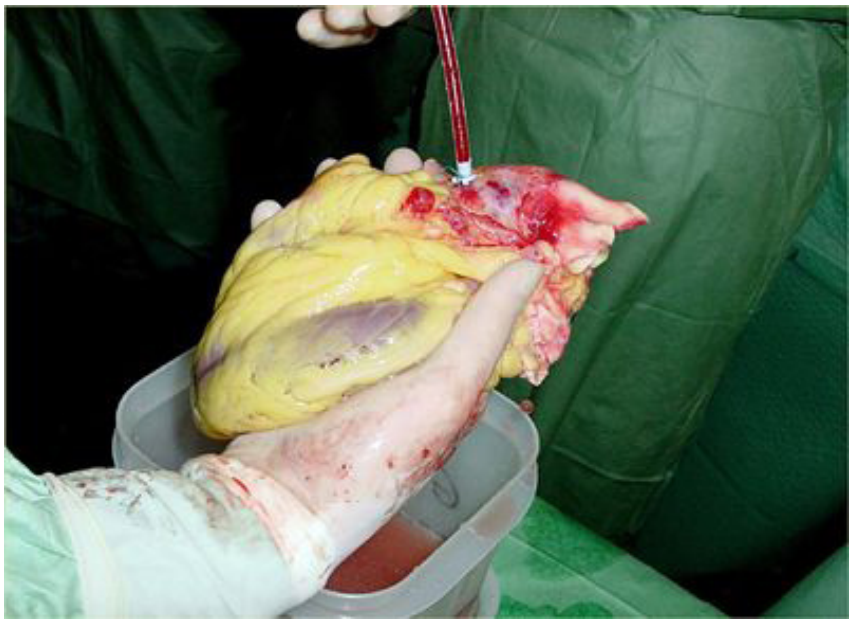

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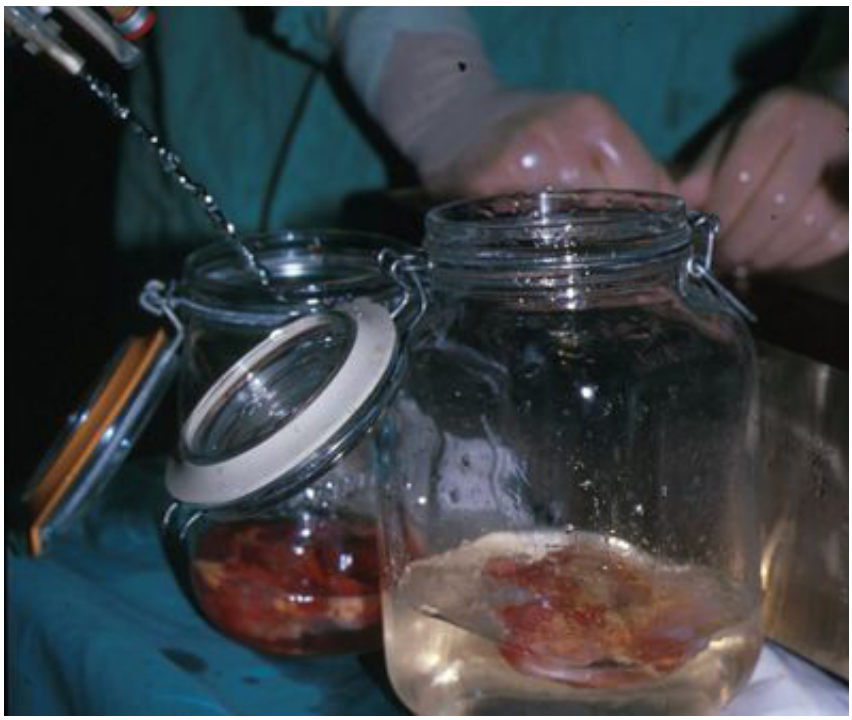

Figure 41.

Figure 42.

Two different techniques: classic and quick cannulation technique

There are two different techniques for the recovery of abdominal organs:

Classic technique

All organs are dissected while surgery is performed on the deceased donor and the heart is beating. This technique requires prolonging the first phase at abdominal level as the liver and pancreas require a longer surgery time for total dissection.

Quick cannulation technique (Nakazato) [18]

Dissection time decreases substantially. Apart from cannulating the vessels, all dissection is performed during bench surgery once the abdominal block has been removed from the deceased donor. This is very useful for unstable or asystolic donors.

Surgeons who are well trained in both techniques may combine them. They can begin with the classic technique and change to quick cannulation, finishing the rest of the dissection during bench surgery (Figure 43).

It is essential for the TPM to know which technique abdominal surgeons will employ in order to estimate clamping times and organize the transport logistics for the different teams.

KEY IDEA

Dissection times at thoracic level are almost always similar, but at abdominal level times may differ according to the technique employed.

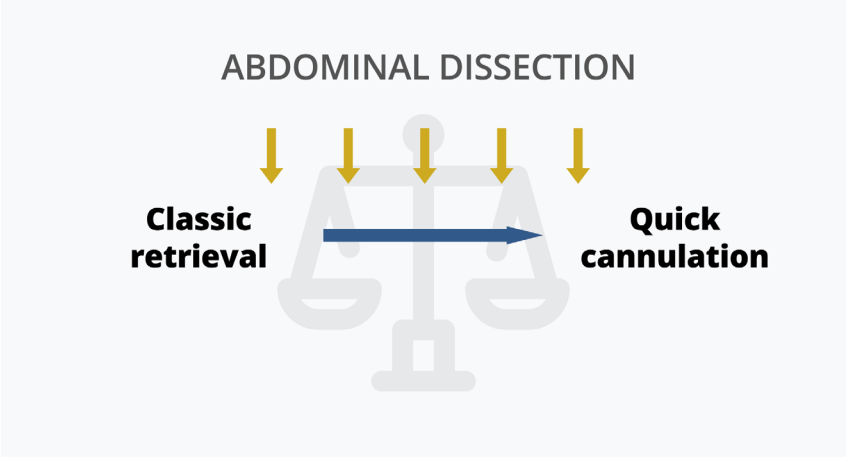

Figure 43.

2.3 Summary

There are four different phases in multiorgan recovery:

- Inspection-dissection
- Cannulation
- Clamping-perfusion
- Organ removal and preservation

The TPM does not participate in the surgery but must be present to record all essential information.

It is very important to understand the entire surgical process performed at two levels: thoracic and abdominal. The objective is to prepare the organs and create perfusion circuits.

FURTHER INFORMATION...

Review the following article to learn more. Total abdominal evisceration: an en bloc technique for abdominal organ harvesting [18].

During the first phase, organs are dissected and evaluated. Depending on the technique chosen, abdominal surgeons may delay thoracic surgeons.

During the second phase, the vessels which are going to perfuse the circuits are dissected and cannulated.

With the clamping, cold ischaemia time begins; it is a key moment in the entire process [19]. Lines are opened and outflow for the circuits is achieved.

Finally, organs are removed in the order of their cold ischaemia time.

3. SECTION 3: PRESERVATION

The success of organ transplantation is determined by the quality of the organs removed and the excellence of the recovery process. Success is influenced by a variety of factors such as donor age and pre-existing disease, donor management, the duration of hypothermic storage, the type of flush solution, and events related with reperfusion. Brain death results in a series of perturbations, all of which are thought to contribute to donor organ dysfunction. The organ recovery and transplantation process exposes an organ to a compulsory period of ischaemia and reperfusion.

Traditionally, hypothermic organ storage has been used to protect organs from ischaemic injury, but each organ differs markedly in its capacity to withstand hypothermic ischaemia.

In this chapter, we discuss the strategies used to minimize the adverse consequences of ischaemia-reperfusion injury for solid organs as well as the characteristics and formulation of flush solutions.

This section contains the following subsections:

- Hypothermia
- Consequences
- Buffer substances
- Protect the interstitial space
- Preservation solutions
- Two applicable preservation methods
- Resume

3.1 Hypothermia

Organ preservation is based on hypothermia, which reduces the rate at which intracellular enzymes break down the essential components necessary for organ vitality. Hypothermia does not stop metabolism but slows it down, delaying cell death. In animals at 37°C, there is a 1.5 to 2-fold decrease in the activity of most enzymes with every 10°C reduction (Van't Hoff's law). Hence, some enzymatic processes slow down between 12 and 13 times when the temperature drops from 37°C to 0°C.

Many organs tolerate warm ischaemia for 30 to 60 minutes without losing their functions. Cooling an organ from 37°C to 0ºC can prolong the preservation time by 12-13 hours. The use of an appropriate flushing solution can increase kidney storage times by a factor of approximately 3 (up to 30 hours) [20,21].

Organ intravascular flushing needs to be performed with a liquid with low hydrostatic pressure that flushes out elements formed, isoagglutinin and clotting factors. Inadequate flushing would facilitate the presence of microaggregates of red blood cells in the microcirculation, making blood reperfusion and subsequent organ function difficult.

KEY IDEA

To obtain the optimal protective effect in kidneys, all renal compartments (vascular, extracellular, tubular) must be equally balanced with the liquid. This balance is attained with 10 to 12 minutes of perfusion, and it is recommended to perfuse the organ with a volume 10 times the weight of the kidney.

3.2 Consequences

Cells are normally bathed in an extracellular liquid that is rich in sodium and low in potassium, unlike the intracellular liquid which has a high potassium content. This difference is maintained by the Na/K-ATPase pump. The pump keeps sodium from penetrating cells, acting against the colloidal osmotic pressure exerted by proteins and other anions unable to penetrate the cell. Cold ischaemia suppresses this pump. As a result, chlorine and sodium enter the cell through a density gradient and the cell swells due the accumulation of water.

Thus, electrolyte composition is important in most preservation fluids. Generally, it is similar to the intracellular compartment fluid, with a low sodium and high potassium concentration. The addition of cell-impermeable substances (impermeants) such as simple sugars is a key component in preservation.

Another consequence is the intracellular overload of calcium. Such alterations, especially in heart preservation, impede correct cell functioning in reperfusion [22,23].

KEY IDEA

Preservation solutions should attain an osmolarity very similar to that of plasma, about 310 mOs/kg.

3.3 Buffer substances

Ischaemia, even submitted to cold, stimulates glycolysis and glycogenolysis, increasing the production of lactic acid and concentration of hydrogen ions. The accumulation of hydrogen ions activates the membrane sodium-hydrogen ion exchanger, which is inactive under normal circumstances. Its mission is to exchange intracellular hydrogen ions for extracellular sodium ions. The result is an accumulation of intracellular sodium, which alters the direction of the second membrane exchanger (sodium-calcium), which in turn exchanges intracellular sodium for extracellular calcium. Thus, the net effect of intracellular acidosis during ischaemia is a greater accumulation of intracellular calcium.

Tissue acidosis damages cells, activates lysosomal enzymes and alters mitochondrial properties. These alterations stimulate the production of cytokines that attract macrophages, thereby initiating an inflammatory response. Preservation solutions should therefore include buffer substances to maintain the pH as saline as possible [24,25]. The most widely used buffers are bicarbonate, citrate, phosphate, lactobionate and histidine. The addition of buffer substances is a critical point for the development of preservation solutions.

3.4 Protect the interstitial space

Theoretically, colloid solutions prevent expansion of the interstitial space better than crystalloids. Most preservation solutions do not contain colloid osmotic substances. Belzer solution contains hydroxyethyl starch, which remains in the vascular space, exercising a colloid osmotic effect.

Oxygen-free radicals are mass-produced during cold ischaemia and reperfusion. These molecules da-

mage and produce loss of cell function. Many experimental references support the mediator role of oxygen-free radicals in reperfusion injury.

The addition of exogenous scavenging substances may potentially slow down the damage caused by oxygen-free radicals. The most commonly used scavengers are reduced glutathione and mannitol [26,27]. The addition of allopurinol, which inhibits xanthine oxidase, is also effective in organ preservation.

During cold ischaemia there is a rapid loss of ATP and other high-energy phosphate compounds. Renal reperfusion requires rapid Na/K-ATPase pump reactivation, as well as other metabolic pathways requiring ATP.

DID YOU KNOW?

The most commonly used ATP precursors are inosine and adenosine.

3.5 Preservation solutions

In the 1970s, Collins developed a hyperosmotic intracellular-type preservation solution that proved highly effective. It was modified and named EuroCollins. In Australia a hyperosmolar citrate (HOC) solution based on citric acid as the impermeant anion was developed.

In the 1980s, Belzer designed the University of Wisconsin (UW) or Belzer UW® solution, an intracellular electrolyte-type solution without glucose and with the addition of new non-metabolizable impermeant, phosphate and sulphate as buffers, adenosine as the precursor for ATP resynthesis and an effective colloid, hydroxyethyl starch.

DID YOU KNOW ...?

UW solution was the best for several years and represented a great improvement in comparison with EuroCollins.

Brettschneider was initially a cardioplegic solution and is now used for the preservation of all organs. It is an intracellular-type solution, which is practically calcium-free with very low sodium levels and mannitol, histidine hydrochloride (buffer), tryptophan, ketoglutarate (membrane protectors) [28,29].

Celsior solution combines HTK and Belzer solutions. It has a low potassium content. Lactobionate and mannitol are used as an impermeant and histidine as a buffer. Its high magnesium content prevents calcium overload. It contains glutathione and its viscosity is very low (Table 1).

Table 1. Recovery and preservation of organs

	MECHANISM OF ACTION
Free radical scanvengers	
Catalase* Superoxide dismutase* Nafazatrom	Scavengers of hydrogen superoxide and hydrogen peroxide
Mannitol Dimethylthiourea Dimethyl sulfoxide mercaptopropionyl-glycine	In-hospital cardiac arrest is anticipated Diagnosis of death by circulatory criteria is made
Histidine*	Scavengers of reactive oxygen species
Inhibitors of free radicals production	
Allopurinol	Inhibitor of xanthine oxidase
Deferoxamine	Iron chelator agent
Neutrophils inhibitors	
Adenosine*	Superoxide anion production modulation
Transforming growth factor beta Monoclonal antibodies against complex CD11-CD18	Neutrophil adhesion inhibition
Antiproteases	Inhibition of neutrophil protease activity
Perfluorochemicals	Neutrophil chemiotaxis and lysozyme degranulation suppression
Antioxidants	
Vitamin E (a-tocopherol)* Propranolol Calcium channel blockers Captopril Nafazatrom	Peroxidation blocking
ISCHAEMIC PRECONDITIONING	A1 adenosine receptors Heat shock proteins
HYPOTHERMIA	Metabolism reduction

3.6 Two applicable preservation methods

There are two applicable preservation methods for the clinical setting, simple hypothermic storage, which is the most common, and hypothermic perfusion with pump devices, which is more expensive but of great use for suboptimal donors with more prolonged ischaemia times.

- Simple hypothermic storage
  - Kidney: Vascular flushing is performed with the appropriate solution and the kidney is stored in ice. This is effective for kidneys recovered in optimal conditions. 18 to 36 h (EuroCollins, UW and Custodiol) [30-32].
  - Liver: This is the most commonly used method. 12 to 18 h
  - Pancreas: 12 h (UW, Celsior, HTK)
  - Heart: 4-6 h (cardioplegic, Celsior)
  - Lungs: 4-6 h (Perfadex, Celsior). Pre-treating the donor with a vasodilator -PGE1 or prostacyclin- improves storage [33]
- Hypothermic perfusion (6-10°C)
  - Kidney
    - Pulsatile hypothermic perfusion
    - Non-pulsatile hypothermic perfusion
    - Mainly to preserve kidneys from suboptimal donors with prolonged ischaemia times
  - Liver: to extend times. Expensive (EuroCollins, UW, Celsior and HTK) [34,35]

DID YOU KNOW?

There are major differences between the organs to be transplanted (kidney, liver, pancreas) in terms of metabolism. For this reason, some preservation solutions have been especially designed to give optimal results for a certain organ.

3.7 Summary

Organ preservation is an essential part of the transplantation process. Keeping organs viable as long as possible is critical for the successful outcome of a transplantation. Hypothermia is a key element in preservation. Decreasing the organ temperature to 4ºC allows us to reduce cell metabolism and protect proteins.

Several mechanisms and drugs have been developed to avoid ischaemic-reperfusion injury. They act to:

- avoid hypothermic-induced oedema;
- prevent intracellular acidosis;
- avoid interstitial space expansion during reperfusion;
- annul generated free radicals injury;
- add regeneration precursors to give energy.

We have seen the different preservation solutions in current use, their components and acting mechanism. Finally, this section reviewed clinical preservation methods according to each organ.

4. SECTION 4: PULSATILE DEVICES FOR PRESERVATION

This section reviews organ preservation with pulsatile perfusion devices and analyses the differences between normothermic and hypothermic circulation.

- Impact of pulsatile perfusion
- Portable perfusion systems
- Pulsatile perfusion versus simple cold preservation (SCP)
- Differences between normothermic and hypothermic circulation
- Ischaemia-reperfusion lesions and pulsatile devices
- Summary

4.1 Introduction

An increasing demand for transplants led to the development of new strategies to expand the donor pool. Pulsatile perfusion (PP) provides a better preservation environment for compromised organs as well as the opportunity to evaluate an organ and determine its viability prior to transplantation.

Pulsatile perfusion decreases organ discard rates from expanded criteria donors (ECD) and the incidence of delayed graft function.

Currently, the average donor is older and has associated co-morbidities. Organs from such donors can be safely transplanted with optimal preservation and a thorough evaluation prior to transplant [36-38].

Another group of patients that benefit from PP are those who receive organs recovered from DCD (donation after cardiac/circulatory death) donors.

In brief, organs from ECD or DCD donors have a risk of reduced viability since the organs have suffered additional damage. For such organs, PP is used after their recovery and enables quantification and evaluation of their function before transplantation. Use of PP allows the clinician to improve organ evaluation techniques and potentially increase the number of organs used.

4.2 Impact of pulsatile perfusion

The use of organ perfusion techniques not only allows the recovery of more organs, but also improves function after transplantation. The origins of PP were in the USA in the 1960's with Dr. Belzer. It is important to note that the perfusion machine was created with the initial objective of improving prolonged preservation periods but not necessarily to improve the evaluation techniques used to take decisions about viability. Improved diagnostic techniques, using perfusion parameters provided by the machine, were an indirect benefit of the use of this technique.

Many articles have shown the beneficial effects of PP compared to static cold preservation [39]. However, these data need to be understood in the correct context. Results generally come from retrospective studies using different systems and perfusion protocols. Moreover, the data reported come from a mixed pool of donors, including both standard and extended criteria donors in addition to both controlled and uncontrolled DCD. Results suggest that the use of PP leads to better outcomes when compared to cold static preservation [40-42].

4.3 Portable perfusion systems

Perfusion systems consist of a pump that forces the perfusion solution through the kidney (or other organ) at adequate temperatures (4-6°C). This pumping action can be pulsatile or continuous. Normally, the machine uses a simple ice-water bath which is pumped through a heat exchanger to cool the preservation solution. The perfusion is pumped through the cooling system and into the renal artery, which has been placed in the sterile disposable cassette. The inner cassette remains sterile. The entire system can be moved from the theatre to the perfusion laboratory [43].

There is also a temperature probe. A pressure manometer measures systolic and diastolic pressure. Flow probes are placed onto the tubes and the flow can be increased. Finally, renal resistance (RR) [44,45] is measured as a ratio of the mean pressure divided by the imposed flow (Figures 44, 45, 46). Renal resistance has proved to be an important and useful perfusion parameter that should be used to evaluate the organ. Studies show that low RR values (0.25) predict which kidneys will show lower rates of delayed graft function (DGF) [46-48].

KEY IDEA

The perfusionist evaluates and reports these variables, helping the medical team to reach a decision. Especially in ECD, RR is an important parameter when deciding the viability of organs.

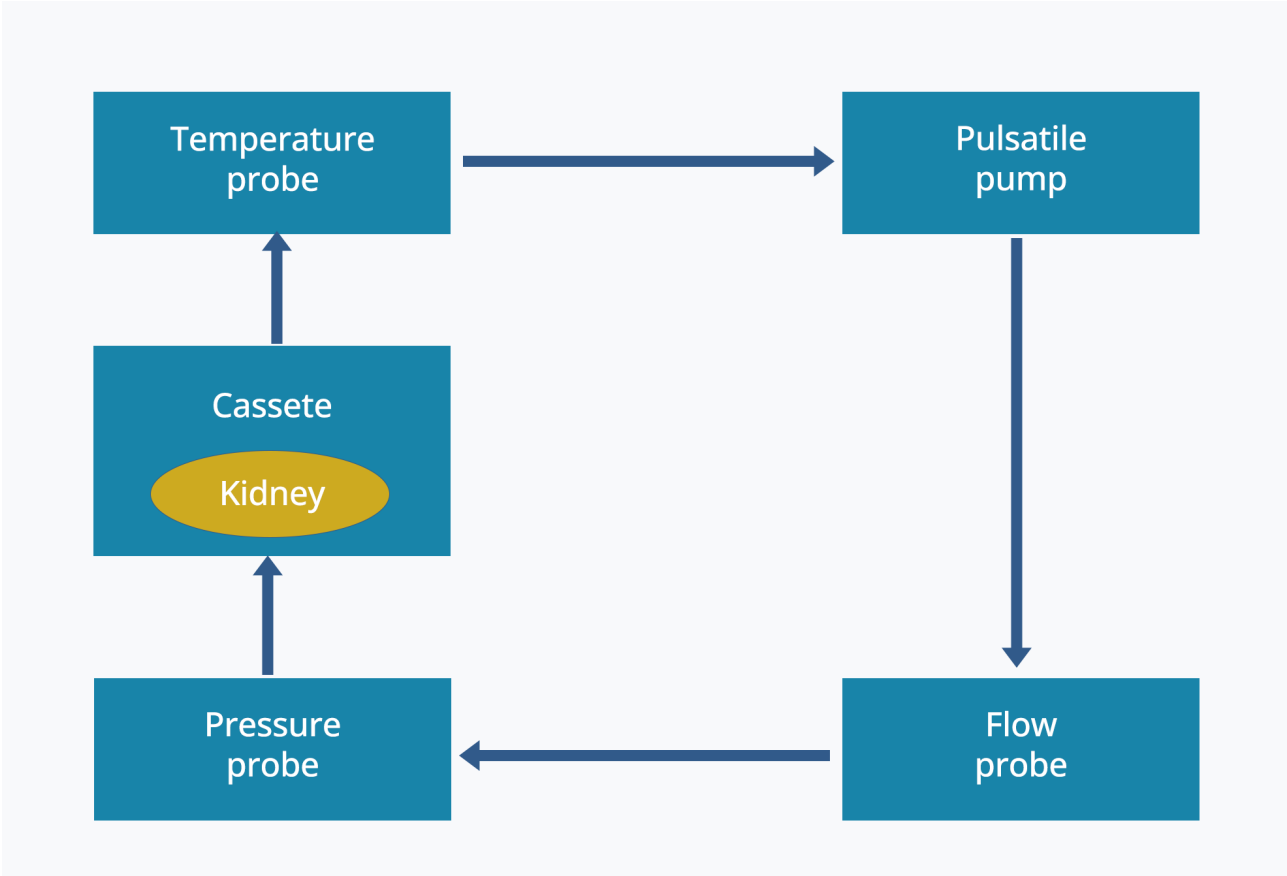

Figure 44.

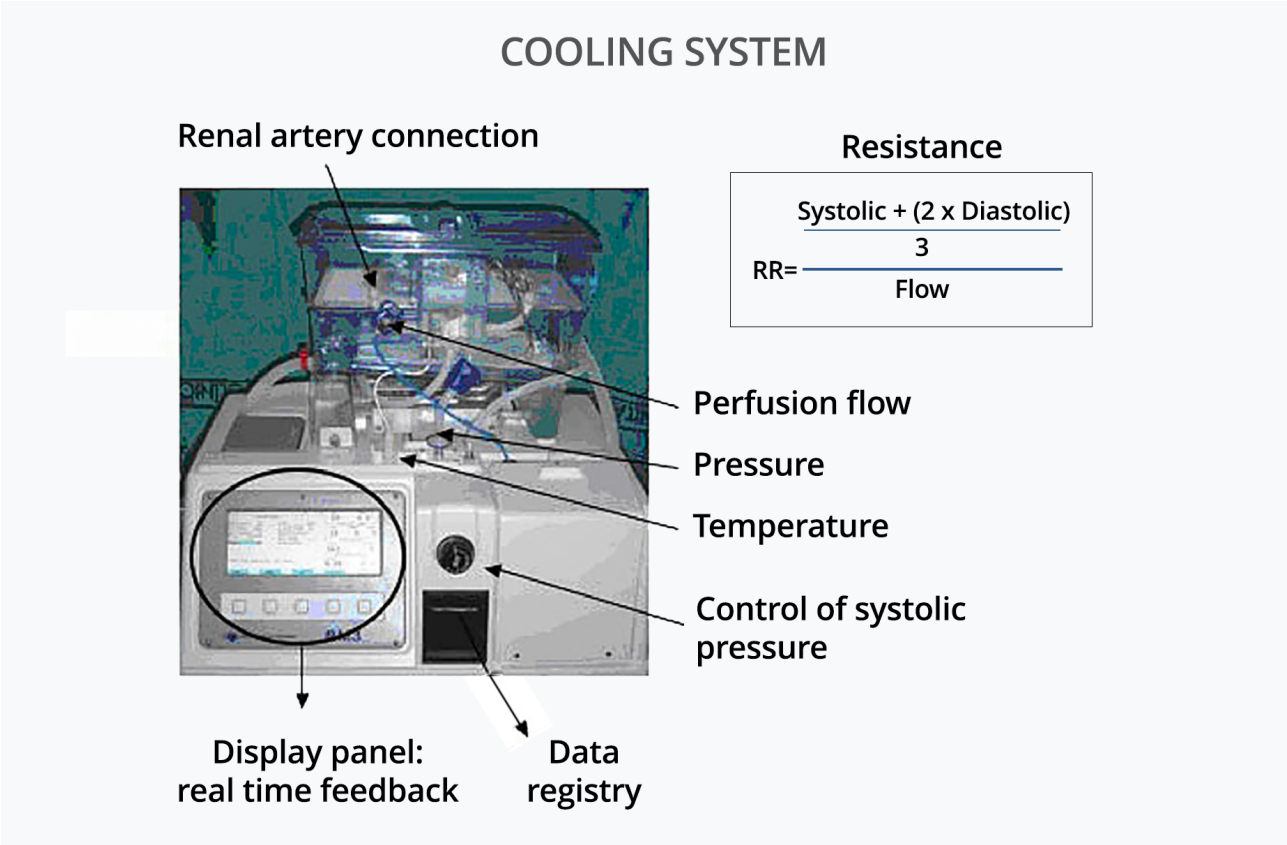

Figure 45.

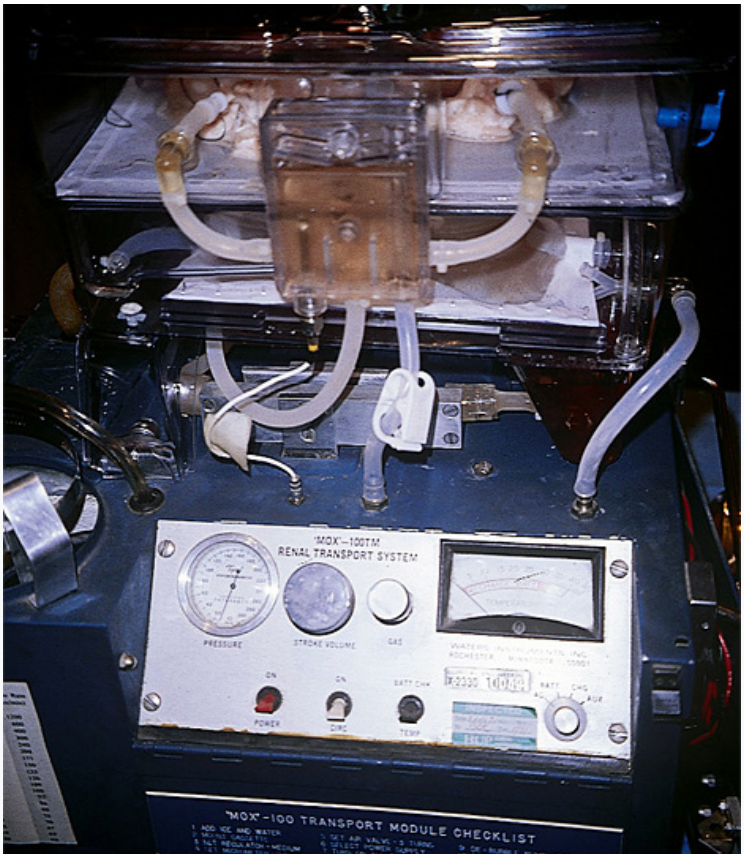

Figure 46.

4.4 Pulsatile perfusion *versus* simple cold preservation (SCP)

1. The initial vasoconstriction is modified, and renal resistance decreases during the preservation period as the organ progressively "opens up".
2. PP guarantees adequate perfusion.
3. Stable hypothermic temperatures. During PP, temperature is regulated and controlled.
4. Regulated pulsatile pressure. The optimum pressure is determined as a function of the organ's needs and is also dependent on donor features (hypertension, DCD, hypotension).
5. Macroscopic changes. In SCP there are no macroscopic changes. However, in PP such changes can be observed and evaluated.
6. Evaluation of renal effluent. PP systems allow the perfusionist to observe renal effluent. Moreover, the perfusionist can take samples of solution for further testing.
7. Biopsies. Parameters measured by the machine can be used to provide additional information to the surgeon in order to request a biopsy if necessary.
8. Drug intervention. Organ-specific drug manipulation ex vivo can only be performed when organs are perfused.
9. Evaluation. PP machines provide functional parameters to further evaluate the organ.

4.5 Differences between normothermic and hypothermic circulation

Pulsatile perfusion techniques can be modified for either hypothermic perfusion (HP) or normothermic perfusion (NP), with HP currently used for kidney preservation.

Despite the fact that NP appears to be a promising option, as it maintains the organ in more physiological conditions -ideal when evaluating organ function ex vivo-, which could be especially useful for ECD organs, we have limited experience of NP. Normothermia would require new perfusions with more nutrients and oxygen transporters to enable effective tissue oxygenation and avoid clotting problems [51,52].

In liver preservation, dual roller pumps are incorporated in similar perfusion systems to perfuse the hepatic artery and portal vein, with different oxygenation rates, mimicking physiological conditions. Normothermic perfusion technology incorporates an extracorporeal bypass system with oxygenation. The system runs at 37°C with oxygenated donor blood. Blood perfuses only the abdominal organs and reports show an improved quality in the organs recovered from uncontrolled DCD; NP improves preservation through ischaemic preconditioning in liver and kidney [53-55].

KEY IDEA

Normothermic perfusion improves the quality of organs, and theoretically it is more appropriate than hypothermic perfusion, but it is both more complex and more expensive, which limits its use.

4.6 Ischaemia-reperfusion lesions and pulsatile devices

Understanding the cellular alterations that occur during ischaemia-reperfusion can help to improve organ preservation systems. During ischaemia, ATP levels decrease by being consumed but not replenished as oxygen is no longer available. As a consequence, the ATP used in active transport that pumps Ca++ out of cells stops, with an increase in intracellular Ca++, and activation of lesion mechanisms (oxygen free radicals, xanthine oxidase system, apoptotic death, eicosanoids). Sodium-potassium-ATPase also stops, provoking the plasmatic membrane imbalance that results in Na++ and Ca++ entering the cell

with water, which causes cell swelling and cytolysis. Anaerobic metabolism and lactate accumulation in the cytosol reduce pH1.

Hypothermia at 4-7°C reduces the cell metabolic rate 10-13 times and ATP consumption is also reduced.

The composition of the perfusion solution is also critical. Solutions must have suitable ionic compositions which include osmotic and oncotic agents controlling the membrane imbalance. Solutions are perfused under pressure, as previously described. Cells are better preserved by opening microvessels.

4.7 Summary

Reperfusion devices enable a continuous, controlled perfusion flow, and consist of a pump, usually pulsatile, with a preservation solution at 4ºC, and the organ submerged in a saline solution in a sterile cassette. Systolic and diastolic pressure and infusion flow are measured, providing useful data on RR, which is a very useful parameter for kidney evaluation and has a direct relation with graft quality. In theory, normothermic perfusion would be the best option, but it is both more expensive and more complex.

With a continuous controlled perfusion flow, reperfusion is ensured, organ vessels kept open, and thus, peripheral resistance decreases, thus avoiding ischaemic-reperfusion injuries.

Pulsatile perfusion is clearly better than SCP and allows the efficient use of organs from ECD or DCD donors, as well as organ evaluation prior to transplantation.

CONCLUSIONS

Donation and transplantation is a process that involves different phases that it is important to understand. One phase consists of organ recovery and preservation. A transplant coordinator must be familiar with details such as:

Organization of multiorgan recovery, which deals with the logistic organization of a multiorgan recovery that involves several surgical teams, usually from different centres. The TPM needs to plan and organize the recovery of organs and tissue, have good knowledge of the procedure and bench surgery, finish the recovery and ensure the storage and transport.

Technical aspects, which include useful information about the surgical teams involved, phases of recovery surgery and cannulation techniques.

Preservation, which consists of the strategies used to minimize any adverse consequences of ischaemia-reperfusion injury for solid organs, in addition to the characteristics and formulation of flush solutions.

Pulsatile devices for preservation, a subject that includes knowledge of organ preservation with pulsatile perfusion devices and an understanding of the differences between normothermic and hypothermic circulation.

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TOPIC 7 - Unit 1

Organ allocation criteria

ORGAN DONATION

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INTRODUCTION

Organ allocation is a complex process that is the interface between organ recovery and transplantation. In accordance with medical science, organ allocation conforms to general immunological and morphological matching principles [1].

Because most candidates for transplantation experience life-threatening functional organ failure, organ allocation requires strong guarantees in terms of justice and equity [2]. Allocation criteria also take into account specific conditions related to the recipient such as emergency situations or low access to transplantation [3]. Organ allocation policies usually strike an empirical compromise between equity, justice, efficacy, practicability, quality of posttransplant results and technical constraints related to organ recovery and preservation [4].

1. SECTION 1: FROM ORGAN SHARING TO ORGAN ALLOCATION

1.1 The historical perspective

In the early stage of transplantation activities, organs from deceased donors were given to local recipients. In the late 1980s, the possibility of saving urgent patients, increasing the number of HLA-matched transplantations, obtaining long-term graft survival by prioritizing full HLA match kidney transplantation, or achieving fair results for hyper-sensitized kidney recipients prompted many countries to establish organ sharing agreements and define categories of patients that could benefit from allocation priorities [5-8]. Another crucial step in organ allocation was the progression towards a patient-based allocation system. This development meant that optimization of organ allocation became a major issue.

KEY IDEA

The scarcity of organs implies that they should be used with the highest possible guarantees of outcome.

1.2 The geographical diversity of organ allocation policies

Different countries have implemented a wide range of allocation systems, the diversity of which may result from variations in cultural and historical contexts. The importance given to "medical decision", the concept of "local priority", the geographical distribution of organs, "organ sharing" and evidence-based medicine in allocation policies are all examples of possible reasons for such variations.

Individual medical decisions play a central role in some countries: the waiting lists are managed at centre level and interference with medical decisions is limited to general principles (ABO matching, general ethical statements). On the other hand, some countries have defined very precise policies to regulate both the allocation decision and inclusion on the waiting list.

DID YOU KNOW?

In most countries, allocation is a mixture of nationwide allocation priorities and general donor-recipient matching principles, combined with regional and local allocation practices.

1.3 Organ allocation procedures

The allocation procedure is triggered by the identification of a deceased donor. It comprises the distribution of all the organs recovered to a group of recipients. The procedure ends with the transplantation of each organ recovered to the final transplant recipient.

The allocation procedure is a non-stop process that continues 24 hours a day, 365 days a year. It involves the management of offers to transplant programmes and is interrelated with organ and tissue recovery; allocation also has to deal with logistical issues related to the transportation of organs and surgical staff. The allocation of a given organ usually conforms to a predefined scheme and the data required for organ allocation must always be available. In addition to any other logistical issues, information related to lab tests, HLA and crossmatches must be available.

KEY IDEA

"We must have a policy in place that moves decision-making from the more visceral, good-feeling approach to a rational decision based on a projected outcome that is more appropriate for maximizing the utility of our scarce resources. Heartbreaking, yes, but just." [9]

1.4 Centre-based allocation systems

In centre-based allocation systems, organ allocation is a distributed decision. The organ is proposed to a transplantation centre by the transplant coordinator, usually according to a geographical scheme referred to as "local priority". The ultimate allocation decision is the responsibility of the transplant centre medical staff, who will choose the most suitable patient from the local waiting list. Under this approach, a national waiting list is not necessary unless it is required by law as mandatory since this is an efficient means to support transparency, traceability and auditing of the allocation system.

DID YOU KNOW?

The "local priority" system is a "centre-based" approach to organ allocation. It links the level of transplantation activity to the level of organ recovery in a given area. It may provide a strong incentive for organ recovery, but it deals with few prevalent recipients on the waiting list.

1.5 Patient-based allocation systems

With a patient-based allocation system, the process of organ allocation itself is centralized. However, transplant physicians have already discussed the allocation schemes over a long period of time. Before its implementation, it is possible to simulate a new allocation scheme. A patient-based allocation scheme typically has a scoring system that takes into account multiple and contradictory allocation criteria. Such an approach implies that all patients must be registered on a national or supra-national waiting list. The management of the waiting list and the allocation schemes are supported by an information system. The transplant coordinator will offer a given organ to transplant centres following the rank order computed for each patient on the waiting list according to their score.

DID YOU KNOW?

In a centre-based allocation system, offers are made for a specific patient.

1.6 The need for review and evaluation of allocation policies

Evaluation of results ensures that organs are allocated efficiently, both to obtain the maximum benefit from a donated organ and to minimize the distances that organs need to travel between the donor hospital and the transplant centre. Another key consideration of any allocation scheme is to ensure equity of access for patients, both to the transplant list and subsequently to any suitable donated organs.

Organ allocation schemes need to be subject to regular review that ensures they are adhered to appropriately and are suitable for the population they serve. Reviews should include examination of factors such as the proportion of the national transplant list according to different blood groups, time on the waiting list and waiting time before transplantation.

KEY IDEA

"The evaluation of the organ allocation process is required to ensure that it is fair, transparent and consistent with the underlying allocation schemes".

1.7 The interest of simulation tools

For ethical and practical reasons (it is difficult to randomize patients between allocation regimens), organ allocation is poorly accessible for prospective studies. In countries that record data on donors, recipients and allocation processes, the allocation policy is usually evaluated by means of cyclic studies. Such studies usually motivate changes in allocation policies when results demonstrate anomalous outcomes or adverse side effects.

Another trigger for changes in allocation policies is the publication of new biomedical facts [10] or the emergence of a new allocation paradigm relevant to organ allocation, for example: the shift from best posttransplant results to best individual benefit as an allocation criterion [11,12].

KEY IDEA

Simulation is a relevant means to compare various allocation schemes and forecast the behaviour of a new system according to its parameters [13].

1.8 Summary

No definitive solution has been reached for organ allocation: it remains an open and changing issue. It is to be expected that further changes will arise in the future as medical science develops, the needs of the population vary, and demographic changes occur.

More accurate and comprehensive allocation criteria that address the individual benefit of transplantation are likely to profoundly change the approach to organ allocation.

Finally, the results of surveys and statistical evaluation will progressively show whether the established objectives of allocation schemes have been met in terms of equity, transparency, practicability and efficacy.

KEY IDEA

The use of simulation tools to promote evidence-based debate with transplant centres is likely to support changes in allocation policies.

The key-points in organ allocation clearly form part of the functions and responsibilities of national transplantation organizations in Europe [14]. The Alliance-O Consortium white paper provides recommendations [15].

2. SECTION 2: GENERAL ORGAN ALLOCATION CRITERIA

Allocation policies must not be influenced by favouritism or discrimination based on political influence, national origin, race, sex, religion, socio-economic status or personal/behavioural history. Policies must be designed to be as equitable as possible while making the best use of the limited number of organs.

This section provides the general criteria to ensure equitable access to transplantation and guarantee, as far as possible, that no group of patients waits longer than another group.

These criteria may be used both in centre-based and patient-based allocation schemes.

2.1 Urgency

The objective of this priority is to ensure equitable access to transplantation for a patient whose condition means that they cannot wait for a long period on the waiting list.

An "urgent priority" may be given to patients on a waiting list for heart, lung or liver when the recipient is suffering a rapidly deteriorating disease. It can also be given to kidney or small bowel recipients when transplantation becomes the only medical solution for life-threatening conditions. For each organ, the recipient must fulfil specific criteria for inclusion on the urgent waiting list.

In most countries, nationwide allocation priority is given to patients who are suffering life-threatening conditions so that they may benefit from transplantation.

2.2 ABO blood group

The immunological possibility of offering organs from blood group O donors to all recipients, and organs from A or B donors to AB recipients cannot be systematically followed without adverse effects on the transplant access rates for O recipients [16]. To maintain equity, organ allocation usually respects blood group identity between the donor and recipient. Restricted blood group compatibility is often used for subgroups of patients with poor access to transplantation: it consists of the allocation of organs from A donors to AB recipients, and the allocation of organs from O donors to B recipients. However, such prioritization should not discriminate against blood group O recipients.

DID YOU KNOW?

Incompatible blood group transplantation is no longer an insurmountable obstacle in transplantation medicine, nor for living kidney donation or the transplantation of organs from deceased donors [17,18].

2.3 Geography and distance between donor and transplant centres

The geographical distribution of donor centres in relation to transplant centres is a major allocation criterion in centre-based allocation systems. It is also an important criterion in many patient-based allocation systems because it is necessary to deal with logistical constraints and minimize cold ischaemia time. Depending on the type of organ, the entire process from organ recovery to transplantation may last no longer than a few hours. In an allocation system where scores are calculated to define the ranking lists, a recipient close to the donor centre may receive more points than a recipient who lives far away from the donor centre.

2.4 Access to allocation priorities

Access to allocation priorities often implies a demand from the transplantation centre that will be examined by the staff of the organ allocation authority or by external experts. In some situations, special priorities may be considered in accordance with the allocation policy, for instance, paediatric recipients, multi organ transplants, retransplant within a given time (e.g., after acute rejection).

In some areas, policies give priority to people who are themselves registered donors. Such policies provide an incentive to register as organ donor.

2.5 Living donation

Organ donation during lifetime has become a source of organs for patients on the waiting list. The use of an organ from a living donor is generally restricted by law to a related recipient. The emergence of "living donor clubs" in some countries will certainly raise the ethical issue of organ allocation in this context. Donor and recipient matching constraints are taken into account in the selection of donors.

Living donors may donate a kidney, a portion of liver or, less commonly, a portion of lung or small intestine.

The number of living donors depends on how much a country supports and promotes living donation, which may vary widely from one area to another. The major ethical issue in living donation consists of the risk the donor is exposed to. Internationally, numerous guidelines have been developed outlining acceptable donor evaluation and donor acceptance criteria [19].

Living donors should benefit from a lifelong follow-up in order to ensure the evaluation of postoperative outcome [20].

DID YOU KNOW?

Living donation chains enable us to overcome the obstacle of biological incompatibility, which can prevent the transplant of a kidney offered by a living donor to a loved one. American surgeons and physicians were the first to link together donor/patient pairs in open-ended "chains" of reciprocity that rely on altruism (e.g., Figure 1).

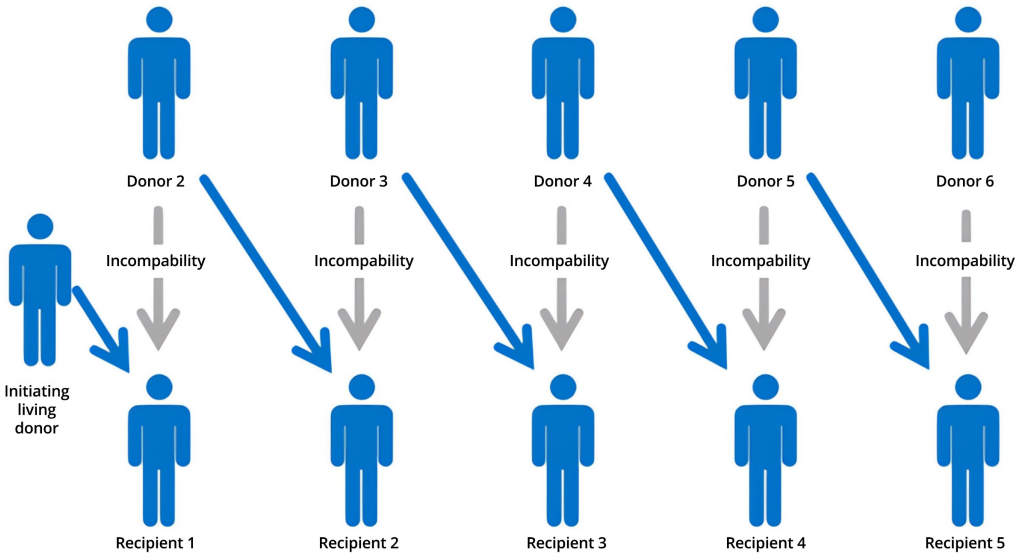

Figure 1. Kidney donor.

2.6 The individual benefit of transplantation: the “therapeutic zone”

For liver or heart transplantation, less ill patients have the best posttransplant survival rate, but a higher risk of dying after receiving a transplant than if they had remained on the waiting list [21,22]. The model for end- stage liver disease (MELD) score was primarily used to improve transplant access rates for critically ill patients and hence, to minimize the occurrence of death while on the waiting list. However, it has also become a good predictive tool to ascertain which patients will receive no individual benefit from transplantation: potential recipients with a MELD score below 15 have a higher risk of death when transplanted than if they remain on the waiting list.

Below this cut-off score of 15, transplantation is “futile”, that is to say it occurs “too early”. In the case of liver transplantation, critically ill patients still have an individual benefit from transplantation. Conversely, for other organ transplantations, there may be a degradation of individual benefit in very ill patients, with the covariate adjusted hazard ratio of death defining “too late transplantations” above another cut-off point. The “therapeutic zone” of transplantation is represented by scores that are between the two cut-off points.

3. SECTION 3: DECEASED DONOR KIDNEY ALLOCATION

Kidney allocation seeks to substantially enhance posttransplant survival benefit, to increase access for biologically disadvantaged candidates and to use the maximum number of donated kidneys. Most policies take into account scores to assign points to highly sensitized recipients.

Current kidney allocation criteria consider characteristics of both the donor and the potential recipient. A combination of factors working together determines who receives which organ.

These factors include:

- Tissue matching
- Blood type
- Antibody levels
- Waiting time
- Age
- Geographic factors (depending on the area)

In common with other organs, kidney allocation should be equally efficient and effective. In many countries, nationwide allocation priority is given to patients who have no further possibility of dialysis due to a lack of access to either haemodialysis or peritoneal dialysis, or because of severe neuropathy.

3.1 Age matching

3.1.1 Recipient age

Due to the high benefit of kidney transplantation compared to dialysis in young patients, children (aged <16 or <18 according to the country) receive a national and/or a regional allocation priority for kidneys under most allocation schemes. Giving priority to children or to young transplant candidates has both an ethical and a utilitarian motivation.

3.1.2 Donor-recipient age matching

Age matching is often claimed to be a major allocation criteria by transplant physicians when deciding whether to accept a proposed kidney. It may also be included among the allocation scoring functions in patient-based allocation systems. It is usually a condition in paediatric kidney priorities.

DID YOU KNOW?

There is an "Old For Old" kidney allocation principle? For further information, see Eurotransplant Senior Program [25,26].

3.1.3 Alloantibodies

HLA antibodies

To minimize the risk of a positive crossmatch, recipients with alloantibodies against donor HLA A, B, DR or DQ are usually excluded from the list of potential recipients for this given donor.

PRA level

The percentage of panel reactive antibodies (PRA%) is used to identify immunized (PRA from 5 to 10%) and hyper-immunized (PRA from 80 to 85%) patients. To improve their access to transplantation, such patients benefit from national/regional allocation priority for very well matched donors (0 or 1 mismatches) in many allocation systems. Access to allocation priority is automatically computed according to the PRA level each time an organ donation is performed. These allocation priorities are usually combined with blood group ABO compatibility rules. Acceptable antigens can be determined for hyper-immunized patients: this "extension" to their own HLA phenotype helps find more suitable donors, minimize the risk of a positive crossmatch and obtain good posttransplant results [27].

3.2 Donor-recipient HLA matching

Human leukocyte antigen (HLA) matching significantly influences posttransplant results. Although the importance of HLA matching has come into question now that new immunosuppressive treatments exist, multivariate evaluation of posttransplant results still demonstrates an influence of HLA matching.

3.2.1 Class I

(A and B)

3.2.2 Class II

(DR, DQ)

There are two ways to compute HLA matching: the number of HLA-matches and the number of HLA mismatches, the latter deals more accurately with homozygous loci. Full-match or zero-mismatch patients usually receive a nationwide allocation priority, with or without a condition on their PRA-level. In patient-based allocation scoring functions, DR can receive more points than A and B matching. The possibility of optimizing age and HLA matching in centre-based allocation systems is very limited. Only large scale organ sharing and multivariate scoring as in patient-based allocation systems tend to optimize age and HLA-matching without adverse effect on cold ischaemia time, as the distance between donor and recipient hospitals can be included in allocation criteria.

3.3 Donor-recipient CMV matching

In the context of kidney transplants, CMV may be a significant underlying cause of morbidity and mortality. In order to avoid transmission by transplantation, special priority can be given when both donor and recipient have no detectable IgG anti-CMV antibodies in plasma.

3.3.1 Duration of dialysis and time on the waiting list

Principles of social justice and ethical considerations state the waiting time as a major criteria in the allocation of scarce resources. Waiting time is most often calculated using time on the waiting list, and some allocation schemes also take the duration of dialysis into account.

3.3.2 Local/regional priority

Geographic criteria and local precedence may assign priority to a recipient in the donor hospital's area.

3.4 Summary

The percentage of panel reactive alloantibodies (PRA%) is used to identify immunized (PRA from 5 to 10%) and hyper-immunized (PRA from 80 to 85%) patients and to increase access to transplantation for biologically disadvantaged recipients.

Donor-recipient HLA matching significantly influences posttransplant outcomes.

Transmission of CMV from the donor to recipient may be a cause of morbidity and mortality in kidney transplantation.

4. SECTION 4: DECEASED DONOR LIVER, PANCREAS AND SMALL BOWEL ALLOCATION

4.1 Introduction

For the allocation of abdominal organs, certain general allocation rules are followed, such as blood group compatibility and priority for high urgency.

This section provides information about special requirements in the allocation of the liver, pancreas, and small bowel.

4.2 Liver allocation

In the allocation of donated livers to patients waiting for transplantation a compromise must be made between medical urgency and efficiency: a lifetime without a liver versus a lifetime with a liver transplant.

Currently, there are four main allocation criteria used for liver allocation:

- Category of liver disease
- Severity of liver disease
- Time on waiting list
- Recipient age

4.3 Category of liver disease

The nature of the underlying liver disease is very important in liver transplantation. Patients with acute, life-threatening liver failure such as fulminant hepatitis, acute Wilson's disease, Budd-Chiari Syndrome, early graft failure, anhepatic conditions (trauma, liver resection) require highly urgent access to transplantation as their life expectancy without a transplant is very short (a few days). Such patients benefit from national or supra-national allocation priorities in all allocation schemes, with some variations in definitions between one country and another. Chronic liver diseases require different allocation modalities depending on whether the condition is a chronic end-stage liver failure due to cirrhosis, malignancy or a non-cirrhotic liver disease requiring liver transplantation.

4.4. Severity of liver disease

The MELD and PELD (Paediatric end-stage liver disease) scores are the numerical scales currently used in patient-based allocation scoring for cirrhotic, non-urgent patients to optimize "just-in-time" transplantation. They can also be used at local level to prioritize patients with the highest MELD/PELD score but have limited impact in terms of optimization of liver use when the local waiting lists are small. Some schemes apply an artificial MELD score to non-cirrhotic patients.

Both MELD and PELD scores include objective and verifiable medical data and are approved as a good predictor of the risk of death in patients with cirrhosis who are listed for transplantation. Such data include:

MELD

INR, creatinine, bilirubin for liver recipients >12 years.

PELD

INR, albumin, bilirubin, growth failure and age when listed for transplant, for recipients <12 years.

4.5 Other liver allocation criteria

4.5.1 Time on the waiting list

Instead of an artificial MELD score, the points allotted to patients with liver malignancies can increase over time until the patient reaches the maximum score, which offers them good access to transplantation before they can no longer be transplanted due to metastasis. Time on the waiting list together with disease-specific severity criteria (amyloid neuropathy, Rendu-Osler disease) can be used for other non-cirrhotic, non-tumoral liver diseases.

4.5.2 Age of the recipient

Paediatric priority is generally used in most allocation schemes, both for ethical reasons and for morphological matching. Split liver transplantation is currently used for priority patients and paediatric priority patients.

4.5.3 Morphological donor-recipient matching

Morphological donor-recipient matching is more frequently used as the criterion for acceptance/refusal of a graft than for allocation purposes. The transplant team will not accept small size livers in order to avoid liver dysfunction in the case of a "small-for-size" liver graft.

4.6 Pancreas allocation

The pancreas is most frequently transplanted in conjunction with a kidney in patients with type 1 diabetes where the disease has also caused kidney failure. A low number of patients with diabetes receive a pancreas graft alone.

Pancreas islets are also transplanted to selected patients after their extraction from the donor's pancreas. They are transplanted into the liver of the recipient patient. Short ischaemia time is one of the most important factors to ensure a large number of extracted islets from the donor pancreas.

In common with kidneys, pancreas and islet allocation is also regulated by HLA donor-recipient match.

4.7 Small bowel allocation

Intestinal (small bowel) transplantation is an established treatment for selected patients with inadequate intravenous access, life-threatening line sepsis, advanced liver disease, or severe fluid/electrolyte disturbances with intestinal failure. Recipients may require only the intestine, or a multivisceral transplant (liver, bowel, pancreas, with or without stomach), or the intestine with any combination of kidney or pancreas transplantation. If there is a mismatch between donor and recipient size, components of the recovered grafts may be reduced to enable transplantation.

Allocation schemes for small bowel include:

- Blood group compatibility
- Weight and age match
- Geographic parameters
- Rules for combined (multi-transplant) transplantations
- Waiting time
- Urgency

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TOPIC 8 - Unit 1

Uncontrolled DCD

ORGAN DONATION

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Since the introduction of the concept of brain-death, following the declaration of the Ad Hoc Committee of Harvard Medical School in the 1960s and the agreement on the criteria for diagnosis of brain death, heart-beating (brain dead) donors have become the main source of organs for transplantation. Despite efforts to optimize donation programmes in brain death, with an epidemiological change in their profile, the continuous increase in organ transplants, and a growing demand for organs has led to a shortage of organs and longer waiting lists. For these reasons, transplant centres have developed programmes for donation after circulatory death (DCD) as alternative sources of valid organs for transplantation.

A DCD is a donation that takes place after death has been confirmed by using circulatory criteria and occurs in patients for whom donation after brain death is not possible or appropriate.

The subject of DCD is complex and raises significant ethical and logistical concerns. Traditionally, DCDs have been considered as marginal donors who require rapid organ retrieval after death, because warm ischaemia following cardiac arrest (CA) has significant deleterious effects, and most organs are highly sensitive to periods of ischaemia. Several factors have contributed to minimizing this effect:

- Better knowledge of the mechanisms involved in ischaemia-reperfusion injury.
- Organ preservation techniques.
- Development of new logistic models.
- Long-term outcomes of DCD that are similar to brain-dead donation.

For many transplant centres, DCD programmes could represent a partial solution to the shortfall between available organs and organ demand.

INTRODUCTION

Uncontrolled or unexpected DCD (u-DCD) is increasingly accepted and used, mostly in Europe; however, it is still limited to a few countries. In particular, Spain and France have improved their rates of transplantation using u-DCD and demonstrated good clinical outcomes. The expansion of u-DCD must occur under the guidance of highly experienced centres and countries due to ethical issues, legal barriers and the technical complexity of the procedure.

In comparison to DBD, u-DCD are usually younger individuals who have led a completely normal life until the time of their death. They are patients who have suffered a sudden death but have not previously been admitted to an ICU, or who have not been exposed to hospital-acquired infections, catecholaminergic storm or the inflammatory process associated with brain injury or brain death.

Although it requires more complex organization, u-DCD provides an opportunity to significantly expand the pool of potential deceased organ donors.

The objectives of this unit are to:

- define the inclusion and exclusion criteria for u-DCD;
- describe out-of-hospital and in-hospital procedures;
- learn how to perform the determination of death by circulatory criteria;
- learn about available organ preservation techniques;
- review some outcomes of u-DCD organ transplants.

1. SECTION 1: TERMINOLOGY AND DETERMINATION OF DEATH

1.1 Organ donor terminology

The terminology used to refer organ donors with a determination of death following cardio-circulatory and respiratory criteria has evolved during recent decades in parallel with the development of the medical concept of the diagnosis of death.

» Non-heart-beating donor (NHBD). This term was adopted to differentiate organ donors who had suffered a cardio-respiratory arrest from donors who had died with a beating heart in a brain death situation. In 1995, during the first International Workshop on Non-Heart-Beating-Donors, Kootstra et al. determined what is known as the Maastricht Classification. This classification has four different categories, each with their own peculiarities concerning ischaemia time, preservation, viability of organs, ethical aspects, etc. Even, today, there remains widespread variability in the practice of NHBD in European countries.

» Donation after cardiac death (DCD): was the term that reflected the criteria used for the diagnosis of death, defining which vital organ was clinically evaluated to determine human death.

These two previous terms were initially adopted by most teams, with DCD used to distinguish between this group of donors and donors after brain death (DBD).

» Donation after circulatory death (DCD): medical advances permitted physicians to generate breathing and a heartbeat when the capacity to spontaneously breathe had been irreversibly lost, and currently certain techniques may even be used to replace cardiopulmonary functions for days or weeks. The accepted standard for determining death is the permanent absence of spontaneous respiration and circulation. So, a new concept for defining organ donors after cardio-respiratory arrest arose, and many centres now use a "circulatory" definition rather than a "cardiac" one, as death is based on the loss of circulatory rather than cardiac function, hence the modified meaning of the abbreviation DCD.

» Donation after circulatory determination of death (DCDD): this term highlights that the death was determined by circulatory criteria. This was the term selected in the description of the donation process of deceased people recently published by the WHO.

1.2 More classifications

In addition, DCD may also be classified as controlled or uncontrolled.

» Controlled or expected DCD (c-DCD) occurs after a planned withdrawal of treatment and cardio-pulmonary arrest following non-survivable injuries/illness, or when treatment is considered futile. Cardiac arrest is always witnessed by a medical team and may be expected, so the transplant team can prepare the procurement process.

» Uncontrolled DCD (u-DCD) describes donation after a patient is dead on arrival or has ongoing CPR that fails to restore spontaneous circulation. Cardiac arrest (CA) is unexpected; the medical or transplant team is unaware of the death and has no control over the times or circumstances under which death occurs.

Donors can also be classified according to the phase of the donation process in which the person suffering the cessation of circulatory function remains. The WHO recently published this classification in the "Critical pathways for organ donation" as part of an initiative to address common challenges and make recommendations on how to maximize deceased donations (including DBD and DCD). The pathways provide clear definitions for possible, potential, eligible, actual, and utilized donors, enabling better national and international comparisons to be made (Figure 1).

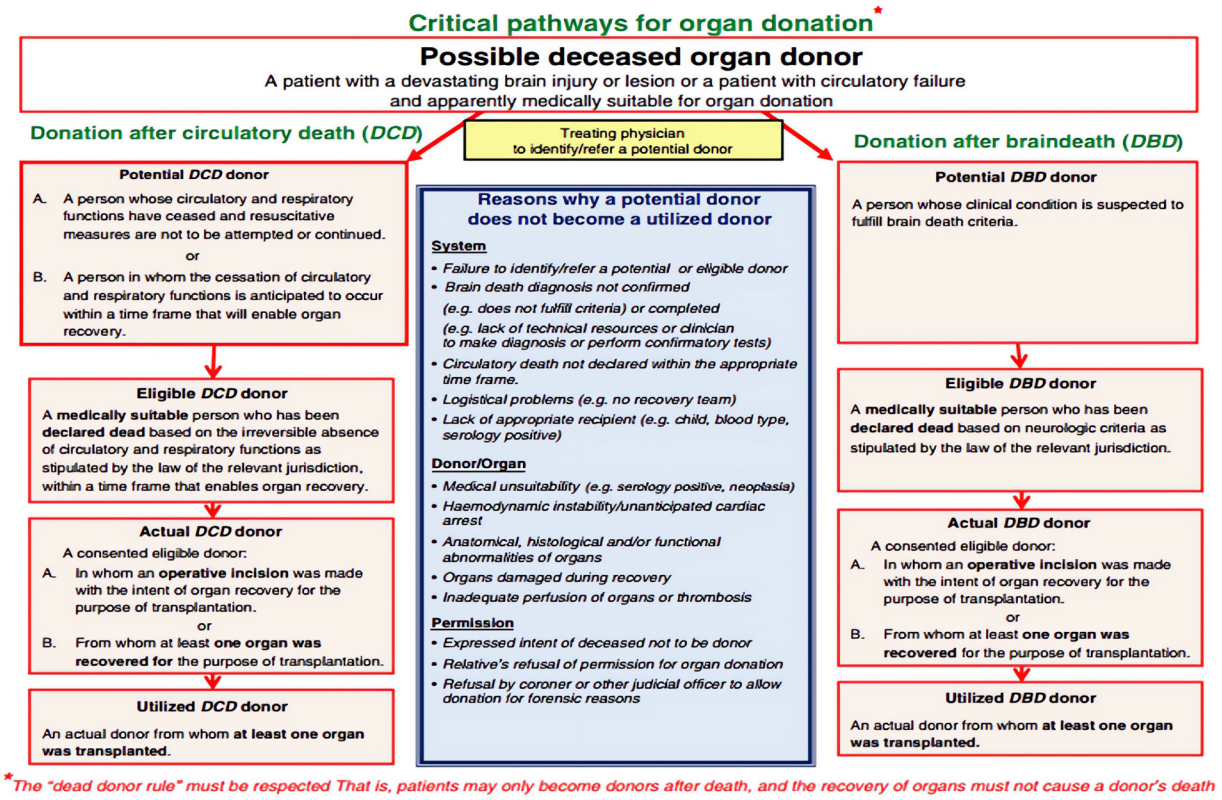

Figure 1. The critical pathway for deceased organ donation.

1.3 Certification of death

The medical definition of death is a scientific issue that is always based on the best available evidence and involves the irreversible loss consciousness and the capacity to breathe, essential capacities controlled by the brain. This may occur due to either an intra-cranial or an extra-cranial cause.

Death can be diagnosed using three different sets of criteria: somatic, circulatory or neurological:

» Somatic criteria are those that can be applied by performing a simple external examination of the corpse, with no requirement to search for signs of life or evidence of internal organ function. Examples include rigor mortis, decapitation or the presence of decomposition, which are the oldest criteria used for the diagnosis of death.

» In the 17th century, William Harvey described the circulation of blood and the function of the heart as a pump. Based on this concept, death occurs when the heart and circulation stop.

» In 1968, the Ad Hoc Committee of Harvard Medical School culminated a decade of research and debate with the publication of neurological criteria for the diagnosis of death.

The most appropriate criteria to use are determined by the circumstances in which the medical practitioner is called upon to diagnose death.

In a sudden CA, the primary goal of resuscitation is to save the patient's life. Nonetheless, in case of the failure of CPR, the goal of resuscitation could change to the preservation of organs for possible donation. Procedures should avoid any possible interference from the donation/transplant team in the resuscitation team's decision making process.

1.4 Circulatory death

Standardization of diagnostic procedures is necessary in this case, because for the purposes of organ donation a point in time is required in order to move forward with a DCD. With u-DCD, death is declared using circulatory-respiratory criteria. Circulatory criteria are based on the knowledge that the brain suffers anoxic structural damage when cerebral circulation halts.

There is a consensus that mechanical asystole is sufficient and electrical asystole is unnecessary because the standard for declaring death requires the absence of circulation, not the absence of electrical function. Neither circulation nor heartbeat can occur during electrical asystole in the absence of external cardiac or circulatory support.

Traditionally, physicians determined mechanical asystole by indirect CA measures by palpating arterial pulses or listening for a heartbeat. In u-DCD, to prevent errors in the determination of death, these habitual means may be inadequate to distinguish a complete loss of circulation. It may, therefore, be necessary to use complementary tests to determine the absence of cardiac electrical rhythm (ECG), pressure -measured through an arterial catheter- or aortic flow by means of echocardiography.

The urgency inherent in DCD, along with the required adherence to the dead donor rule, dictate the establishment of a precise waiting period long enough to ensure the irreversibility of cardio-circulatory functions but short enough to maintain organ viability. Most guidelines or statements mention the terms "irreversibility" of circulation and "consciousness", but not all give definitions for the meaning of the terms. Irreversibility is recognized as the persistent cessation of function during an appropriate period of observation and implies that circulation cannot be restored by means of any known technology and that a return of spontaneous circulation (ROSC) will not occur. This observational period, also called the "no touch" or "hands off" period, can range from 2 to 20 minutes, although in most countries it is stipulated as 5 minutes.

DID YOU KNOW?

The first organ transplants were from donors after circulatory death, until brain death criteria were established in 1968 (A definition of irreversible coma. Report of the Ad Hoc Committee of the Harvard Medical School to Examine the Definition of Brain Death. JAMA. 1968;205:337-40).

1.5 Warm ischaemia

The ischaemia resulting from CA induces damage which may result in reduced graft function in the recipient and can exacerbate the deleterious effects of cold ischaemia. An accurate knowledge and management of warm ischaemia (WI) is critical when assessing the viability of DCD organs for transplantation.

Ischaemic damage implies severe metabolic disorders. A decrease in oxidative phosphorylation leads to the degradation of ATP and the accumulation of xanthine and hypoxanthine, important sources of superoxide radicals that can induce cytotoxicity. The loss of Na-K-ATPase integrity also results in the loss of the transmembrane electrochemical gradient, which results in calcium, sodium and water entering the cell, which in turn produces an activation of phospholipases, proteases and nucleases. In addition,

changes in microcirculation occur during ischaemia, which include increased cell volume with vessel protrusion, leukocyte adhesion to the endothelium, platelet aggregation, and vasoconstriction, with an imbalance between vasoconstrictor and vasodilator molecules such as nitric oxide (NO) and endothelin (ET). Other phenomena that occur are the activation of Kupffer cells and complement factors. The consequence of this is the production of proinflammatory mediators, leukocyte migration and adhesion, cell degradation and apoptosis.

1.6 Ischaemia in u-DCD

During circulatory arrest, systemic ischaemia and red cell stasis provoke the activation of the inflammatory cascade, tissue factor release and thrombin generation. Evidence suggests that endogenous fibrinolysis may be impaired in this context, leading to the formation of clots in end-organ microvasculature. Some authors have suggested that the viability of organs from u-DCD may be improved through the application of fibrinolytic therapy, but recent studies have shown that patients with sudden circulatory arrest, considered u-DCD, suffer from endogenous hyperfibrinolysis, not hypercoagulability. It seems that the incidence of hyperfibrinolysis increases in direct relation to the length of warm ischaemia. So, there is no role for additional treatment with fibrinolytic drugs in u-DCD.

In u-DCD, total WI time (WIT) is defined as the time between circulatory arrest and the initiation of organ preservation manoeuvres. This period includes: an asystole phase, time of CPR, observation period for diagnosis of death by circulatory criteria, cadaveric preservation with mechanical thoracic compressions and ventilation, and surgical cannulation of femoral vessels. Depending on the different protocols, this period may range between 90 to 150 minutes.

The time of circulatory arrest, when advanced CPR has not yet been started, has been identified as the most critical time of the procedure. This period should be under 30 minutes in kidney transplantation, or less than 15 minutes in the case of liver recovery. This period is also known as the “no-flow period” or “true WIT”. The period including CPR, death diagnosis, “no touch” period and cannulation until organ preservation is also known as the “low-flow period”, “partial WIT” or “relative WIT”.

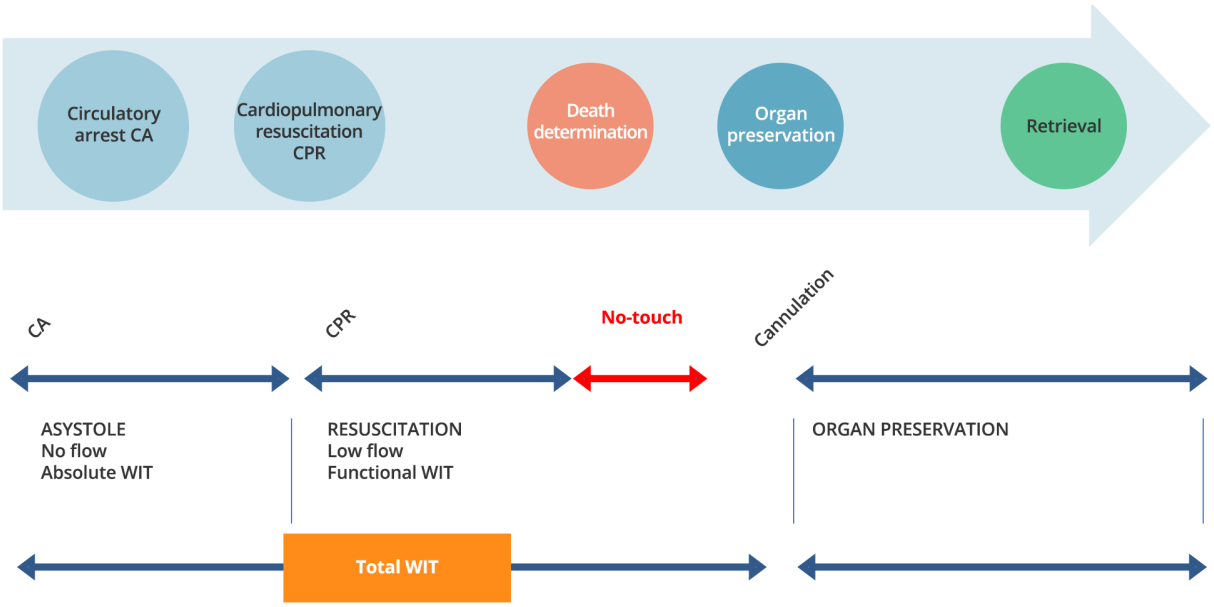

Figure 2. Uncontrolled DCD process.

1. No flow: Kidney <30 min; Liver <15 min. 2. CPR duration: >30 min. 3. No-touch period: 2 min to 20 min. 4. Total WIT: 120 min to 150 min. Transplant International 2016; 29:749-759.

1.7 Inclusion and exclusion criteria for u-DCD

The selection criteria for potential uncontrolled DCD must be very strict to ensure organ viability.

- Age between 1 and 65 years (variable according to different protocols).
- Asystole period: time between cardiac arrest and cardiopulmonary resuscitation less than 15 minutes (<30 minutes in some protocols).
- Warm ischaemia time: period between cardiac arrest and start of organ preservation less than 120-150 minutes.
- Absence of external signs of parenteral use of drugs.
- Absence of bleeding in thorax and/or abdomen.
- Absence of systemic infection or neoplasia.

2. SECTION 2: PROCEDURES AND LOGISTICAL ISSUES

2.1 Out-of-hospital procedures

Emergency services play a fundamental role in the detection of potential u-DCD. When a person suffers a sudden circulatory arrest, emergency medical physicians arrive at the scene and initiate CPR, attempting to resuscitate the patient. Performance of CPR must follow international guidelines, such as those of the American Heart Association or the European Resuscitation Council. If the patient does not recover circulatory function after the estimated time of resuscitation, the patient can be considered an eligible u-DCD. The emergency staff should conduct an initial assessment of the main inclusion and exclusion criteria. From this moment, mechanical ventilation and external thoracic massage are continued to ensure organ perfusion until the patient arrives at a hospital.

The transplant coordinator is contacted, and an initial evaluation is made to assess the viability of the potential u-DCD in addition to verifying the time of asystole and time of reanimation. It is the TC who is responsible for accepting the transfer of the patient and notifying all members of the transplant team, emergency and/or intensive care departments.

During transportation of the patient, the emergency team ensures oxygenation and ventilation (orotracheal intubation with iFO_2 100% and a frequency of 15 per minute), thoracic massage (100 compressions per minute) and places a venous access of antecubital choice, avoiding overhydration and not administering drugs. Mechanical compressions have been associated with less hands-off time and higher perfusion pressures during CPR, as well as fewer discarded organs due to poor perfusion.

Out-of-hospital emergency services need to develop procedures for considering u-DCD, with a specific reference donor centre. Direct contact with the transplant coordinator can facilitate a better evaluation and follow up of the cases before arrival at the hospital. It is recommended that arrival at the receiving hospital should be within 90 minutes of the initial circulatory arrest. Transfer of the patient should be fast and effective, and include information regarding patient care, with special importance given to the times of the process, age, gender, previous pathologies if known, possible cause of circulatory arrest, existence of haemorrhagic injuries, endotracheal tube status (presence of blood or vomiting), initial rhythm, ROSC during resuscitation, etc.

2.2 In-hospital procedures

Certification of death is made on the patient's arrival, and it is based on the demonstration of unequivocal and irreversible absence of electrocardiographic activity and spontaneous breathing for a period

of at least 5 min (the "no touch" period). The transplant coordinator remains uninvolved until death has been declared, performing only an external evaluation of the suitability of the donor but not interfering with management of the patient.

The transplant coordinator must be present when the u-DCD arrives at the hospital, and it is the TC who coordinates all the teams that will participate in the donation process if, with the information available at that time, the potential u-DCD fulfils the general criteria for organ donation and the specific ones for DCD.

Once death has been certified and the eligible u-DCD has been accepted, the steps for donor preparation begin. Blood samples are obtained (biochemical test, blood group, Rh and serology), the u-DCD is immediately heparinized (3 mg/kg of body weight, IV); orotracheally intubated (if not already); and subjected to external ventilation and cardiac massage by means of a mechanical thoracic compressor. After this, preservation techniques, which must be set up within 120-150 minutes from the time of circulatory arrest, are initiated.

2.3 Donation authorization

Until we are able to ascertain the deceased patient's wishes, preservation techniques can be started without the family's consent, as long as presumed consent is accepted by local legislation. The family or next-of-kin must be located as soon as possible to communicate what has happened and to obtain their informed consent for organ donation.

Death is communicated by the physician who was in charge of the patient upon their arrival at the hospital, if possible, with the presence of the transplant coordinator in order to identify the different family members and to establish initial contact.

The circumstances of a u-DCD imply the sudden and unexpected death, often of a young patient, which means that the situation of mourning and assimilation of the bad news can make communication difficult or almost impossible.

Unlike DBD, the time available to obtain the family's consent is limited due to the characteristics of u-DCD, and the need for a fast response will frequently be transmitted to the family. Information regarding organ preservation techniques must always be explained and clarified.

The transplant coordinator must request the clinical history of the potential donor, investigating the general aspects that allow validation of the donor, and any specific aspects that may affect the viability and functionality of the organs to be transplanted.

2.4 Preservation techniques

Traditionally, u-DCD have been considered marginal donors, mainly due to the high incidence of primary non-function (PNF), delayed graft function (DGF), and a lower graft survival when compared to organs from DBD. Organ hypoperfusion during circulatory arrest (warm ischaemia), cold storage (CS) of organs (cold ischaemia) and their subsequent reoxygenation following transplantation (ischaemia-reperfusion) are considered the main factors responsible for the poorer outcomes initially obtained. This issue has changed in recent years thanks to better knowledge of the mechanisms involved in ischaemia-reperfusion injury, so protective strategies against the "insults" that inevitably occur in these organs may be included in u-DCD protocols.

After identification of a potential donor, the main objective is to attempt to reduce warm ischaemia time to the minimum and start *in situ* organ preservation measures as soon as possible. There are different techniques to preserve u-DCD organs, some of which focus on stopping ischaemic damage by reducing the cellular metabolism through fast cooling; others try to return to the physiological situation prior to the circulatory arrest, recovering cell metabolism and energetic load.

KEY IDEA

Each hospital adapts the organizational and operational system of procedures for u-DCD according to their centre's characteristics and needs.

2.5 Abdominal organ preservation

2.5.1 Rapid retrieval

This concept covers maintenance of mechanical thoracic compression, ventilation and abdominal counter-pulsation until transfer of the patient to the operating theatre, where fast perfusion and recovery of abdominal organs are performed.

2.5.2 *In situ* perfusion

In situ perfusion (IP) consists of femoral cannulation (Figure 3) with a double balloon triple lumen catheter (Figure 4) placed in the abdominal aorta between the aortoiliac bifurcation and the superior mesenteric artery, to perform cold perfusion of kidneys with a cold organ preservation solution (Figure 5). A drainage cannula is also placed in the femoral vein to allow washing of the blood content. A pump can be used to maintain perfusion pressure at around 70-80 mmHg. Once intravascular lavage has been performed (haematocrit <0.03l/l), the system can be closed with a continuous cold recirculation of the preservation solution.

In cases where there is a loss of vascular integrity, this may represent the only valid preservation technique, although most organs are discarded due to excessive ischaemia.

Different organ preservation solutions have been used (HTK, Belzer solution, IGL-1, Celsior©). The use of several drugs such as vasodilators, anticoagulants and fibrinolytics has also shown beneficial effects in organ

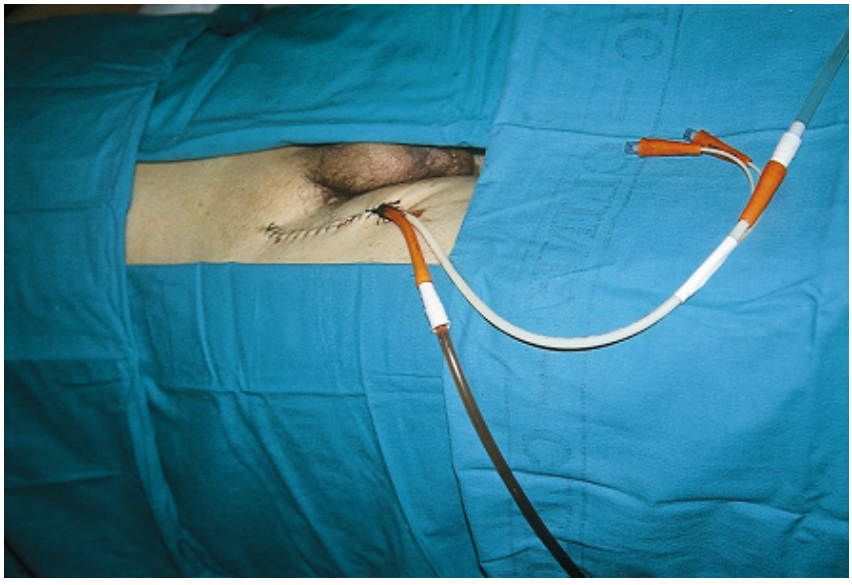

Figure 3.

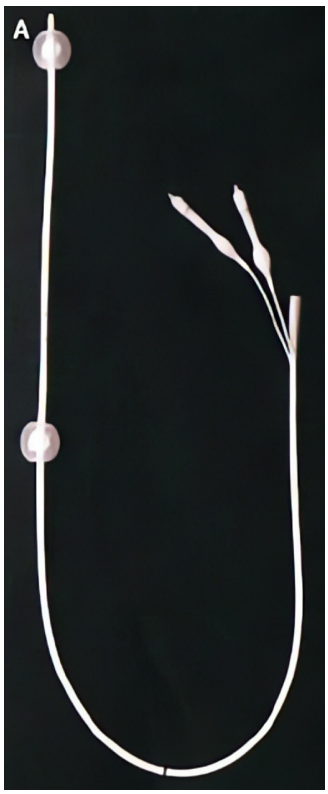

Figure 4.

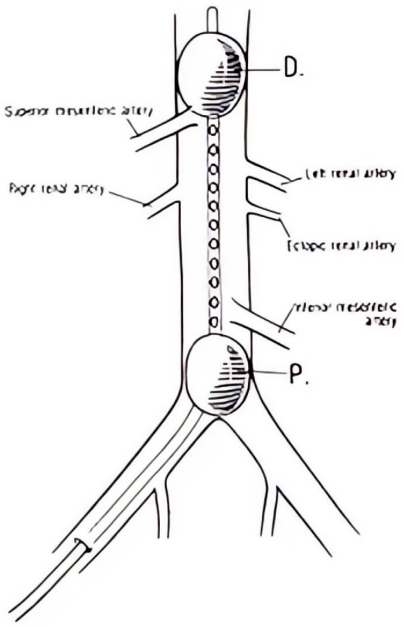

Figure 5.

2.5.3 Total body cooling

Total body cooling (TBC) is the use of an extracorporeal recirculation system with external oxygenation and temperature exchanger. Cannulas are placed in the femoral artery and vein. Blood is oxygenated and cooled to 15ºC. A Fogarty balloon catheter, introduced through the contralateral femoral artery, is positioned in the subdiaphragmatic aorta and insufflated with contrast, enabling its position to be checked with a chest X-ray (Figure 6). Thus, recirculation is selective in the abdominal area. Recommendations are that expert surgeons participate in order to decrease cannulation time, which should be under 20 minutes.

This system achieves a smoother, and more progressive cooling than with IP, giving better peripheral perfusion and oxygenation during hypothermia.

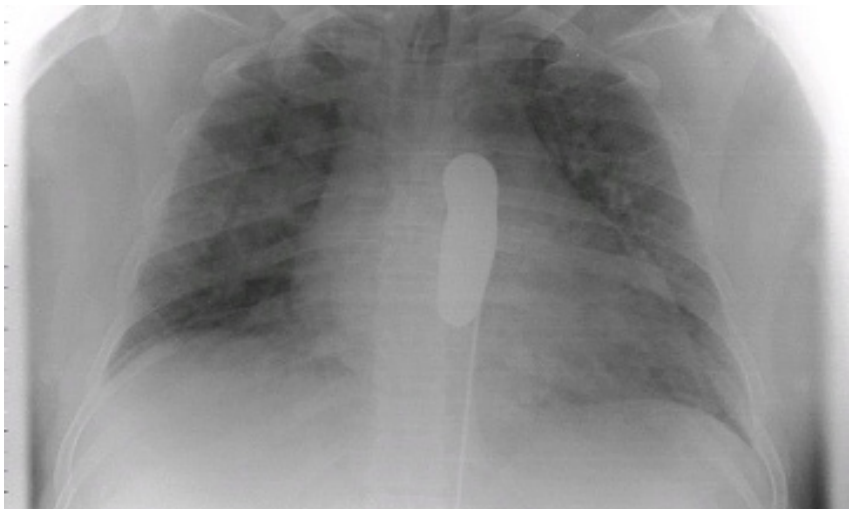

Figure 6.

2.5.4 Normothermic regional perfusion

Normothermic regional perfusion (NRP) refers to the extracorporeal recirculation of oxygenated blood at a temperature of 37°C, prior to recovery and cold storage. It is recommended that the pump flow range is kept between 1.8 and 2.5 L/min/m^2. During NRP it is possible to obtain samples of the recirculating blood to evaluate the feasibility of potentially transplantable abdominal organs, to assess and to adjust the acid-base balance and ionic profile, and to control abdominal perfusion (liver and kidney) through a bypass pump flow (Figure 7). The minimum NRP time before recovery is 30-60 minutes with a maximum of 4-6 hours, depending on whether biochemical, blood gas and haematological parameters are kept under control.

Not only does NRP clearly increase the survival of transplanted abdominal organs, but it is also associated with a decrease in the incidence of DGF and PNF, thereby allowing organs not to be considered marginal, and ensuring that their functionality is close or similar to the organs obtained from a DBD. These differences are especially significant in liver transplantation. The first studies in this field were undertaken by Hoshino and the usefulness of the technique has been demonstrated by Spanish groups. Using NRP involves an increase in circulating adenosine levels, with protective effects against warm ischaemic injury. Adenosine causes an increase in the production if nitric acid and, consequently, has a protective effect on microcirculation, which means less endothelial and cellular injury.

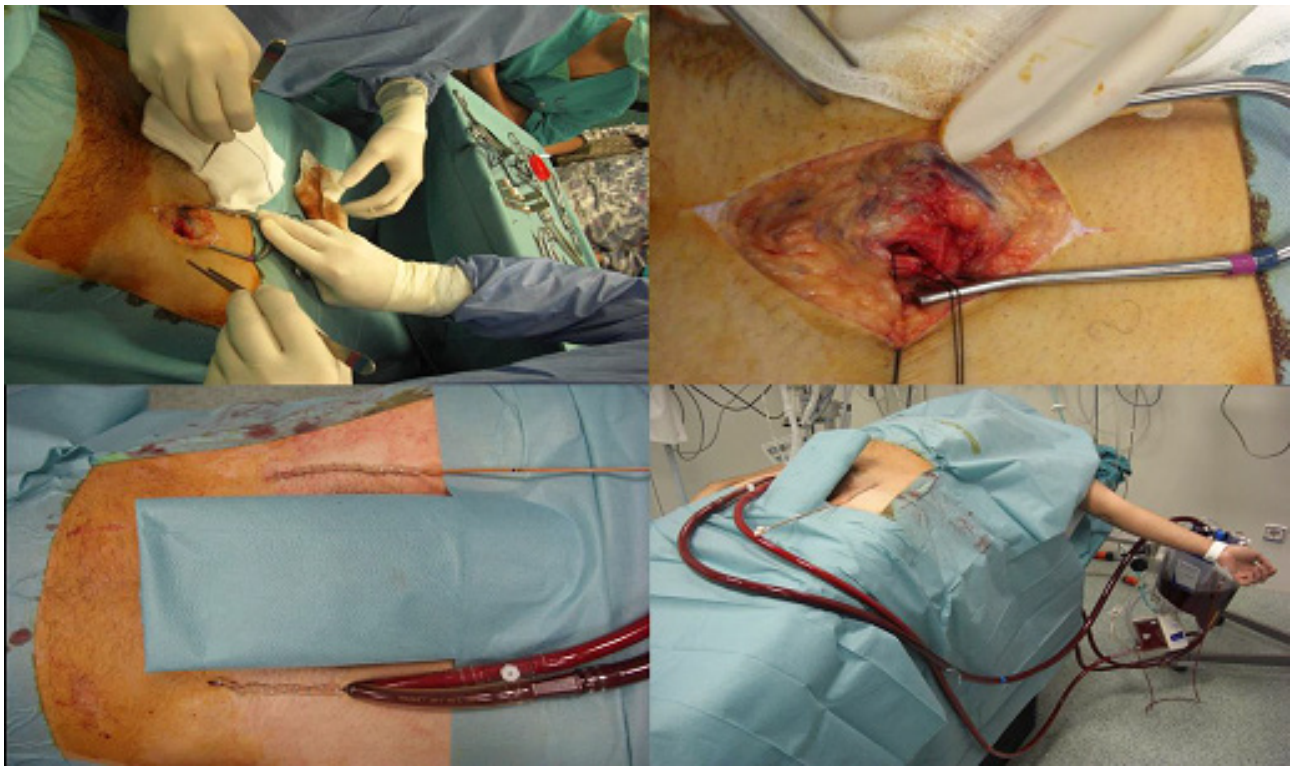

Figure 7.

DID YOU KNOW?

Both rapid retrieval and IP are considered acceptable for kidney transplantation, which has stricter donor selection criteria (age, asystole time, warm ischemic time, etc.).

2.6 Thoracic organ preservation

2.6.1 Pleural cooling

Lung tissue remains oxygenated after the declaration of death, with residual air remaining in the alveolus, and arterial circulation is not required to maintain the aerobic metabolism. After stopping mechanical ventilation and beginning abdominal preservation, the procedure consists of the insertion of bilateral thoracic drainage through the second intercostal space with a mid-clavicular line, through which cold preservation solution is infused into the pleural cavity at 4°C for topical cooling. Around 4 litres per hemithorax are necessary. In abdominal NRP, the use of a pump is recommended to adequately maintain the temperature; to facilitate its use, another two thoracic drainages are placed in the sixth intercostal space.

At the beginning of the procedure, it is necessary to obtain 300 ml of venous blood from the u-DCD in a transfusion bag, preserved at 4°C for a maximum time of 4 hours, to later conduct a functional pulmonary study (Figure 8).

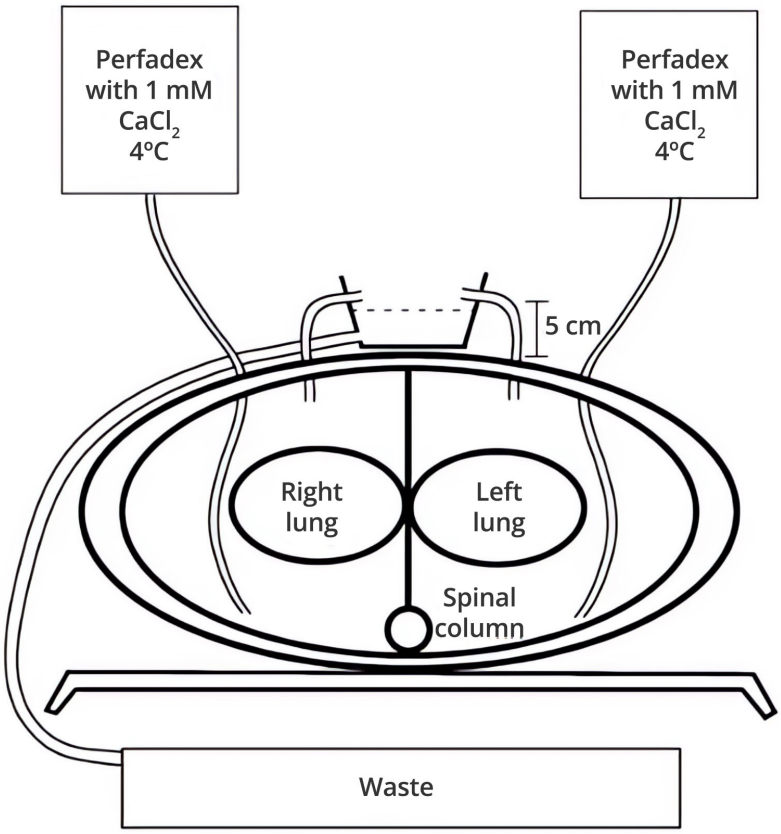

Figure 8. Schematic drawing of topical cooling method.

2.7 Organ recovery

Step 1

After the organ preservation procedures have been established and family consent has been obtained, if the eligible u-DCD meets the criteria to be an actual u-DCD, the donor can be transferred to the operating theatre for retrieval of the potentially viable organs. In cases with open legal proceedings regarding the cause of death, after the initial authorization for preservation, a second authorization for organ recovery is needed. Organ allocation and recovery policies are usually determined by the national or local

transplant offices. During organ preservation, recovery teams organize and accept the organs with the information available at the time, pending further information about the remaining processes and surgical validation. The time taken to organize the surgical team must be reduced to the maximum so that ischaemic time is as short as possible.

Step 2

Once the u-DCD is in the operating room, surgeons perform a fast recovery technique with a median laparotomy and flush the organs with the cold preservation solution. It is not necessary to perform an initial, accurate dissection of the organs as this can be done after cold perfusion. An arterial flush through the cannula already placed in the femoral artery is recommended, as well as venous drainage through the cannula placed in the femoral vein. Only the portal system will require cannulation. With a Fogarty catheter, it is not necessary to clamp the supracoeliac aorta, although it can be clamped to ensure leak-tightness of perfusion. Ice slush is placed intraperitoneally to aid topical cooling of the organs.

Step 3

At the discretion of the retrieval team, kidneys can be subjected to further cold perfusion on the back table before cold storage. After procurement, the majority of u-DCD organs are preserved in simple static cold storage, and the remainder undergo cold pulsatile machine perfusion.

Step 4

Lung recovery starts with drainage of the solution for topical cooling, followed by ventilation with oxygen 100% and a PEEP of 5 cm H_2O. With rapid retrieval, an anterograde pulmonary perfusion through the pulmonary artery is performed. Finally, gas exchange is tested at the left atrium by recirculating the venous blood obtained from the donor after infusion through the pulmonary arteries. The procedure is completed with a retrograde perfusion of cold preservation solution, recovery and cold storage of lungs at 4°C.

3. SECTION 3: ETHICAL CONCERNS IN U-DCD

The u-DCD process involves organ recovery after the determination of death subsequent to cessation of CPR in a patient who has experienced sudden circulatory arrest. A u-DCD should only be declared dead after the irreversible loss of spontaneous breathing and spontaneous circulation, generally established by a 5 to 10 minute waiting period, in accordance with the legal framework and after an adequate period of advanced life support (ALS) following international standards. Every patient presenting a circulatory arrest who does not have a clinical contraindication for organ donation should be considered as a potential u-DCD until it is certain that they are not. A professional involved in the treatment of a potential u-DCD must focus on performing adequate resuscitation, and if necessary, providing comfortable and peaceful end-of-life care to the patient. To avoid a conflict of interests, the resuscitating team should avoid participating in assessment of the potentiality of a donation or in any other aspect of the donation process. The decision to stop CPR must be exclusively made following strict medical criteria and has to be independent of the possibility of donation.

Interventions in u-DCD that are carried out after the declaration of death should be applied in such a manner that determination of the death is not compromised in any way.

The possibility of an organ donation should not be discussed with relatives before the decision to cease therapeutic CPR has been taken.

4. SECTION 4: U-DCD OUTCOMES

The outcomes of u-DCD are usually acceptable, as long as the selection criteria of the DCD donor are strict (age, WIT periods, biochemistry markers, pump flow, NRP maximum 4-6 hours).

The outcomes of transplanted kidneys retrieved from DCD are similar to those of kidneys retrieved from DBD. In the case of livers, there is a higher incidence of primary graft failure and also a higher incidence of biliary duct complications (mainly intrahepatic ischaemic-type biliary strictures). Some of these recipients require retransplantation. In the case of lungs, some studies have shown that long-term patient and graft survival rates after DCD lung transplantation are equivalent to or even better than those after DBD.

4.1 Kidney transplant from u-DCD (1/2)

Several transplant teams still consider kidneys from u-DCD to be suboptimal, and such kidneys remain a marginal source of organ procurement given the logistical difficulties and WIT injuries. The clinical requirements for a person who has suffered an irreversible circulatory arrest to be considered as a potential kidney u-DCD are general donation criteria, age less than 55 years (up to 65 years, in some cases), a maximum of 60 minutes of oligoanuria before circulatory arrest, a maximum 150 minute total WIT and a maximum 240 minutes on NRP, maintaining NRP pump flows over 1.7 L/min.

The main limitation in the use of u-DCD kidneys is PNF. The literature reports PNF rates of between 0 and 30%, with the most frequent rate being around 5 to 10%.

Donor age, pulmonary thromboembolism or trauma as cause of death, WIT and CIT are risk factors associated with PNF, but the predictive value of each one by itself is poor and there is no clear established limit.

The incidence of DGF is higher in u-DCD kidneys compared to those of SCD and DBD, and of ECD-DBD. It has been suggested that DGF in DCD is caused by different mechanisms than in DBD (ischemic injury *vs.* neurogenic inflammation). In DBD kidney transplants, DGF is considered to be a major predictor of acute rejection and graft loss; in contrast, DGF in DCD seems not to affect graft survival. Despite a higher degree of acute tubular necrosis due to warm ischaemia (which involves oligoanuria and sometimes dialysis), it does not present any differences in terms of graft function and survival.

From 3 months onwards, the estimated glomerular filtration rate (eGFR) does not differ significantly between u-DCD and c-DCD or ECD-DBD kidneys. Patient and graft survival rates are comparable to ECD-DBD, but inferior to SCD-DBD transplants. If censored for PNF, 5-year graft survival rates are also comparable between u-DCD and c-DCD.

4.2 Kidney transplant from u-DCD (2/2)

The viability of these kidneys essentially depends on WIT. In order to obtain good outcomes, it is essential to start the organ preservation procedure as soon as possible. Once the kidney graft has been retrieved, the macroscopic examination (uniform perfusion of the whole organ, less than 40% increase in the weight of the organ) and microscopic examination (biopsies with a low degree of glomerulosclerosis, tubular necrosis and fibrosis) are essential to guarantee that the organ functions correctly once transplanted.

Traditionally, kidney graft preservation has been in cold storage (simple hypothermia). The use of NRP is associated with a reduced risk of DGF and improves early and long-term outcomes of u-DCD transplants in comparison to *in situ* cold perfusion, with results similar to those of SCD-DBD.

However, one of the great advances in improving kidney graft function from u-DCD or expanded donor criteria is preservation with a hypothermic pulsatile perfusion machine (HPPM), which is now routinely

used for these types of organs. This kind of preservation, unlike simple hypothermia, enables elimination of cells and aggregates accumulated in the graft's microcirculation during the process of death, and the preservation solution is more consistently distributed throughout the graft.

Machine perfusion makes it possible to preserve kidneys for longer periods and obtain additional parameters to assess viability, such as renal resistance and arterial flow. Furthermore, tissue injury markers may also be measured in the perfusion solution and used as predictors of *ex situ* graft viability.

In u-DCD, HPPM has achieved improvements in immediate kidney function (lower creatinine levels and reduced number of haemodialysis sessions), thereby decreasing the incidence and length of DGF and the incidence of PNF. However, graft survival at 1 and 5 years are similar in kidneys preserved with HPPM to those preserved with cold storage. The elevated cost of an HPPM system is offset by a reduction in dialysis sessions and length of hospital stay.

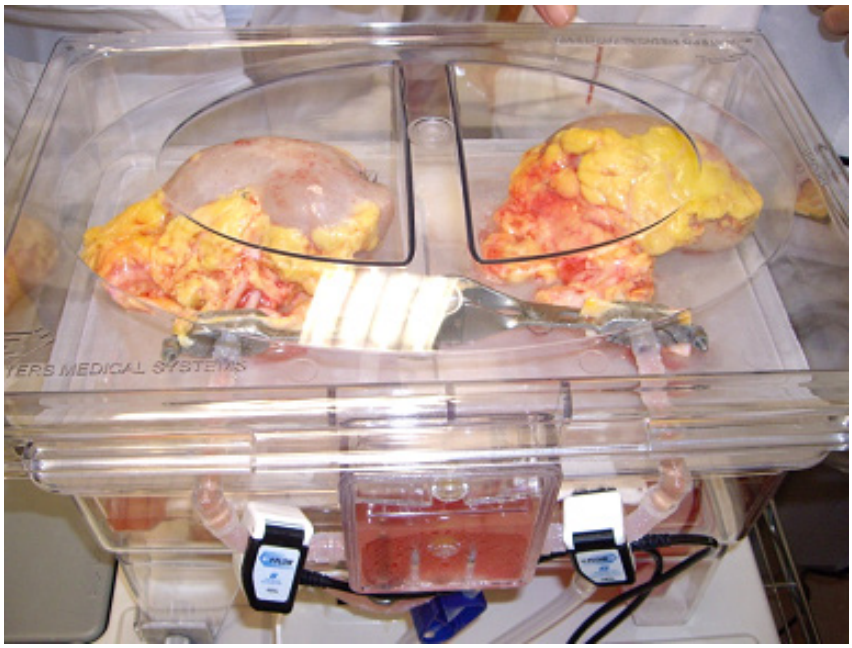

Figure 9.

4.3 Liver transplant from u-DCD (1/2)

The number of liver transplants is lower than the number of kidney transplants due to the liver's high sensitivity to ischaemia and subsequent reperfusion. In the case of these livers, the secondary injuries due to warm and cold ischaemia have clearly differentiated patterns: warm ischaemia fundamentally injures the hepatocytes; cold ischaemia injures the endothelium of the liver sinusoids with leukocyte and platelet accumulation, while the epithelial cells of the bile ducts are extremely sensitive to reperfusion. Liver transplants from u-DCD are associated with a higher incidence of PNF and reduced graft survival, although the increasingly extended use of NRP allows for favourable outcomes with graft survival rates over 70% at one year. Unlike kidney failure, treatment for liver graft failure is problematic and normally requires a retransplant since, unlike the kidney, its function cannot be substituted with artificial techniques. Although the rate of liver survival is inferior to that associated with DBD liver transplants, results are comparable to those achieved with c-DCD livers obtained with rapid retrieval.

One of the main problems of liver transplants from u-DCD is the development of biliary complications (up to 41%), specifically ischaemic intrahepatic biliary stenosis that is unrelated to biliary anastomosis. This may result in graft loss and, in spite of current percutaneous and endoscopic treatments, a high percentage require reconstructive surgery or in some cases, a retransplant. However, results are also comparable to those reported with c-DCD, ranging between 10% and 50%.

In order to attempt to obtain the best possible outcomes, strict compliance with the following times should be respected:

» The start of CPR techniques must be no longer than 15 minutes after circulatory arrest.

» Warm ischaemia time must be less than 150 minutes and reduced as much as possible.

» The total time to liver recovery (including the NRP) must not exceed 4 hours.

It is also recommended not to perform body cooling prior to organ recovery and infusion of hypothermic preservation solution. The recommended age limit of the donor is 50 years, although each case can be assessed individually up to 65 years.

Based on experimental studies and clinical results without advanced organ maintenance, NRP is critical for obtaining viable livers from u-DCD. Graft viability assessment is facilitated by NRP with the cardiopulmonary bypass technique: a pump flow greater than 1.7 L/min is associated with an increase in graft survival, since it ensures an appropriate blood flow through the hepatic artery and portal vein. During this procedure, blood samples may be obtained which enable quantification of the impact of warm ischaemia on the liver, thereby ruling out cases with hepatic enzymes 3-4 times higher than the normal maximum values.

4.4. Liver transplant from u-DCD (2/2)

Another factor that must be taken into account is minimization of cold ischaemia time, preferably to less than 8 hours. Once the organ has been removed, a macroscopic assessment by the liver surgeon will determine whether the liver is viable for transplant. The organ must be of an appropriate consistency, with no signs of congestion, washed uniformly with a preservation solution, and have no post-exsanguination patches. A certain degree of steatosis may be permitted, but the presence of a marked macroscopic steatosis should be a reason for exclusion. The histopathological study of the pre-transplant liver is not normally useful in predicting its viability because signs of necrosis are very frequently undetected. At present, it is believed that the degree of vacuolization in the hepatocytes, reflected in the accumulation of ischaemic insults, may be an independent predictive factor for post-transplant graft function.

In medical literature, we may find an incidence of PNF between 50-75% and a 6-month graft survival of 17-50% following a liver transplant from a u-DCD. However, following strict compliance with the previously mentioned criteria, these values have been amended to 18% and 83%, respectively. Despite this improvement, the outcomes are still worse in comparison with those obtained with DBD livers, which has led to multiple cytoprotective strategies that are currently under development.

Although the usefulness of liver preservation from uncontrolled donors with *ex vivo* hypothermic or normothermic machine perfusion has been demonstrated in animals, clinical studies promoting their use in human livers is being assessed at present and could represent an option for increasing the applicability of a u-DCD liver transplants. Porcine models of DCD liver transplants have shown that the sequential use of NRP with ex vivo NMP improves hepatic injury, inflammation and function compared to NRP followed by cold storage.

4.5 Lung transplant from u-DCD (1/2)

The main causes for the low rate of lungs obtained from DBD are the inevitable ICU stays of patients who develop brain death and the also inevitable need for mechanical ventilation. On the other hand, u-DCD do not undergo a prolonged period of ventilation. Instead, the maximum time is 210 minutes, with a low risk of colonization/infection and pulmonary barotrauma/volutrauma. This all encourages a high rate of valid lungs obtained for transplantation after donor selection.

Very few centres report experiences with u-DCD lungs. Using the procedural criteria of cold *in vivo* blood gas measurement and visual inspection, some centres report 1-year survival rates similar to those of DBD. Mortality is around 17%, the incidence of posttransplant infectious complications is lower than that of a transplant after DBD, acute rejection is comparable in both groups and lower in the u-DCD group in the long term (bronchiolitis obliterans syndrome as a form of chronic lung allograft dysfunction). However, the higher rates of primary graft dysfunction and the impact of this on early mortality are significant and mean that stricter acceptance criteria and methods of evaluation should be used for these donors.

The specific lung preservation protocol differs substantially from that performed on abdominal organs. After establishment of NRP for abdominal organ preservation and cessation of both mechanical ventilation and thoracic compression, the preservation method of choice is *in vivo* topical cooling of lungs through 4 thoracic drains, placed in the pleural cavity to achieve lung collapse. Each hemithorax is perfused with 4 L of Perfadex® solution at 4°C. The lungs can be maintained in this situation for a maximum of 240 minutes.

4.6 Lung transplant from u-DCD (2/2)

Validation of the organ by means of:

- emptying both hemithorax and reinstating mechanical ventilation (FiO_2 1, PEEP +5 cm H_2O);
- evaluation of macroscopic lung appearance;
- confirmation of the integrity and quality of the airway using a bronchoscope;
- cannulation of the pulmonary artery and of each of the 4 pulmonary veins;
- flushing from the artery to the pulmonary veins;
- circulation of 300 ml of blood previously obtained from the donor (during cannulation to set up the bypass) to which prostaglandin E is added from the artery to pulmonary veins, carrying out blood gas determination at both levels (correction of PaO_2 depending on the temperature). If the difference of PaO_2 between the pulmonary artery and veins is greater than 300 mmHg, the lung is considered valid for transplantation.

Other exclusion criteria that are different than those commonly used for u-DCD are a pathological chest radiography on the patient's arrival at the hospital, the presence of blood or purulent secretions in the orotracheal tube, the presence of an exsanguinating chest trauma ruling out advanced life support, and clinical suspicion of bronchoaspiration or active respiratory infection.

In this setting, ex vivo lung preservation (EVLP) gains importance for conditioning and assessing the lungs before transplantation, as lung function before donation is unknown. No specific EVLP criteria for deciding on u-DCD lung function are currently available.

4.7 Summary

Organs from u-DCD represent a new source of organs for transplantation that does not compete with DBD or c-DCD. Out-of-hospital emergency services play a fundamental role in donor detection and transfer to transplant centres. A complex and collaborative logistical approach must be taken to coordinate u-DCD procedures between health professionals. The standardization of protocols following strict selection criteria in the different phases of the process, in addition to the use of NRP and ex vivo machine perfusion devices may allow us to achieve results that are equivalent to those of DBD, or even those of ECD.

TOPIC 9 - Unit 1

Controlled DCD

ORGAN DONATION

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INTRODUCTION

A c-DCD donation occurs after a diagnosis of death certified by circulatory criteria in a patient who had been admitted to an ICU after a withdrawal of life-sustaining treatment (WLST), agreed by the patient's medical team, based on the futility of treatment and the absence of prognosis, or in the context of a refusal of treatment. The most common pathologies are brain injuries without a predictable evolution to brain death and chronic respiratory or cardiological diseases with a catastrophic functional prognosis. c-DCD forms part of the end-of-life care of patients, and complements brain death donation.

The issue of DCD is complex and raises significant ethical and logistical concerns. After death occurs, DCD requires rapid organ retrieval because most organs are very sensitive to periods of ischaemia.

The objectives of this unit are to:

- define the inclusion and exclusion criteria for c-DCD;
- describe WLST and c-DCD preservation/recovery procedures;
- learn how to perform the determination of death by circulatory criteria;
- review outcomes of c-DCD organ transplants.

Controlled DCD (c-DCD) is the most common DCD pathway in many countries, including the United States, the United Kingdom, Australia, the Netherlands and Canada, and several guidelines have already been published. Faced with a severe shortage of transplantable organs, and little or no increase in deceased donors, various professional bodies in these countries encouraged the development of DCD programmes. Various reports by the Institute of Medicine, active promotion and education by the US Organ Procurement and Transplantation Network, and changes in policy by the primary hospital accrediting agencies have all contributed to a significant growth in DCD. With the exception of a very small number of Maastricht IV DCD, almost all DCD in the aforementioned countries are carried out following a planned withdrawal of life sustaining treatments (WLST) from a patient in the ICU or emergency department (Maastricht III DCD category).

Because the number of brain dead donors has remained relatively constant, DCD now represents more than 13% and 42% of all deceased donors in the USA and the UK respectively. This growth primarily represents an additional pool of potential donors, allowing the recovery of organs from patients who are not brain dead and have little likelihood of progressing to brain death. However, in the USA this increase also reflects certain changes in the management and outcomes of patients requiring neurointensive care, including the use of interventions that make a progression to brain death less likely. Furthermore, there is a willingness/desire among families and clinicians to terminate life support earlier in patients with severe head trauma or cerebral bleeds, for which further treatment is deemed not to be in the patient's best interests.

1. SECTION 1: WLST AND PREDICTING THE LIKELIHOOD OF ASYSTOLE

1.1 Inclusion and exclusion criteria for c-DCD

Strict criteria for the selection of c-DCD are the key to obtaining good results after transplantation. The distinctive factor of c-DCD is functional warm ischaemia time (FWIT). This period begins with the significant hypoperfusion after the withdrawal of life-sustaining therapies (WLST) and continues until the start of organ preservation. The most generally followed recommendation is to accept an FWIT lower than 30 minutes for liver and pancreas, and lower than 90 minutes for kidneys and lungs. The definition of when significant hypoperfusion begins depends on different international standards (See Table 1), when the patient's systolic arterial pressure (SAP) decreases below 50-60 mmHg determined by invasive arterial monitoring, and/or when arterial oxygen saturation decreases below 80-70%, determined by pulse oximetry.

Total warm ischaemia time (t-WIT), which is the period from WLST to the start of organ preservation, also provides guidance about ischaemic damage, although it is less precise than FWIT because it includes a normal perfusion period of variable duration (from WLST to significant hypoperfusion). The most commonly accepted t-WIT is <120 minutes.

Other factors that have been associated with good results for c-DCD are age <65 years old and a body mass index (BMI) <35 kg/m^2. However, after an individual assessment, donation may be considered if these limits are surpassed, as long as no other risk factors are present.

In addition, the absolute contraindications for donation should be verified and excluded:

- unknown cause of death;
- HIV positive or presence of risk factors;
- past or present history of neoplasia (except in case of *in situ* carcinoma of the cervix, cutaneous basocellular carcinoma, certain CNS tumours with no ability of metastasize, or tumours with a high cure rate after treatment, with rare late metastases and a disease-free survival of at least 5 years);
- systemic viral, fungal or bacterial infections. Do not exclude systemic bacterial infections with an identified germ, with a sensitive antibiogram and an established treatment of least 48 hours with a good clinical and analytical response: continue the treatment in the recipients.

Table 1. Different international standards

	ASTS (USA)	ONT (Spain)	CCDT (Canada)	BTS (UK)	MHMRC (Australia)
Total warm ischaemia time (t-WIT) (withdrawal – preservation)	- LIVER <30-45 min -KIDNEY <45-60 min -PANCREAS <45-60 min	(<120 min) -LIVER <30-45 min -KIDNEY <45-60 min -PANCREAS <45-60 min -LUNGS <90 min	- LIVER <30 min -KIDNEY <45-60 min -PANCREAS <60 min -LUNGS <60 min	-LIVER, KIDNEY AND PANCREAS: Not specified -LUNGS: WLST-Asystole <60 min Asystole-Cold Flush <90 min	Not specified WLST-Death <90 min
Functional warm ischaemia time (FWIT) (hypoperfusion – death: definition)	MEAN ARTERIAL PRESSURE <60 mmHg	SYSTOLIC ARTERIAL PRESSURE <60 mmHg (± Sat O_2 <80%)	SYSTOLIC BLOOD PRESSURE <50% BASELINE Sat O_2 <80%	SYSTOLIC BLOOD PRESSURE <55 mmHg	SYSTOLIC BLOOD PRESSURE <50 mmHg
Functional warm ischaemia time (FWIT) (hypoperfusion)	-LIVER 20-30 min	-LIVER 20-30 min	Not specified	-LIVER <20 min -KIDNEY <40 min	-LIVER <30 min -KIDNEY <60 min -PANCREAS <30 min -LUNGS <90 min
Cold ischaemia time (CIT) (preservation – transplantation)	-LIVER <8-10h -PANCREAS <18 h -KIDNEY <24 h	-LIVER <8-10 h -PANCREAS <18 h -KIDNEY <24 h	Not specified	Not specified	Not specified

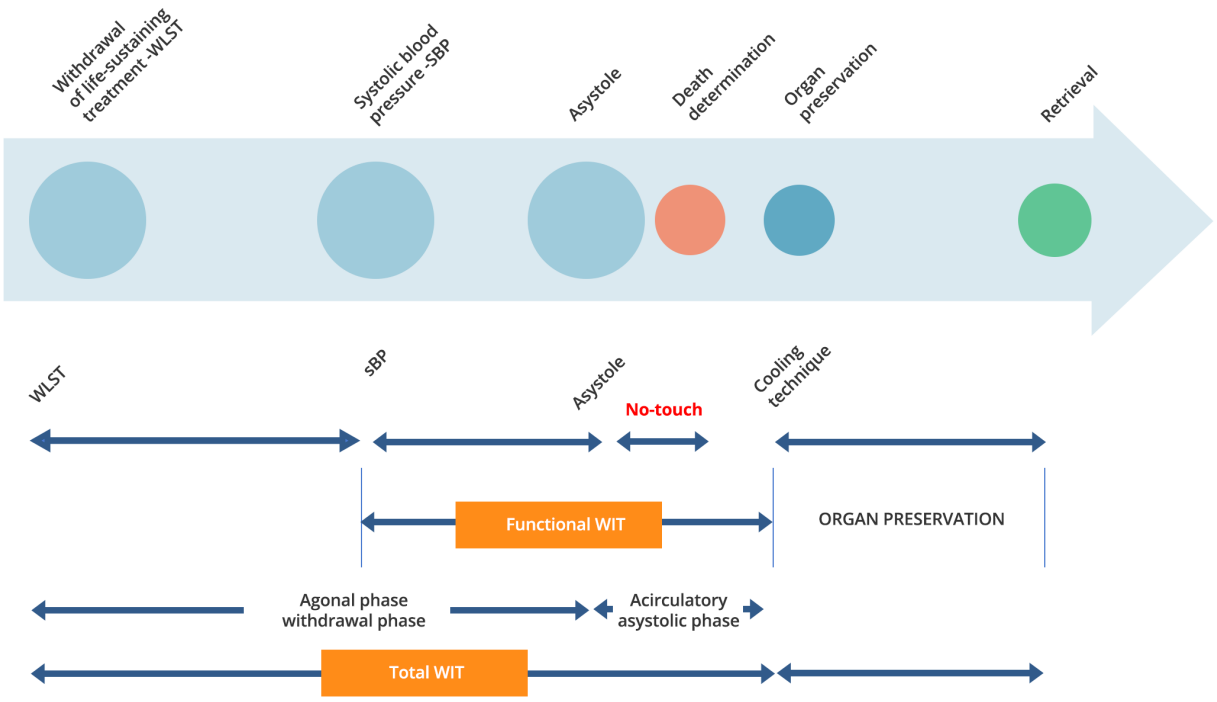


Figure 1.

1.2 WLST

A c-DCD takes place after a death that follows the planned withdrawal of treatments which have been considered futile or of no overall benefit to a gravely ill patient. The medical decision of WLST is a clinical judgement taken in a defined manner within a multi-disciplinary approach, consistent with local/national guidelines and legal requirements, by the clinical team in consultation with the family. This decision must be prior to and independent of the possibility of donation. Any discussion about c-DCD takes place as part of end-of-life management planning and only after the withdrawal of cardio-respiratory support has been discussed and agreed. It is important to understand that WLST does not provoke the death of the patient but rather allows the process of death as the inevitable progression of the patient's disease, for which continuing treatment provides no prospect for recovery or is not considered to be in the patient's best interests. It is good medical practice and a standard of quality care. Not performing WLST if it is indicated could be considered therapeutic obstinacy and does not prolong life but prolongs the process of death. At this point, therapeutic efforts are guided towards providing comfort to the patient.

Healthcare professionals have an ethical obligation to respect the known wishes of patients. In most circumstances, family and friends will respect a patient's decision regarding donation. Ethical concerns surrounding the withdrawal of cardio-respiratory support are not specific to c-DCD.

Consenting to donation will usually result in a significant delay in the withdrawal of cardio-respiratory support, due to the complex logistics associated with arranging donation and transplantation. The family must be prepared for and consent to this physiological support (e.g., inotropes, oxygen); it may be necessary to stabilize the patient between consent for c-DCD and WLST. Withdrawal of cardio-respiratory support should be agreed upon and undertaken at an appropriate time and location. The location of withdrawal of cardio- respiratory support will depend on the organs and the preservation methodology contemplated; the distance between the intensive care unit and the operating room; the ability to provide a quiet and private space for family requirements; the details of where and how to continue palliative

care if the patient does not die within 120 minutes; and finally, hospital logistics, local policies and guidelines. Irrespective of the location for withdrawal, if they wish to do so, families should receive support to be present during WLST and until certification of death.

All aspects of the management of withdrawal of cardio-respiratory support are the responsibility of the treating intensivist and the intensive care team. The person responsible for the withdrawal of cardio-respiratory support must work independently of the retrieval and transplantation teams. After WLST, the heart rate, oxygen saturation, respiratory rate and blood pressure should be recorded. Warm ischaemia is currently considered to be the time at which systolic blood pressure (SBP) falls to 60 mmHg or below. An accurate and consistent record of the sequence of events must be made. If cessation of circulation does not occur within a timeframe consistent with successful donation, c-DCD cannot proceed, and the patient should be given continuing end-of-life care in the place and manner previously discussed with the family.

Figure 2.

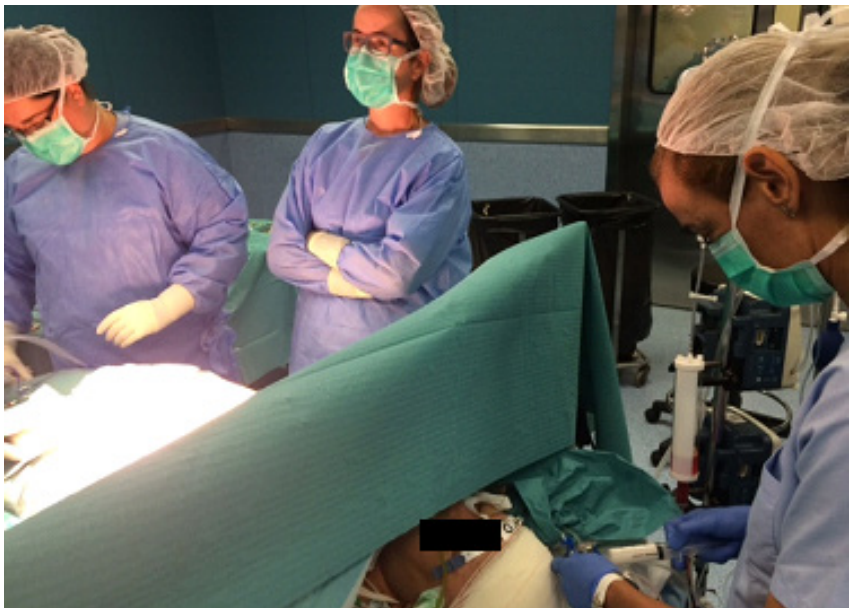


Figure 3.

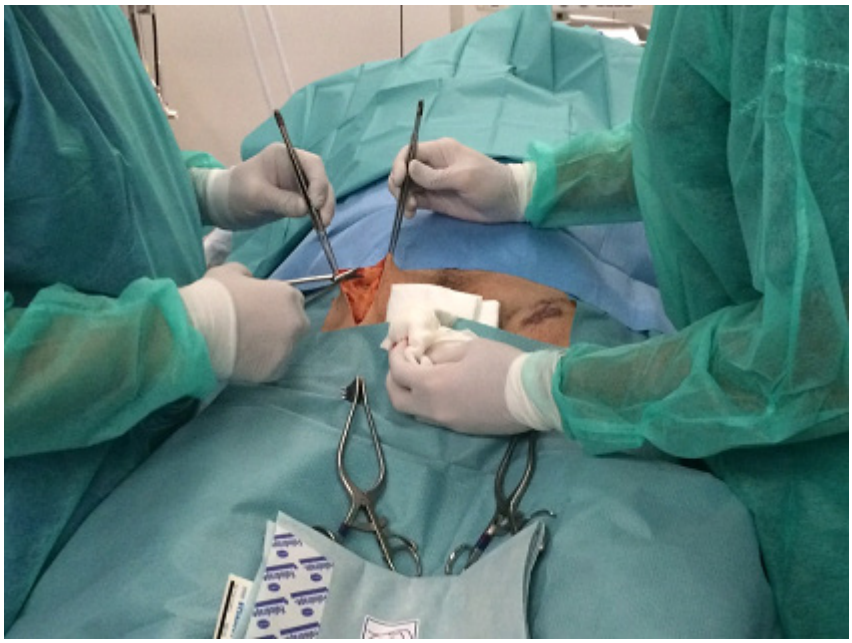
1.3 *Ante-mortem* interventions

In the case of DBD, several *ante-mortem* interventions can be performed before death. The aims of these interventions are to maintain organ viability, determine organ suitability and allow the identification of suitable recipients. The procedures to follow for c-DCD are:

- serological, blood group, tissue typing and other blood tests to determine organ suitability and allocation;
- changes to the site and timing of the withdrawal of cardio-respiratory support compared to other dying patients;
- maintenance of physiology to support organ viability;
- examination and screening of the potential donor to determine organ allocation;
- interventions to assist with assessing organ quality (e.g., bronchoscopy, abdominal echography);
- interventions to improve organ viability (e.g., administration of heparin, vasodilators, antibiotics);
- femoral cannulation.

These interventions must comply with jurisdictional legislation, guidelines and institutional protocols. They are performed for the benefit of potential recipients; however, they must be consistent with the best interests of the patient, which includes respecting the patient's wishes regarding becoming an organ donor. They are ethical if they contribute to the likely success of the transplantation and do not harm the patient.

Measures should be taken to prevent any pain or discomfort associated with any *ante-mortem* interventions. Informed consent from the next of kin is required.



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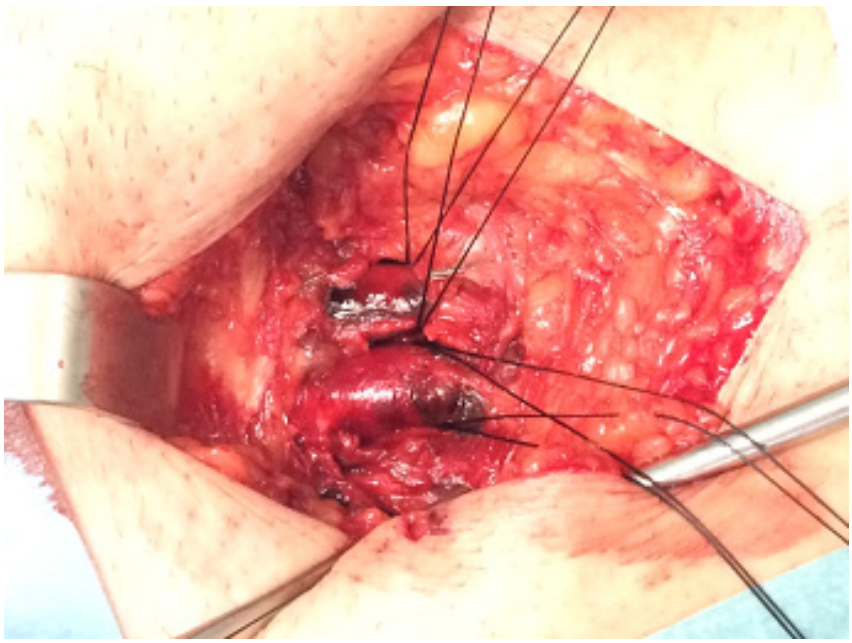

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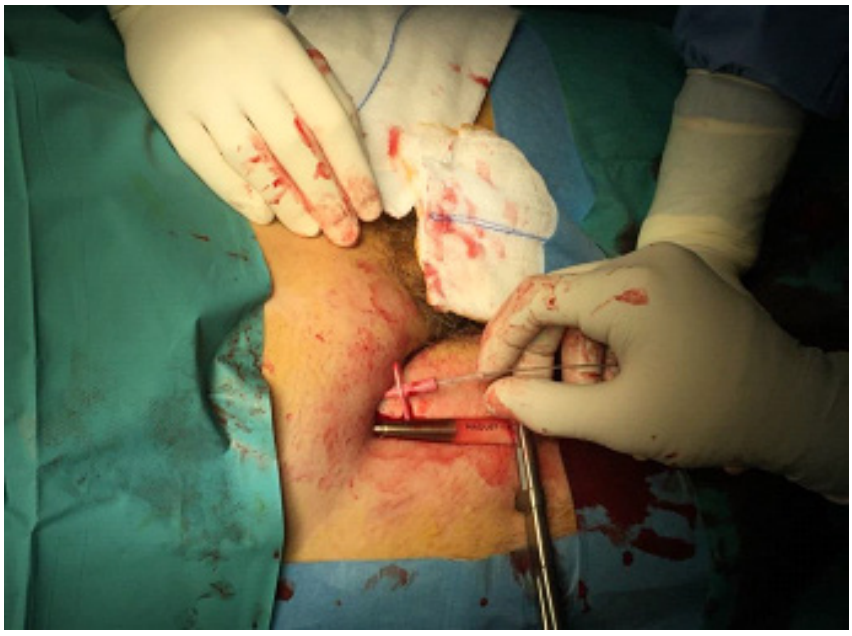

Figure 6.

1.4 Donation authorization

Families have the right to be informed about relevant circumstances, and to receive information in a manner appropriate to their understanding and experience. All the processes and aims must be explained in detail before seeking written consent. The responsibility for consent to WLST, *ante-mortem* interventions and c-DCD falls to the family, who are provided with overwhelming amounts of information.

It would be desirable to have completely separate discussions about WLST and donation, although sometimes this is not possible. It can be natural for a family who accept WLST to ask about what will happen next. This is the moment when a prior request for donation can be made, and donation is only raised when it is clear that a family have understood and accepted the inevitable loss.

Once WLST has been agreed with the family, the transplant coordinator approaches the family to explore the possibility of c-DCD if death is declared. Any request should be clear and focus on all aspects of the process. Regardless of the decision taken regarding c-DCD, WLST will take place. Families may change their minds and withdraw consent at any time. In a limited number of cases, for example in patients with end-stage respiratory or cardiac disease or a high cervical spinal injury, the patients will be competent to consent themselves.

It is important to clarify WLST is unpredictable and the time until death is not certain: the possibility exists of a prolonged time -which could make donation impossible- or even that circulatory arrest may never occur, a circumstance in which the continuation of treatment for the patient will be considered and previously established. The family's desire to be with the patient before, during or after WLST should be facilitated, and some characteristics of the process may have to change as a consequence.

Any legal requirements for reporting a death to the court or the coroner must be met. The designated officer, responsible for authorizing the removal of organs and tissue for the purpose of transplantation, should be informed when there is a potential donor suitable for c-DCD and of the wishes or consent of the donor and/or the family. All the information and consent regarding the patient and the c-DCD donation process should be addressed to the designated officer for the necessary evaluation.

Arrangements may need to be made immediately after the determination of death for a formal authorization of donation. To avoid additional ischaemia, a legal application may also be made before WLST to obtain permission conditional on determination of death of the patient.

1.5 Predicting the likelihood of reaching asystole in required timeframe

Transplant clinicians are usually only willing to consider the use of organs from c-DCD if the time from WLST to the start of preservation techniques (FWIT) is less than 30 to 90 minutes, depending on the organ. Longer periods have been associated with a high percentage of complications. Thus, accurately predicting the successful progression to circulatory arrest after WLST avoids an unnecessary commitment of hospital and resources, as well as the family's disappointment that the donation could not go ahead.

Several algorithms have been developed in an attempt to predict the speed of progression to circulatory arrest, some of which involve tracking the degree of physiological decline during a trial period of disconnection from mechanical ventilation. One example is the University of Wisconsin scoring tool.

Factors that have been suggested for evaluation include:

- presence or absence of spontaneous breathing;
- respiratory rate, tidal volume, and negative inspiratory force;
- oxygen saturation after a period of disconnection from the ventilator;
- presence or absence and dosage of vasopressors and inotropes;
- tracheal intubation *vs.* tracheostomy;
- vital signs: blood pressure, pulse, oxygen saturation,
- body mass index;
- age (>30 and >50).

However, it is not possible to reliably identify potential DCDs who will die within 1 or 2 hours after the WLST. Consequently, a donation procedure should be considered in every potential donor. Any currently existing tools have yet to be validated prospectively, do not consider the use of pharmacological comfort care following WLST, and remain of uncertain benefit.

1.6 Certification of death

The criteria for diagnosis of death vary between countries since each country has its own legislation. In an attempt to reach a consensus on scientific, biological and medical aspects, some principles have been established:

Principle 1

Death is a biological event and should be diagnosed using biological parameters.

Principle 2

The criteria used to diagnose death should remain valid regardless of any subsequent *post-mortem* intervention, and should be functional rather than anatomical, based upon the loss of circulatory and neurological functions.

Principle 3

Death occurs when there is a permanent loss of:

- the capacity for consciousness;
- all brainstem functions, including the capacity to breathe.

Principle 4

The state of death can be reached in various ways, for example, through permanent loss of circulatory function or following more direct injury to the brain.

Principle 5

The dead donor rule should be preserved.

With c-DCD, the word "irreversible" is frequently changed for "permanent". Both designate that a condition is stable and unchanging. However, there is a difference between them. "Irreversible" implies impossibility: irreversible loss of circulation means that circulation cannot be restored by means of any known technology. However, "permanent" admits possibility, relying on intent and action to be realized: permanent loss of circulation means circulation will not be restored due to spontaneous return or as a result of a medical intervention because resuscitation will not be attempted. Because of the characteristics of each process, c-DCD can be diagnosed in terms of permanency and u-DCD in terms of irreversibility.

Any schedule for the diagnosis of death must include:

- mechanical asystole or absence of circulation;
- observation period (to ensure the absence of any possibility of a spontaneous return of circulation);
- demonstration of the loss of consciousness and brainstem functions, including respiration.

This period, the so-called "no touch" or "hands off" period, is stipulated as 5 minutes in many countries, but it can range from 2 to 20 minutes. This debate arises from the publication of cases of autoresuscitation (spontaneous return of circulation) after failed attempts of CPR. A recent systematic review of autoresuscitation in c-DCD showed no cases of autoresuscitation when invasive treatment was withdrawn.

Transplant coordinators or members of the retrieval teams should not participate in the diagnosis and confirmation of death if c-DCD is being considered.

Figure 7.

Figure 8.

2. SECTION 2: PROCEDURES AND LOGISTICAL ISSUES

2.1 Referral to the Organ Procurement Organization

The aetiologies of brain injury in potential c-DCD are similar to those that can result in brain death. These patients should only be identified as potential c-DCD if the criteria for brain death are not likely to be achieved.

Protocols should establish who refers the donor, when the referral should take place and how the patient should be cared for whilst undergoing donor assessment.

Professionals are encouraged to refer all ventilated patients with significant brain injury as early as possible so that the transplant coordinator can assess the potential for c-DCD. All patients for whom a WLST decision is anticipated should be referred, regardless of the patient's diagnosis. If this referral becomes a routine in end-of-life care, the perception of any conflict of interest reduces. Earlier referral can also reduce the distress for the family by reducing the delay in WLST.

Once fully informed about the potential to recover and transplant more organs if the patient becomes brain dead, some families agree to delay WLST if there is some expectation that the patient might progress to brain death with 48-72 hours.

2.2 Location of withdrawal of ventilatory support

Depending on hospital protocols, operating room space availability, architectural considerations and family wishes, the withdrawal of support may occur in the ICU, emergency department (ED) or operating room. From the perspective of minimizing ischaemic damage, it is preferable for WLST of the patient to occur in the operating theatre or a preoperative area. However, it must be remembered that potential c-DCDs are still alive, and it is essential that, wherever treatment is withdrawn, the same expertise in end of life care is provided for the patient that would have been provided in the ICU. If WLST is undertaken in the ICU or the ED, the waiting period between asystole and the declaration of death (typically 5 minutes) may be used to transport the patient to the operating room, allowing the organ recovery to proceed as soon as death is declared.

Transporting the patient should in no way interfere with the proper observation of the patient required to make the diagnosis of death based on circulatory criteria.

In some hospitals, the family's desire to be with the patient at the time of asystole may be accommodated by bringing family members to the operating room where the withdrawal will occur. This procedure can be accomplished effectively only when protocols have already been developed and operating room staff have received appropriate training in advance. Family members should be supported throughout by staff who have received appropriate training in end-of-life care and who understand the hospital's DCD protocol.

Location of WLST should consider:

- comfort, privacy and dignity of both the patient and family;
- ongoing support for the family after the death of the relative;
- plan of ongoing care if the donation cannot go ahead;
- implications of staff withdrawing from the operating room (need for end-of-life care, WLST and death certification);
- avoidance of the transplant team being involved in the care of the potential c-DCD.

2.3 Preservation techniques

2.3.1 Super-rapid technique

In c-DCD this is the most frequently used technique for preserving abdominal organs. It consists of a rapid laparotomy and cannulation of the aorta to start the cold flush just after determination of death. The technique normally takes place in the operating theatre.

2.3.2 Normothermic regional perfusion

In u-DCD, after the declaration of death, chest compressions and ventilation are restored while the femoral vessels are cannulated in order to perform normothermic regional perfusion (NRP). This involves recirculating blood in the abdominal area and maintaining the blood temperature at 37°C with a heat exchanger. This technique can be also used in c-DCD, with or without *ante-mortem* cannulation of the femoral vessels. Depending on the family's wishes, *ante-mortem* cannulation can even be performed in the ICU.

2.3.3 Total body cooling

Total body cooling (TBC) is similar to NRP, but the blood temperature is maintained at 15°C.

All of these systems have demonstrated the ability to reverse warm ischaemia injury, but the use of NRP changes the period of circulatory arrest (warm ischaemia) to a period of preconditioning (ischaemic preconditioning). In comparison with direct perfusion, this technique reduces the incidence of DGF.

After retrieval, organs must be preserved until the moment of transplantation. Static cold storage (CS) has traditionally been used for all organs. Nevertheless, various studies have focussed organ preservation through the use of hypothermic pulsatile perfusion machines (HPPM) until transplantation in the recipient. These studies have demonstrated an improvement in graft function in ischaemically damaged organs. The HPPM preservation technique reduces the vascular resistances increased by ischaemic injury and facilitates the elimination of blood from microcirculation. Perfusion parameters, such as renal resistance (RR) and arterial flow (AF), represent additional assessment tools when deciding organ viability. Hypothermic machine perfusion is widely used in kidneys as it has already demonstrated it can reduce the need for dialysis in the first week (DGF), hospital stay, and in some cases PNF and allograft survival.

More recently, several teams have been working on the development of lung or liver perfusion devices that use blood in normothermia, in order to add a period of normothermic recirculation *ex situ*, for better preservation and to perform a proper evaluation of the grafts. Most of these studies have not yet reached conclusive results on the usefulness of their techniques.

For better organ preservation, heparin should be administered prior to the withdrawal of support, once informed consent has been obtained from the family, or once the patient has entered functional warm ischaemia time. Morphine or other analgesics or sedatives should always be administered according to the hospital's protocol for WLST, irrespective of whether donation is a possibility or not. Their administration should be decided by the physician responsible for the patient's care, and the retrieval team should play no part in this decision making.

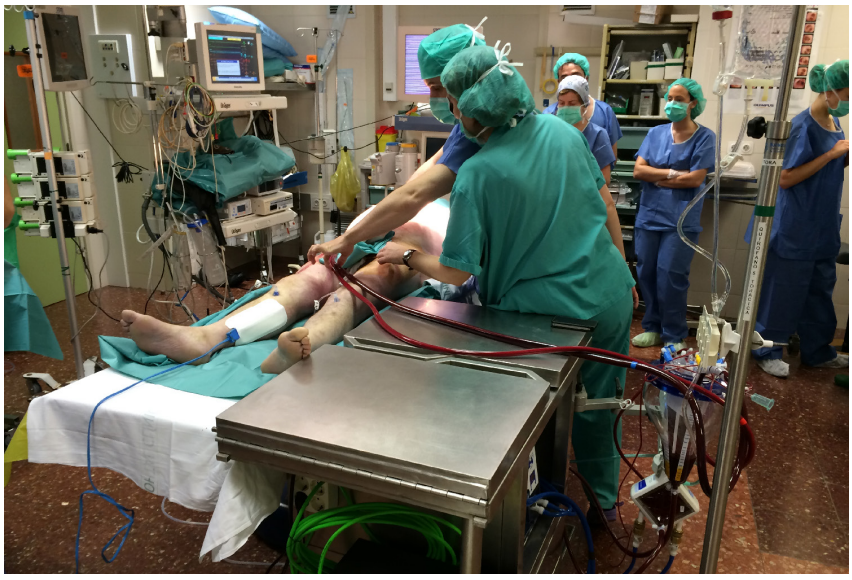

Figure 9.

Figure 10.

Figure 11.

2.4 Recovery techniques

If treatment is withdrawn in the operating room, prepping, draping and positioning of the patient may be undertaken by the organ recovery team before the withdrawal of support. This saves valuable time once death has been declared, thus minimizing WIT. Once the preparation is complete, no members of the organ surgical recovery team should have further contact with the patient until circulatory arrest, the required waiting period and the declaration of death have occurred. However, the transplant coordinator may remain with the donor the entire time in order to observe the WLST procedure and record necessary data related to vital signs during the agonal period.

Organ retrieval needs to begin without any delay after death. Normally, family members have little time with the patient after circulatory arrest, so after the observation period, organ retrieval starts as soon as possible. Operating room staff are previously informed about the patient, the organs for retrieval, the roles and responsibilities of each person in the operating room, and the timing of WLST.

Blankets can be placed on top of the sterile drapes to allow family/patient contact. The sterile back tables with instrumentation/equipment will be covered with sterile drapes so that they remain out of view. The family will need scrubs or overalls.

2.5 Patients who do not progress to asystole

Some patients are not declared dead within a time frame compatible with the safe recovery of transplantable organs as determined by protocols. In such cases, the organ donation is aborted and there must be a plan, agreed in advance, for the patient to be returned to the ICU or other unit for continuing end- of-life care and support of the family. A protocol for this process must be established by the hospital. Prior to each donation event, both hospital staff and the patient's family should be adequately informed about what will occur if the donation cannot proceed.

Figure 12.

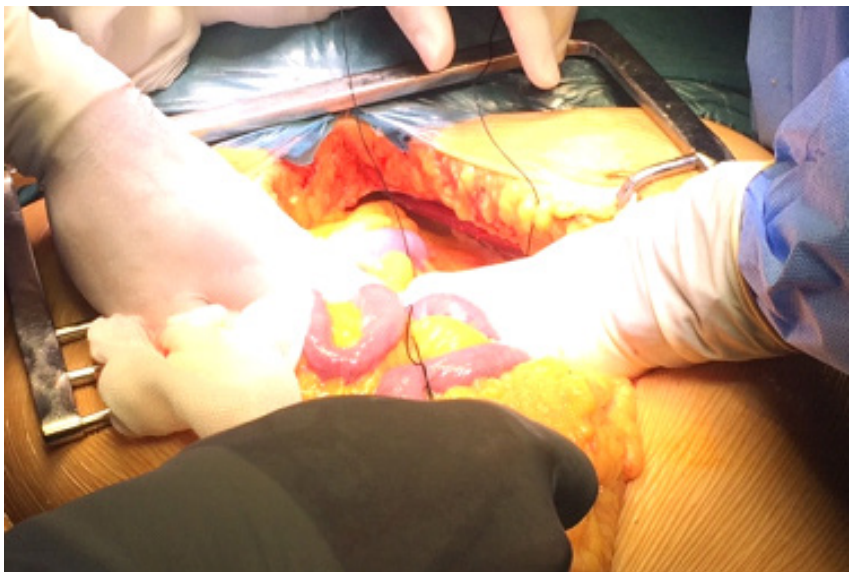

Figure 13.

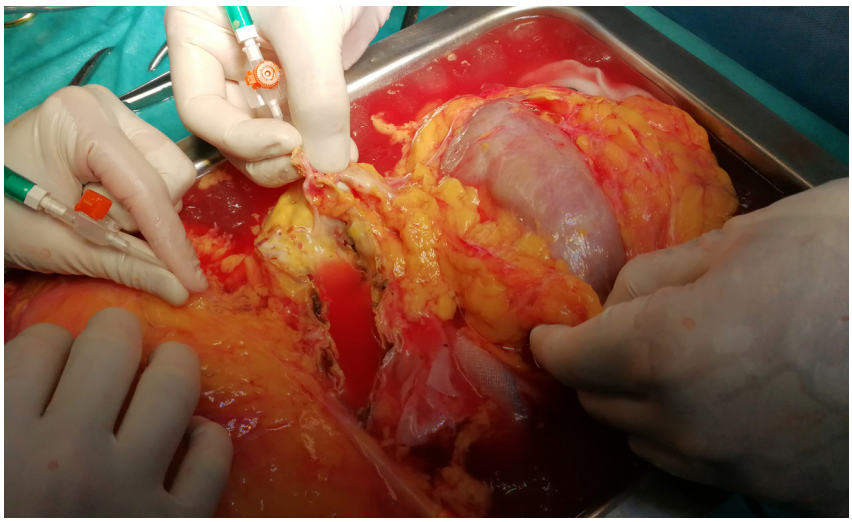

Figure 14.

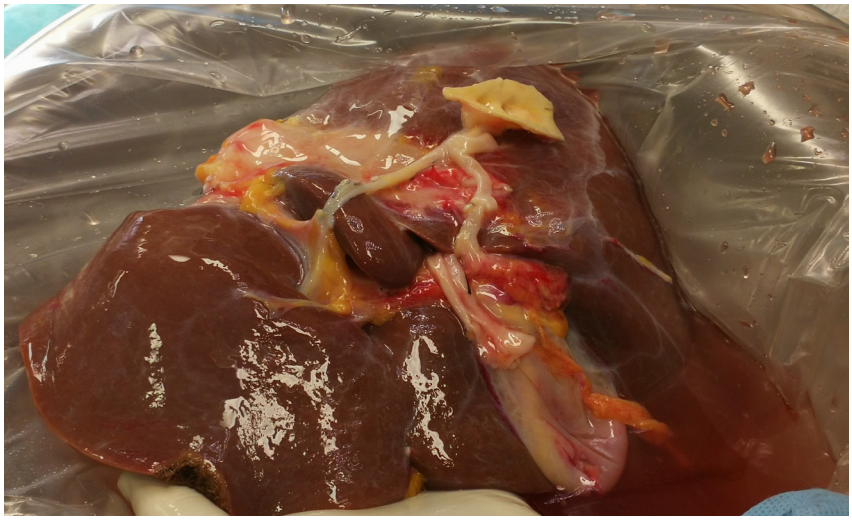

Figure 15.

2.6 Heart procurement from c-DCD DONORS

The concept of c-DCD donor heart transplantation is not new. It was in the late 1960s that Barnard performed the first heart transplants from c-DCD donors. Four decades later, in Denver, three children successfully transplanted with c-DCD donor hearts. Currently, heart transplantation from adult c-DCD donors is an emerging reality in clinical practice in England and Australia and more recently in Belgium and Spain, with highly satisfactory results.

Posttransplant survival and graft function in transplants performed to date are comparable to those observed with brain-dead donors.

In c-DCD, the donor's death is diagnosed on cessation of the heart beating and/or effective blood circulation. Because of concerns regarding the potential deleterious effects of warm ischaemia (WI) on donor heart function and viability, in the early years of heart transplantation, the donor heart was not considered for clinical transplantation. Myocardial damage is thought to be proportional to the duration of time between the withdrawal of support and the confirmation of death. The WI prior to organ explant, seems likely to serve as a primer for further injury during cold ischaemia, exacerbating the effects of ischaemia and reperfusion injury, and making the injury more severe. Ischaemic injury results in the depletion of ATP reserves and anaerobic metabolism, which cause intracellular acidosis, activation of the sodium–hydrogen exchanger, and sodium influx into the myocyte. Minimizing the severity of this

ischaemia-reperfusion injury (IRI) represents the cornerstone of c-DCD cardiac resuscitation. With this objective, two methods of c-DCD heart resuscitation have been created and both have shown successful results in clinical practice.

The first approach is called direct procurement and perfusion (DPP). This involves delivery of a cardioplegic solution during organ procurement that limits the detrimental effects of IRI. With this approach, a rapid cardiectomy is performed, the heart is connected to an *ex situ* heart perfusion (ESHP) device and preserved in a normothermic, beating state until eventual transplantation.

The second approach is called normothermic regional perfusion (NRP). Following the declaration of circulatory death, a rapid median sternotomy is performed, and cerebral circulation is isolated (a clamp is placed across the aortic arch vessels) to avoid cerebral reperfusion. A bilateral carotid Doppler is recommended in order to confirm the exclusion of cerebral blood flow. In order to provide additional reassurance that brain perfusion is not restored, Manara et al. proposed leaving the cephalad ends of the aortic arch vessels open to atmosphere or to a negative pressure before commencing thoraco-abdominal NRP. With the brain excluded from circulation, the donor is placed on veno-arterial ECMO and reperfused for 60 minutes.

The donor is subsequently weaned from ECMO, which facilitates the assessment of donor heart function *in situ*. Graft function is assessed with transoesophageal echocardiography; cardiac output and intra-cardiac pressures are monitored with a Swan Ganz catheter. The acceptance criteria for transplantation of c-DCD hearts after NRP include central venous pressure <12 mmHg, pulmonary capillary wedge pressure <12 mmHg, cardiac index of at least 2.5 L/min/m^2 and a LVEF of at least 50%. Viable organs are then arrested with a traditional cardioplegic solution and may be connected to an ESHP device in a beating state until transplantation or can be transplanted directly. Current protocols for NRP involve reperfusion with donor blood following initiation of veno-arterial ECMO.

3. SECTION 3: ETHICAL CONCERNS IN C-DCD

A key prerequisite for an ethically acceptable DCD programme is to follow the national best practice guidelines for DCD. We should remember that c-DCD involves organ recovery after a planned WLST and a declaration of death according to circulatory criteria. The basis of WLST is the principle of autonomy (the patient's right to plan their own end-of-life care) and the principle of nonmaleficence (avoid futility and therapeutic obstinacy). In ethical terms withdrawing treatment is the same as not starting it. Discussions about WLST should be considered in the same way for patients who are potential organ donors as those who are not.

Organ recovery must begin in compliance with the "dead donor rule", and a c-DCD patient should only be declared dead after the permanent cessation of circulatory function, generally established by a 2 to 5 minute waiting period, in accordance with the legal framework.

Another important ethical issue is how to manage conflicts of interest because the preparation for organ recovery in DCD begins before the declaration of death. All decisions concerning the treatment of the patient should be based on the patient's best interests. These conflicts can be managed in a variety of ways, including informed consent and separation of the roles of each participant (treatment team, donor team and recovery team).

Informed consent should be sought for *pre-mortem* interventions to improve organ viability and clarify all the steps of the process. It should reflect the patient's wishes, and in cases where there is no available evidence of such wishes, the family will be asked to decide on the donation. *Pre-mortem* interventions are acceptable when it has been decided that continuing with life-sustaining therapies is no longer in the best interests of the patient, but organ donation is a possibility so intervention and may improve organ quality and transplant outcomes. In the assessment of the balance of benefits and drawbacks for any intervention, the patient's wishes, beliefs, and values must be considered. A person's interests are wider than simply clinical ones.

Pre-mortem interventions may cause harm (pain or discomfort) or distress (anxiety or gasping), so these symptoms should be controlled using appropriate therapies.

The treatment team should be involved in the discontinuation of life-sustaining treatment or the declaration of death. The decision to withdraw should be prior to and independent of the possibility to donate and must be made based on clinical judgment. Withdrawal will take place regardless of the decision to donate or not. Considering that donation could be the last will of a patient, treating professionals should offer this possibility to their patients. Potential c-DCD should receive integrated interdisciplinary palliative care, including sedation and analgesia. Members of the donation and retrieval team must not be involved in providing this medical care. Once WLST has been performed, if the patient does not progress to death within the timeframe accepted for valid donation, the necessary care and comfort measures included in end-of-life care planning must continue to be applied.

The donation team is responsible for organizing the donation process and obtaining informed consent. The surgical team carries out organ preservation after determination of death and retrieves organs.

4. SECTION 4: C-DCD OUTCOMES

4.1 Kidney transplant from c-DCD

Because of the warm ischaemia injury associated with c-DCD, recipients of these kidneys have a higher risk of developing DGF compared with recipients of DBD kidneys, but DGF rates in c-DCD are clearly inferior to those reported for u-DCD. With DGF, hospital stays are longer and may mask early rejection, but there is no impact on graft survival, which is equivalent to that of DBD recipients. It does not appear that DGF has the same detrimental effect on graft and patient outcomes in comparison to the DGF that occurs after DBD kidney transplantation. The incidence of PNF for both c-DCD and DBD are similar, although they are slightly higher in c-DCD cases.

Regarding the function of renal grafts, in terms of eGFR, at 1 and 5 years, there also seems to be no difference between c-DCD and DBD kidneys. There are, however, risk factors which have a negative predictive value on graft and patient survival: donor age, donor serum creatinine and CIT.

Short and medium-term transplant outcomes are similar in recipients of kidneys from DBD donors. An increasing donor age has c-DCD survival rates that are comparable to ECD-DBD. So, the available evidence suggests that the criteria on which to base the selection of kidneys from deceased donors should be similar for c-DCD and DBD kidneys.

Prolonged CIT is undesirable and may adversely affect the transplant outcome. In c-DCD kidneys, which are especially vulnerable to the effects of cold ischaemia, it is important to keep to CIT to a minimum, preferably less than 12 hours. There is an association between increased CIT and a reduction of graft survival.

Recipients of DCD kidneys are usually older than DBD recipients, which probably reflects the trend to selection of older patients for kidneys that are perceived as suboptimal.

Acute rejection episodes are usually reported more frequently in c-DCD than in DBD, probably related with increased inflammatory activity in the damaged organ due to warm ischaemic injury. Acute rejection appears to be the most important risk factor for death-censored graft loss in c-DCD kidney transplants, and its effect on graft survival is independent of DGF.

Some studies suggest that the use of HPPM instead of CS can reduce DGF, although randomized controlled trials of HPPM have shown conflictive results with respect to DGF, and none have reported a beneficial effect on graft survival. It is also suggested that the benefit of HPPM in c-DCD could be in a subgroup of older donors or with a prolonged CIT.

A wider international development of c-DCD kidney transplantation programmes will help solve the global shortage of kidneys for transplantation.

4.2 Liver transplant from c-DCD

The use of c-DCD may provide a valuable source of livers for transplantation. This kind of donation subjects the liver to warm ischaemia, which may result in hepatic artery thrombosis, intrahepatic biliary strictures, hepatic abscesses or PNF. The perception of these potential complications and failures have prevented a wide acceptance by the transplant community of c-DCD livers.

Excellent mid and long-term patient and graft survival can be achieved with c-DCD liver grafts. Some studies suggest that the use of c-DCD from donors under 60 years of age is associated with poorer outcomes than with livers from DBD under 60 years old. However, these c-DCD <60 have similar results to DBD >60 years of age. Besides, other registries report that when a low-risk recipient is combined with a low-risk c-DCD (FWIT <30 minutes and CIT<10 hours), graft survival rates are not significantly different from DBD grafts. The wide variation in results from one centre to anther may reflect different donor and recipient selection criteria, FWIT, CIT, etc. The overall incidence of graft survival at 1 and 3 years was 81% and 74% respectively (87% and 84% in DBD) (UNOS data).

Using c-DCD with strict criteria and keeping FWIT and CIT to the minimum, PNF and hepatic arterial thrombosis rates are not significantly higher than those of DBD. The development of intrahepatic biliary strictures is the weak point of c-DCD liver transplantation. Their treatment is difficult and frequently results in retransplantation. Ischaemic cholangiopathy is the major source of morbidity after liver transplantation in c-DCD (biliary sepsis, requirement for multiple endoscopic or percutaneous biliary procedures, prolonged antibiotic treatment or others). This is difficult to predict as its physiopathology is not well understood (biliary epithelium sensitive to ischaemia-reperfusion injury, failure to regenerate, bile toxicity, thrombosis or microcirculatory impairment, etc.). Reviews of the literature reveal an average incidence of biliary complications of 26% (11-53%) in c-DCD compared to 16% (6-28%) in DBD, considering biliary complications as: ischaemic cholangiopathy, bile leak, bile-duct necrosis (histologically proven necrosis of the wall), biliary infections, biliary casts, or anastomotic strictures requiring intervention or surgery.

Most surgical teams that consider a liver transplant from a c-DCD perform a rapid retrieval technique, with cannulation of the aorta and the portal system to flush a cold preservation fluid and the cross clamping of the intrathoracic descending aorta. In recent years, several protocols have included NRP as a method to preserve c-DCD livers, with or without *pre-mortem* cannulation and heparinization. NRP can play an important role in mitigating the effects of warm ischaemia. Results with NRP compared to rapid retrieval are promising, reducing biliary complications and PNF, as well as increasing graft survival, and are equivalent to outcomes for DBD livers. In the future, the sequential use of NRP combined with ex vivo normothermic liver machine perfusion could improve the quality of preservation, assess the quality of the organ and allow the organ to be repaired prior to transplantation. This would improve the results of c-DCD livers and increase the transplantation rate: NMP provides a platform for liver optimization strategies.

Some studies have described that WLST in the operating theatre, as opposed to the ICU, can attenuate the difference in graft survival rate between c-DCD and DBD and reduce the incidence of ischaemic cholangiopathy (by diminishing FWIT). The administration of heparin before WLST decreases PNF with c-DCD.

In summary, results from c-DCD livers can be considered as equivalent to those obtained from DBD livers, in addition to enabling an expansion of the donor pool.

4.3 Pancreas transplant from c-DCD

The pancreas is more vulnerable to damage than other organs (obesity, cardiovascular diseases, alcoholism, damage during retrieval, ischaemia), but the careful selection and management of a c-DCD can give good results after transplantation.

Lower conversion rates are related to the perception that a pancreas from a c-DCD is associated with a higher rate of DGF or technical complications. The islet transplantation rate is unknown, but probably marginal. There is a need for practice guidelines that will help to increase c-DCD pancreas utilization. Variables identified as predictive of a 1-year pancreas graft survival are age over 45, DCD status, race (Black, Asian), cause of death (CVA), body mass index (BMI) over 30, cold ischaemia time, renal function, and gender (male). The data were used to construct an algorithm to assign a score to a donor, the pancreas donor risk index (PDRI), which has shown to be predictive of outcome. With the level of evidence available, it is not easy to determine the interaction between risk factors and the fact of being a c-DCD. The use of a c-DCD pancreas is appropriate on the condition that the accumulation of other risk factors is minimized, reflecting the cautious approach taken with these transplants. Donor selection for c-DCD pancreas transplantation is stricter than for other organs.

Cold storage is the standard method for pancreas preservation. Recovery with *in situ* perfusion (IP) by cannulation of the superior mesenteric vein results in poor perfusion because of the pressure increase at the venous side of the pancreas that creates congestion. If portal perfusion to the liver is required, a cannula should be placed via a portal venotomy without compromising the pancreatic venous outflow. The optimal preservation solution for cold storage of DCD pancreas grafts has yet to be established, and further studies are needed.

There is little published evidence of the benefit of NRP in the context of c-DCD pancreas. The few cases reported all had good outcomes. It seems that NRP could have the potential to ameliorate some of the deleterious effects of ischaemic damage.

There is a reluctance to use HMP in the context of c-DCD pancreas. The delicate structure of the pancreas, particularly the endothelium, requires caution and strict pressure and flow limits. It has been related with oedema and congestion, which increases the risk of early venous thrombosis and graft failure. The use of NRP has focused more on improving the yield of islet cells for transplantation than on pancreas grafts.

Most centres that publish the results of c-DCD pancreas do so in the context of simultaneous pancreas and kidney (SPK) and pancreas after kidney (PAK) transplantation. They report DGF rates, 2-day and 30-day serum amylase and lipase levels, technical failures, operative morbidity and a length of hospital stay equivalent to those achieved with DBD. The mean HbA1c is also reported to be normal and similar in both groups up to 5 years of follow-up. Survival rates are over 80% and 70% at 1 and 5 years respectively. Some series report higher incidences of pancreatitis and venous thrombosis. Evidence suggests a potential role for *ante-mortem* heparin in reducing this discrepancy.

4.4 Lung transplant from c-DCD

Only 10% to 20% of DBDs provide lungs for transplantation, despite the increasing use of ECD. With c-DCD, the utilization rate varies from 2% to 20%, but it is only performed by a small number of lung transplant teams. This underutilization is explained by logistical and financial issues, lack of experience, lung quality and recipient outcomes.

In c-DCD, after determination of death, a rapid sternotomy is performed, and lungs are cold flushed. There are no clinical studies regarding the best flush route, antegrade or retrograde, nor the best flush fluid.

Validation is made by interpretation of the partial oxygen pressure (PaO_2) in relation to a FiO_2 of 100% with a standardized PEEP of 5 cm H_2O during mechanical ventilation.

Studies that report c-DCD lung transplantation show a graft survival at 1 year ranging from 90-74%, with patient survival and chronic lung allograft dysfunction comparable to those of DBD. The few studies that report survival at 3 and 5 years also present similar results to DBD lung transplants. As scaled with the primary graft dysfunction (PGD) score proposed by the ISHLT, PGD grades after c-DCD are reported to be equivalent to those after DBD. Some studies report an increase in the length of hospital stay and a prolonged ventilator duration with c-DCD lungs, but these data do not always achieve statistical significance.

Ex vivo lung perfusion (EVLP) may allow assessment of c-DCD lung function and prolong cold ischaemia time to facilitate the logistics of transplantation. It may also be used to accept and assess c-DCD with a FWIT longer than 60 minutes and up to 120 minutes. In EVLP, a preservation fluid with a high oncotic pressure is perfused in a pressure-controlled manner into the pulmonary artery and collected in a reservoir. PaO_2 during EVLP may not be the first indicator of lung injury. Thus, the evaluation of other parameters like compliance and pulmonary vascular resistance must be considered. In c-DCD lung transplantation EVLP can safely increase utilization rates.

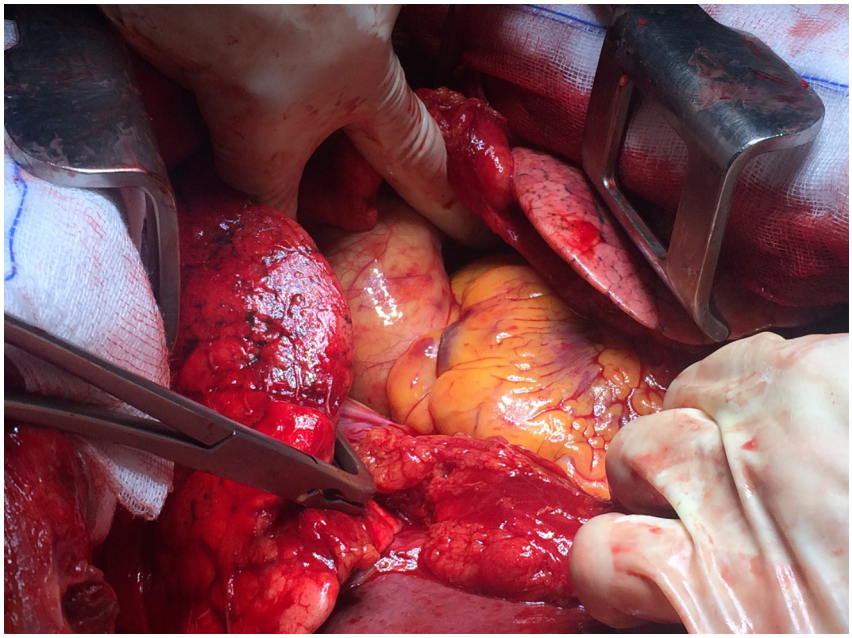

Figure 16.

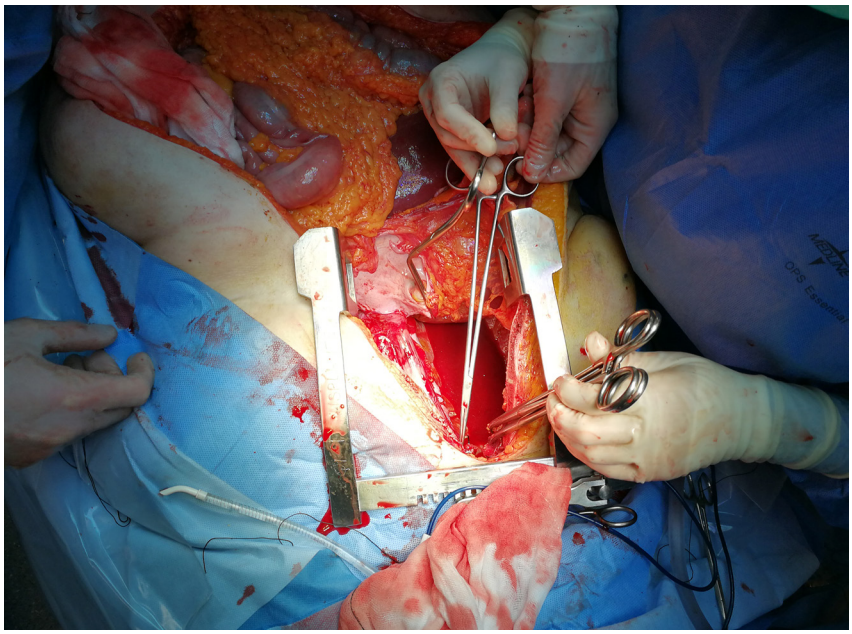

Figure 17.

4.5 Heart transplant from c-DCD

Hearts from c-DCD have an unknown functional status, a risk of occult pathology and substantial warm ischaemic insult. It is necessary to mitigate this ischaemic injury during WLST, preserve the heart once procured, and assess its viability before transplantation. Different approaches to heart recovery from c-DCD have been taken:

4.5.1 Traditional recovery and cold storage

To achieve success, c-DCD have to be matched with the recipients. Furthermore, it is crucial to have *pre-mortem* heparinization and cannulation, in addition to a short no-touch period for declaration of death.

4.5.2 Direct procurement and perfusion

Successful heart transplants from c-DCD have been reported following direct procurement, transport and a viability assessment using NMP. After a cardioplegia flush via the aortic root, the heart is explanted with a transaction at the mid-aortic arch, at the pulmonary artery bifurcation and at the confluence of the superior vena cava with the innominate vein. After the cannulation of the aorta and pulmonary artery, the heart is connected to the NMP. Aortic pressure, coronary flow and arteriovenous lactate concentrations are used to assess cardiac function.

4.5.3 General NRP after the exclusion of cerebral circulation

Function is restored using NRP on the arrested heart of a c-DCD within the donor. After the declaration of death, a midline sternotomy is performed, and the brachiocephalic trunk, left common carotid artery, and left subclavian arteries are cross clamped to exclude cerebral circulation. The ascending aorta and right atrium are cannulated before being connected to the NRP circuit. This technique affords an earlier restoration of coronary circulation to the arrested heart and avoids the urgency of recovering other organs.

When cardiac contractility is sufficiently recovered after a functional assessment (Swan Ganz and Echo), NRP finishes, the heart is flushed with the cardioplegia solution and placed at the NMP. This quality check enables prediction of function within the recipient and reduces the risk of primary graft dysfunction.

At present, most studies suggest that a warm ischaemia time of 30 minutes is probably the upper time limit before the heart starts to suffer irreversible ischaemic injury.

Some recent studies indicate that varying the temperature of the initial perfusion solution to normothermia provides excellent preservation of the c-DCD hearts prior to the institution of normothermic machine perfusion, indicating that profound hypothermia is probably unnecessary and indeed may be harmful. Further research is required.

With a careful selection of c-DCD and recipients, survival outcomes comparable to those obtained from DBD are achievable.

CONCLUSIONS

The use of organs from donors who die as a result of a circulatory arrest after WLST is justified and provides a way of reducing the organ shortage with graft and patient outcomes that are close to those obtained in DBD transplantation.

Logistical, financial and ethical issues need to be addressed by the transplant centres if c-DCD organs are to be more widely used. Efforts that focus on better scoring systems, identifying donor risk variables and reducing cold ischaemia time would contribute to making DCD programmes more economically productive and to improving outcomes. Risk factors that predict early postoperative complications need to be identified.

Under certain circumstances and with increasing experience, acceptable results can be achieved, even from ECD-c-DCD. Collaboration between centres needs to be encouraged, promoting the development of protocols, agreeing guidelines and definitions for FWIT and CIT, standardizing the preservation and procurement processes and developing allocation policies.

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TOPIC 10 - Unit 1

General aspects in living donation

ORGAN DONATION

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Donation can take place after death or during life. Living donors are healthy volunteers who expose themselves to the risk of surgery solely for the benefit of another individual [1]. Currently, transplants with organs from living donors are considered to be an excellent therapeutic option. This is justified by the scarcity of organs from deceased donors, the guarantee of the donor's safety and better outcomes for the recipient, and the reduction in both the length of the waiting list and mortality rates in patients while on the list.

Nevertheless, living donation should complement deceased-donor donation; it should never replace it.

There is a clear parallel between the increase in the number of organs provided by living donors and the greater importance society attaches to them. It was in this context that the Declaration of Istanbul [2] on Organ Trafficking and Transplant Tourism was formulated, and in particular its proposal on ensuring the protection and safety of living donors. Consequently, any living donation procedure must comply with a series of ethical and legal requirements, and count on the collaboration of different healthcare professionals to guarantee a transparency of process and adequate protection for the donor.

INTRODUCTION

Despite its results, living donation (LD) remains a controversial subject that generates medical and ethical debate. This unit discusses the major medical, ethical, and legal issues related with living donation.

After a general overview of the history of LD and the current situation in the world, this unit looks at the conditions that must be met in order to be a living donor, covering the most relevant medical and ethical issues on living donation.

Finally, the most important international laws and regulations on LD are presented, in addition to some joint initiatives on the follow-up of LD in Europe.

1. SECTION 1. LIVING DONATION AROUND THE WORLD

Since 1954, when the first LD kidney transplant between identical twins was performed in Boston, advances in the field of immunosuppressive therapies have contributed to the success of transplants from deceased donors which, in countries with a high rate of deceased donors -such as most European countries- to a certain extent represented a move away from the alternative represented by living donors.

However, other advances, such as the use of less invasive surgical techniques (laparoscopic nephrectomy) with a low complication rate, and desensitisation techniques for ABO-incompatible transplants, have led to an increase in living donation. Pre-emptive living donor kidney transplantation provides better outcomes (in terms of recipient and graft survival rates). The same may apply to other transplant organs from LD as a result of medical advances that employ less invasive surgical techniques for the retrieval and transplantation of the organs, and the use of organ segments, such as the liver, lung, small intestine and pancreas [4-7].

The rates of living donation may vary between different countries depending on the level of development of deceased donation, as well as other cultural and social issues.

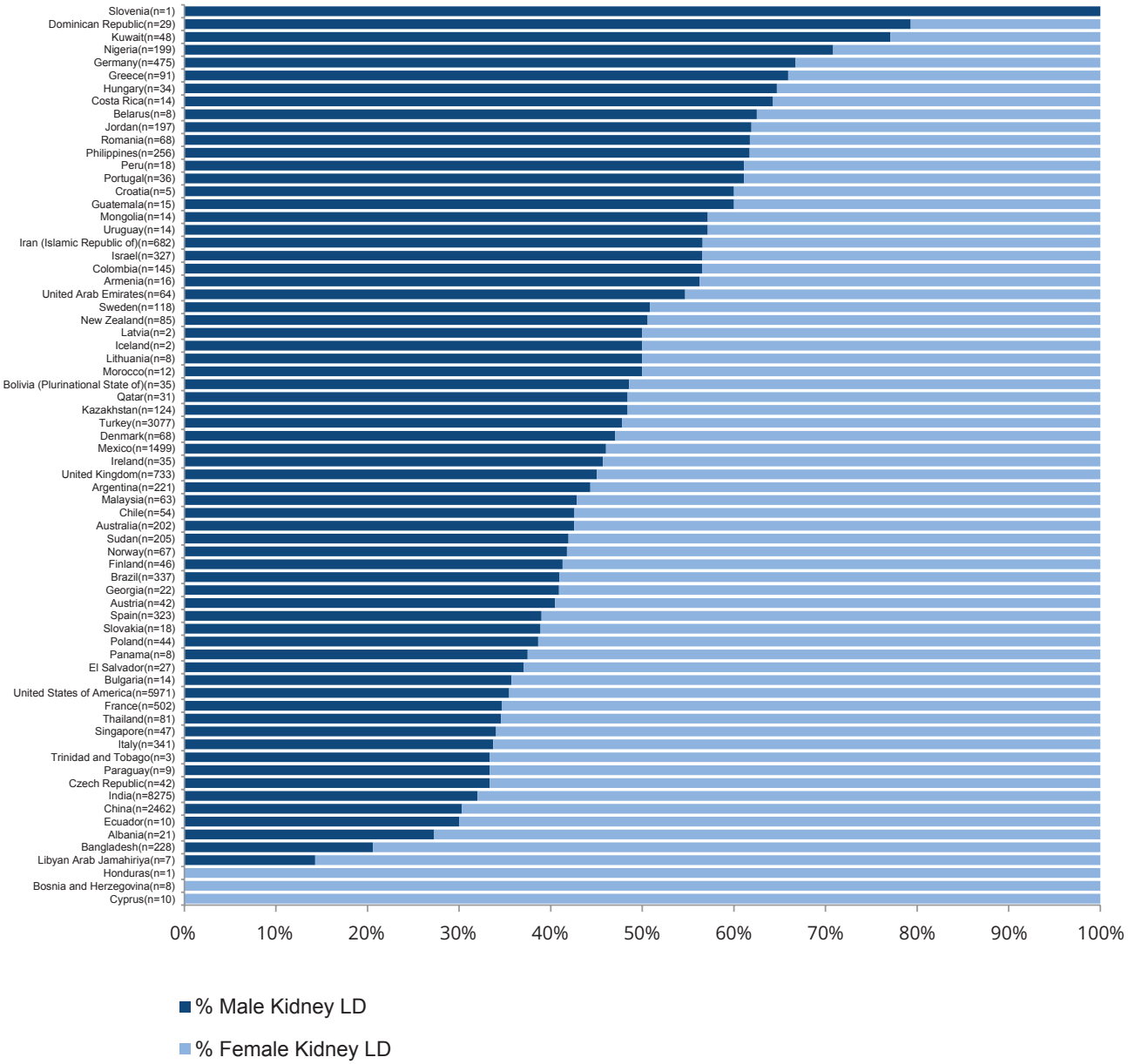
In Asia, the majority of organs used for liver transplant come from LD [8]. This could be a consequence of a low number of deceased donors due to cultural and religious conflicts, or to an absence of legislation on the diagnosis of brain death and a lack of professionalized transplant procurement management (TPM) teams.

In addition, in countries where donation comes predominantly from deceased donors, LD donation has grown as a valid therapeutic option and as a new source of organs to increase the number available for transplant by complementing, not replacing, deceased-donor donation.

Living donation rates vary from country to country. For example, in 2012, the LD rates for kidney transplants in Europe per million population (pmp) ranged from 7.8 pmp in Spain to 29 pmp in the Netherlands. In the USA, the rate was 15 pmp, in Australia 10.4 pmp and Canada 12.3 pmp. Different figures are found in Asia and Latin America, where deceased donor programmes are still not well developed. In Argentina, the living donation rate reached 7.1 pmp, whereas in Mexico it was 16.7 pmp (Figure 1) [9].

Interesting data comes from Iran, where a kidney transplant programme was started in 1967. By 1999, the kidney waiting list had been fully covered [10]. With a population of 76 million in 2012, the LD rate was 19.7 pmp [11].

Living kidney donors by donor sex (%) 2021



N= 70 countries provided information on donor sex

10 460 (38%) male kidney living donors

16 960 (62%) female kidney living donors

Figure 1 .Living kidney donors by donor sex (%) 2021.

2. SECTION 2: WHO CAN BE A LIVING DONOR: ETHICAL CONSIDERATIONS

From its earliest days, living donation was restricted to genetically related persons, but advances in immunosuppressive therapies have allowed the potential donor pool to expand to include people who are not genetically related.

However, this has caused doubts about the donor's motivation to donate. Several authors defend donors with a long-standing and stable emotional relationship with the recipient as ethics gives them the motivation of wanting to help their loved one whether or not a genetic relationship exists [12-14].

Altruistic donors, also known as "good Samaritans", who wish to donate voluntarily to an unknown person on the waiting list, have also generated great controversy. Some authors consider that such people suffer from a kind of psychosocial disorder, or may be donors under coercion, family pressure or for commercial reasons. However, if none of the above factors can be proved, there are no reasons to exclude these donors [15,16].

Living donation is a process that brings out the best in humans and helps reduce waiting list patient mortality rates. However, medical guidelines, legal conditions and practices may vary between countries, different cultural settings and even centres within one country in the determination of who can be a donor.

In general terms, the donor must comply with the following requirements:

- be an adult;
- be mentally competent;
- be willing to donate free of coercion;
- be suitable in medical and medical and psychosocial terms.

A potential donor must also be fully informed of the risks and benefits of donation, for both the donor and recipient, and of any existing therapeutic alternatives that may exist for the recipient [17].

2.1 Motivations for living donation

The feelings and motivations experienced by a person who is planning to become an LD and the way in which the decision-making process is conducted are subjects that have generated much interest. A number of authors have tried to explain these motivations; Lennerling et al. divide the motives into seven categories:

1. A desire to help: a powerful motive, frequently considered as
2. Something natural: the donor simply wants to help a family member or close friend when in need.
3. Increased self-esteem: by doing something that is good and makes them feel like a better human being.
4. Identification: with the recipient's situation.
5. Self-benefit from the relative's improved health: donors assume donation will increase their joint quality of life in many ways.
6. Logic: it is a rational process to analyse risks and benefits. *"If it is possible to live with one kidney, why shouldn't I donate..."*
7. External pressure: coercion by third parties.
8. Feelings of moral obligation: donation is *"something you are expected to do"*.

Of all the above, external pressure is the only unacceptable category. All of the motives are clearly based on subjective feelings, and the donor's decision is mainly based on emotions rather than on an objective risk-benefit analysis [19].

2.2 Risk/benefit assessment of living donation

In living donation, the key question has always been, *"Is it justified to put the life of one person at risk in order to save or improve the life of another?"*

In the early years of transplantation, the answer to this question was yes, due to the low surgical risk of living kidney donation, the strong wish to save the life of a loved one and the lack of other treatment alternatives. Since then, the situation has changed due to achievements in deceased-donor transplantation, advances in the field of immunosuppression, the availability of alternative treatments such as dialysis, and the possibility of living donation of portions of an organ, as in the case of the liver.

Table 1 summarizes the major benefits and risks of living donation.

All these factors have generated debate and discussion on this question. Two basic ethical principles come into conflict in living donation, "beneficence" and "do-no-harm".

- Beneficence implies doing good, and this principle overrides the "do-no-harm" principle if the probability of benefit fully outweighs the risk of the injury to be inflicted [20,21].
- Distributive justice: This principle could particularly affect the lack of supply of organs from deceased donors. It is important to consider that any unnecessary restriction on living donation would worsen the severe scarcity of organs, leading to negative consequences for all potential donors/recipients [20].

Table 1. Different international standards

Benefits of living donation	Risks of living donation
Better graft quality: due to good health of the donor, avoiding any possible organ damage secondary to brain death or during extended cold-ischaemia time.	Short term: morbidity-mortality associated with the surgical process. This is lower in kidney transplantation, especially since the introduction of laparoscopic nephrectomy, and considerably higher in hepatectomy of the right lobe of the liver.
Possibility of choosing the time that the transplant is performed, e.g., cases of pre-emptive kidney transplantation. This helps avoid deterioration in the health of the recipient, increasing the possibility of a successful transplant.	
Increases the donor pool: better access to transplant for the recipient and reduced waiting times for the other recipients on the waiting list; especially in young kidney recipients where the chances of obtaining an age-appropriate deceased donor are lower.	Long term: the rate of long-term complications in LD kidney donors has been shown to be very low, but there are no data for LD liver donors.
Reduction of healthcare costs to society; there is a confirmed lower cost from the first year in favour of transplantation when compared to dialysis treatment.	Psychological: depending on many factors, such as family conflicts, the success of the transplant or the recipient's progress.
Psychological benefits for the donor: increased self-esteem.	

2.3 Informed consent

Informed consent is an expression of a person's autonomy. Autonomy is one of the basic principles of biomedical ethics, which means that people choose and act freely and rationally. Informed consent requires the following [13,22,23]:

- mental competence or capacity to understand and assimilate all of the information provided;
- possession of all the relevant information;
- free and voluntary decision;
- consent and signing of the document.

It is also necessary to give the donor time to assimilate all the information and have all their doubts clarified.

Potential donors must be informed about:

- the nature of the screening and evaluation process;
- the surgical procedure and its associated risks of mortality and morbidity;
- the rehabilitation phase, with its social, emotional, and financial consequences;
- long-term consequences of living donation.

The information should be given in both oral and written form, and it is often necessary to meet more than once with the donor to clarify different issues and questions. Another advantage of multiple consultations is that they give the potential donor the possibility to evaluate the process thoroughly and reach a fully considered and informed decision. In this manner, it can be ensured that the motives for donation are truly altruistic and that the written consent to living donation is based on a full comprehension of the donation process. Some countries recommend that potential donors should also be provided with independent counsellors to avoid the donor suffering any form of coercion. Specific transplant laws usually require some kind of assessment of the donor and the donor-recipient relationship by in-hospital or external ethics committees.

A potential donor should not be burdened with financial or social difficulties during the assessment or donation process. Regulations on how to achieve this vary from country to country. In some parts of the world, certain forms of incentive for the donor are discussed. There is, however, a broad agreement within the transplant community that the sale and purchase of human organs should be illegal and prohibited, as it is in most countries [24].

Further discussion of these aspects of living donation is beyond the scope of this text; however, when it is clear that one or more potential donors are motivated, and no obvious contraindications are apparent, the next phase is the screening process. Its purpose is to ensure compatibility before passing on to the final stage of the selection process: medical assessment.

3. SECTION 3. GENERAL CRITERIA FOR ACCEPTANCE OF A LIVING DONOR

Donor protection should always be guaranteed during the selection and assessment of a living donor [25]. The key factor for a successful living-donor programme is careful attention to every detail and strict routines in donor selection, which will guarantee short- and long-term donor safety, and maximum success for the recipient [26].

3.1 Before donation

The living donor evaluation process follows a different schedule based on each particular case and the facilities available at each centre. In all cases, the process is divided into two phases.

- The first consists of an initial screening (using non-invasive and low-cost tests), which allows contraindications for donation to be ruled out (in both donor and recipient).
- In the second phase, donor assessment varies according to donor characteristics (clinical and psychosocial) and type of organ.

The donor should, in principle, be free of any mental or physical illness, but certain deviations may be accepted without increasing the risk for the donor. These will be discussed in Unit 2.

Initial screening to:

- quickly identify obvious contraindications;
- identify lack of motivation;
- identify obvious psychiatric disorders;
- identify any medical contraindications (i.e., hypertension, heart disease, malignant disease, diabetes mellitus);
- ensure compatibility;
- ascertain ABO and HLA typing.

Clinical examination with emphasis on:

- coronary heart disease and cardiovascular risk factors;
- blood pressure (BP) below 140/90;
- body mass index (BMI) below 30;
- malignant disease with special focus on breast, prostate, and large bowel;
- any malignant disease other than in situ carcinoma of the skin should be avoided;
- history of thromboembolism or bleeding disorders.

Pulmonary function tests in patients at risk:

- Vital capacity.
- Forced expiratory volume in one second (FEV1) and/or peak expiratory flow (PEF).

Heart function tests:

- All subjects should undergo an ECG.
- Exercise ECG in all donors >40 years, and nucleotide perfusion imaging or stress echocardiography whenever any increased cardiovascular risk is perceived.
- A 24-hour blood pressure examination should be performed on all subjects where there are uncertainties concerning the BP.

Imaging:

» Chest X-rays.

» Abdominal ultrasound.

» Computerized tomography (CT) and magnetic resonance imaging (MRI) of the abdomen.

Laboratory tests:

» ABO and tissue typing (duplicate tests).

» Viral serology for HIV, HBV, HCV, CMV, EBV, syphilis and toxoplasmosis.

» General lab values (hematology, liver function, kidney function).

Other health professionals who should evaluate the donor:

» Physician, independent of the team that will perform the transplant.

» Anaesthetist.

» Social worker.

» Psychologist or psychiatrist if indicated.

» For abnormal findings, all relevant medical sub-specialities should be consulted.

3.2 After donation

Another important impact of the follow-up programme is that it is the only way to assess the true performance of the medical treatment the donors have received and detect any possible negative effects caused by the procedure. These regular medical consultations are an additional benefit of the donation. Donors should be seen at regular intervals (e.g., at 1, 3 and 12 months after the operation, and then yearly).

4. SECTION 4. LEGAL REGULATIONS & REGISTRIES

Living donors need to be protected. With that objective, major organisations are working to create regulatory guidelines to ensure the safety and security of LD.

Likewise, a priority of all transplant programmes must be the integral protection and registry of the living donor. A registry represents the transparency of living donation programmes and the traceability of organs.

4.1 Legal regulations

The WHO [11] issued its "Guiding Principles on Transplantation", and the Amsterdam Forum and Vancouver Forum issued international consensus statements that include criteria relating to living kidney donation and living donation of other organs, respectively.

The European Council has also created a series of recommendations on living donation, contained in the "Additional Protocol of The Convention on Human Rights and Biomedicine on Transplantation of Organs and Tissues of Human Origin", drawn up during the Human Rights and Biomedical Convention, and formally approved by the Committee of Ministers in Strasbourg (24 January 2002), in addition to other considerations for the living donor published in the "Guide to Safety and Quality Assurance for Organs, Tissues and Cells" [27].

Appendix 5 of the Protocol, chapter III "Organ and tissue removal from living persons", Articles 9 to 15, makes the following recommendations:

a) General rule: removal of organs or tissue from a living person may be carried out solely for the therapeutic benefit of the recipient and where there is no suitable organ or tissue available from a deceased person and no other alternative therapeutic method of comparable effectiveness.

b) Potential organ donors: organ removal from a living donor may be carried out for the benefit of a recipient with whom the donor has a close personal relationship as defined by law, or, in the absence of such relationship, only under the conditions defined by law and with the approval of an appropriate independent body.

c) Evaluation of risks for the donor: before organ or tissue removal, appropriate medical investigations and interventions shall be carried out to evaluate and reduce physical and psychological risks for the health of the donor. The removal may not be carried out if there is a serious risk to the life or health of the donor.

d) Information for the donor: the donor and, where appropriate, the person or body providing authorization (Article 14, paragraph 2), shall beforehand be given appropriate information as to the purpose and nature of the removal as well as on its consequences and risks. They shall also be informed of the rights and the safeguards prescribed by law for the protection of the donor. In particular, they shall be informed of the right to have access to independent advice about such risks by a health professional having appropriate experience and who is not involved in the organ or tissue removal or subsequent transplantation procedures.

e) Consent of the living donor: subject to Articles 14 and 15, an organ or tissue may be removed from a living donor only after the person concerned has given free, informed and specific consent to it either in written form or before an official body. The person concerned may freely withdraw consent at any time.

4.2 Protection of persons not able to consent to organ or tissue removal:

6. No organ or tissue removal may be carried out on a person who does not have the capacity to consent under Article 13.
7. Exceptionally, and under the protective conditions prescribed by law, the removal of regenerative tissue from a person who does not have the capacity to consent may be authorised, provided the following conditions are met:
    i. there is no compatible donor available who has the capacity to consent;
    ii. the recipient is a brother or sister of the donor;
    iii. the donation has the potential to be lifesaving for the recipient;
    iv. the authorisation of his or her representative or an authority or a person or body provided for by law has been given specifically and in writing and with the approval of the competent body;
    v. the potential donor concerned does not object.

Directive 2010/53/EU of the European Parliament:

Directive 2010/53/EU of the European Parliament and of the Council on standards of quality and safety of human organs intended for transplantation [28] adopted on 7 July 2010 and to be transposed by Member States until 27 August 2012.

The Directive establishes the basic requirements for the protection of the donor, including data protection and confidentiality (Article 16), the need for consent (Article 14) and the voluntary and unpaid nature of the donation (Article 13).

In addition, the Directive contains a number of measures aimed at protecting living donors. These include a correct assessment of the donor's health and comprehensive information about the risks prior to the donation (Article 7), and the development of registers for living donors to follow up their health status (Article 15).

Article 15: Quality and safety aspects of living donation:

Member States shall:

1. Ensure the *"highest possible protection of living donors."*
2. Ensure that *"living donors are selected on the basis of their health and medical history, by suitably qualified or trained and competent professionals. Such assessments may provide for the exclusion of persons whose donation could present unacceptable health risks."*
3. Ensure that *"a register or record of the living donors is kept, in accordance with Union and national provisions on the protection of the personal data and statistical confidentiality"*.
4. *"...endeavour to carry out the follow-up of living donors and shall have a system in place in accordance with national provisions, in order to identify, report and manage any event potentially relating to the quality and safety of the donated organs, and hence of the safety of the recipient, as well as any serious adverse reaction in the living donor that may result from the donation."*

4.3 Joint initiatives

Living donor registries should be in place and used in order to be able to audit the LD programme easily at regular intervals. Besides hospital, local or national registries, there are some European initiatives for the registry and follow up of living donors.

European Living Donation and Public Health (EULID, 2007-2009) promoted and coordinated by Hospital Clinic de Barcelona with the collaboration of 10 European countries. The EULID project aimed to analyse the situation in European countries regarding legal, ethical, protection and registration aspects related to living donors and living donation, in addition to making consensual recommendations on these issues and creating tools for use in all living donation programmes to guarantee the health and safety of living donors.

Results of this project included the creation of an online database to register living donors, an informative leaflet for the public about living donation, and a satisfaction survey for the donation process [29,30].

European Living Donor Psychosocial Follow-up (ELIPSY, 2009-2012) [31], promoted and coordinated by the Hospital Clinic de Barcelona with the collaboration of 6 European partners. The ELIPSY project aimed to contribute to guaranteeing high-quality living organ donation programmes by creating a follow-up model for the psychosocial well-being and quality of life of living donors. The impact of the recipient's outcome on the donor and the donor's perception of the process would also be evaluated in the follow-up model. The ELIPSY project contributed to the harmonisation of living donor psychosocial follow-up practices, promoting high-quality living donation programmes.

The main conclusions to emerge from the ELIPSY project were:

» The survey of psychosocial assessment/follow-up practices conducted in 52 centres of 10 countries showed no consensus among them.

» The methodology applied to evaluate the short- and the long-term psychosocial follow-up of living donors showed no significant differences in the psychosocial outcome of living donors compared to the healthy general population.

CONCLUSIONS

Living donation should complement deceased donation; it should never replace it.

The outcomes of LD transplants are better than the outcomes of deceased donor transplants. Donor morbidity and mortality is low.

Living donor transplant programmers must scrupulously comply with ethical principles and the legislation in force in each country, avoiding inappropriate practices, commercialisation and trafficking of organs.

The integral protection and registry of living donors must be a priority in all transplant programmes.

A registry represents the transparency of LD programmes and the traceability of organs.

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TOPIC 10 - Unit 2

Living kidney and liver donation

ORGAN DONATION

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INTRODUCTION

Although there are other organs or their segments such as the lung, small intestine and pancreas, that can be transplanted from living donors, the kidney and liver continue to be the organs most frequently transplanted from living donors.

This unit discusses specific issues related to living donation of the kidney and liver such as:

- the advantages that living donor transplantation of kidney or liver may represent as an alternative to deceased donation;
- the specific clinical and anatomical requirements needed to achieve successful living donation and transplantation of these two organs;
- the technical surgical challenge that retrieval of these organs from living donors may represent;
- the immediate (postsurgical) and long-term consequences that living kidney and liver donation may pose to the donors.

1. SECTION 1. LIVING KIDNEY DONATION

In 1954, Murray and colleagues performed the first successful living donor kidney transplantation (LDKT) in Boston on identical twin brothers [1]. In Europe and North America, LDKT was introduced as a standard part of renal replacement therapy in the late 1960s. In some countries, such as Norway or the United States, LDKT constitutes up to half of the total number of renal transplants. Today, the concept of using live donors has gained widespread acceptance around the world as the treatment of choice for patients with end stage renal disease (ESRD).

1.1 Advantages of living donor renal transplantation

Kidney transplantation is a life-saving procedure [2] and it is well documented that LDKT offers significantly better graft and patient survival compared with kidneys from deceased-donors [3,4].

Morbidity and mortality rates for patients on the waiting list are clearly related to the time a patient remains on dialysis [2] and it is recognized that ESRD increases cardiovascular mortality by a factor of approximately ten.

One important aspect of LDKT is that it allows for planned, elective procedures, thus making the waiting time on dialysis shorter, and the concept of pre-emptive transplantation possible and feasible in practical terms.

Living donor grafts appear to have better functional outcomes (Figure 1) and even better graft survival rates in two-haplotype mismatched LD transplantations compared with zero-mismatched DD grafts [3,4].

This improved survival is probably related to several different factors, such as high-quality donor selection, optimal timing of the transplant, short cold-ischaemia time and avoidance of the pathophysiological alterations induced by brain death. In particular, LDKT is well-suited to paediatric recipients as it minimizes waiting times and the need for dialysis. From a public health perspective, the use of living kidney donors is the only way to provide functioning renal grafts within a reasonable period of time to a large proportion of candidates who are waiting.

A comparison of international rates of the incidence of renal failure and transplantation clearly shows that countries with well-developed LDKT programmes have the highest transplantation rates and the shortest waiting lists. As a result, a larger proportion of patients treated for ESRD have a functioning graft instead of being dependent on dialysis. Likewise, there is also a significant economic impact because there is a significant reduction in the need for costly dialysis treatment.

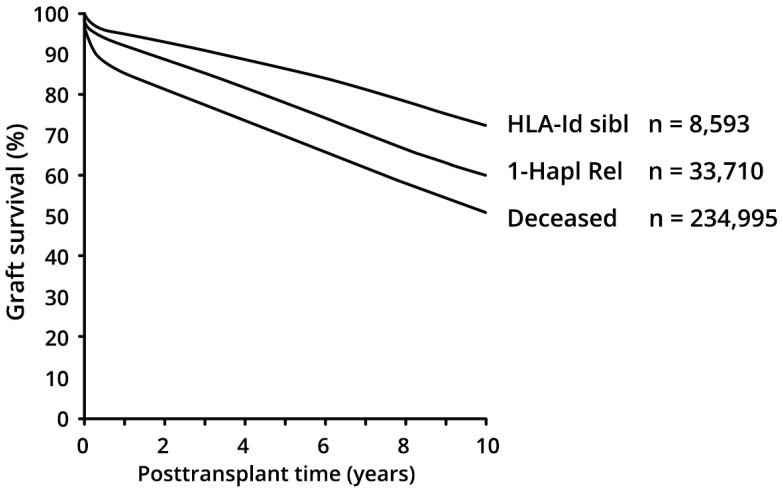

Figure 1. Graft survival after first renal transplant according to donor source.

1.2 Who can be a living kidney donor

The ideal living donor is a healthy adult member of the patient's immediate family, and the majority of LDKT are still from related donors. However, the use of genetically unrelated but emotionally linked donors has gained widespread acceptance worldwide [3] and various guidelines exist on this subject [5, 6].

One alternative in living kidney donation is cross-over donation [7] also known as paired kidney exchange (Figure 2). In 1986, Rapaport et al. [8] proposed the idea of paired kidney exchanges in an attempt to increase the availability of organs for transplantation.

Successful LD paired kidney exchange programmes require a large pool of donor-recipient pairs who are incompatible, and all types of LD (relatives, spouses, close friends and voluntary donors) are potentially available.

Yet another option is the exchange of living kidneys between donor-recipient pairs with ABO incompatibility. This procedure started in 1991 in South Korea. Since then, it has been considered ethically acceptable, and is commonly used in countries like the USA, the Netherlands and the United Kingdom in their national or regional programmes. The donor-recipient pair must be completely informed about the characteristics of the other pair and the surgical procedure must be performed simultaneously.

Another proposal is list-paired exchange, in which a living donor who is incompatible with his/her recipient provides a graft to a patient on the deceased-donor list in exchange for giving transplant priority to the recipient who provides the living donor.

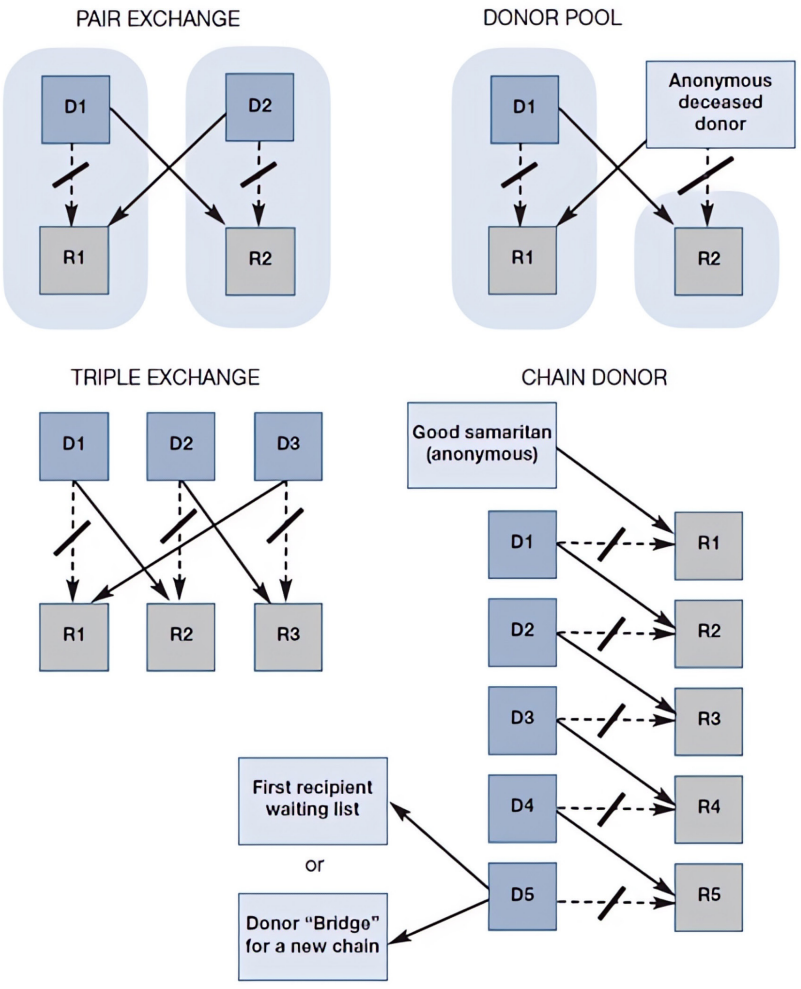

Figure 2. Kidney exchange: different options. (D: donor; R: recipient; continuous line: compatible match - transplant; discontinuous line: no compatible match).

1.3 Specific clinical evaluation of living kidney donors

In addition to the general clinical evaluation that every potential living donor should receive before donation can go ahead (see Unit 1), there are specific organ-related issues that must be assessed in all living kidney donors. These include a thorough evaluation of renal function with:

» assessment of glomerular filtration rate (GFR), not only using formulas but also including creatinine clearance (repeated determinations) and/or isotopic determinations of GFR. Measured GFR should be >70 ml/min;

» radionuclide imaging may be indicated in cases where suspicions exist of significant differences (>60/40) between the right and left side. In this case, nuclear imaging can be used to evaluate whether the poorer functioning kidney provides acceptable renal function for the recipient.

The use of imaging can assist us in determining the presence of structural abnormalities and renal function.

» CT-angiography with arterial, parenchymal, and excretory phase.

» Ultrasound of any undetermined renal cyst.

» Magnetic resonance imaging (MRI) can be used, but has lower sensitivity than CT.

Laboratory tests, such as urine analysis, should be double checked for anomalous albumin, blood and glucose results using microbiology and microscopy.

Certain clinical findings that may appear in the evaluation of potential living kidney donors may advise caution.

» Abnormal urine findings (microscopic haematuria may be accepted after a full workup).

» Marginal renal function in the elderly donor (GFR <70 ml/min/1.73 m^2).

» Discrete unilateral renovascular abnormalities (must be judged on an individual basis, and the affected kidney must be used).

» Borderline blood pressure.

» Overweight (BMI >30).

» Hereditary nephropathies: patients with conditions such as autosomal dominant polycystic kidney disease (ADPKD), Fabry disease or Alport syndrome may be candidates for kidney transplantation. Although renal transplant from a living related donor is not contraindicated in most nephropathies that have an autosomal recessive mode of inheritance, caution should be observed, and the disease must be excluded in the donor by imaging and/or genetic testing. Potential living related donors for patients with Alport syndrome should be evaluated carefully for the presence of microhaematuria and microalbuminuria and should be informed about the possible long-term increased risk of renal dysfunction associated with donation [9].

1.4 Living donor nephrectomy

Living donor nephrectomy represents a major surgical procedure for a healthy individual who will receive no direct benefit from the operation itself. It is therefore of utmost importance that the preoperative medical records are checked and re-evaluated by the surgeon responsible, and that the surgical team has the necessary skill and experience to perform the donor operation with the highest quality and the lowest complication rate possible.

In some donors, abnormalities may be found that can be adequately addressed by suitable prophylactic measures. Which side to choose is determined by surgical anatomy, any split function differences and other factors relating to the donor, such as scars and perceived difficulties in positioning on a particular side should be taken into account.

The general principle is that the donor should always be left with their best kidney if there are differences between the sides. When both kidneys are evaluated as equal, the kidney that imposes the lowest surgical risk on the recipient (i.e., avoiding multiple arteries) should be chosen.

Various techniques are available for donor nephrectomy. Open and endoscopic approaches are practiced, and the decision about the technique largely depends on the surgical team and previous experience. Open donor nephrectomy has been proven to be safe over the years. Since 1995, laparoscopic and retroperitoneoscopic donor nephrectomy have gained increasing popularity and represent the current standard in most centres. A very small number of centres have gone one step further and offer transvaginal donor nephrectomy in selected cases [10]. These methods offer donors faster recovery and less need for analgesia in addition to cosmetic benefits, without jeopardizing the donor or the graft [11]. It is, however, clear that there is a distinct learning curve for most surgeons in mastering laparoscopic operations and endoscopic procedures are associated with complications not seen in open surgery [14]. The choice of method must therefore be based on the skill of the surgical team, anatomy and other donor-related factors.

1.5 Immediate and long-term consequences of living kidney donation

The risk of mortality with living donor nephrectomy is very low, and estimated to be in the region of 0.03% [15].

Major surgical complications, such as significant bleeding, pulmonary embolism and deep infection are rare. The overall surgical complication rate is approximately 5-10%, the great majority of complications are mild and do not pose any risk of long term morbidity [16,17].

Properly selected donors should not experience any increased risk of morbidity following donation. Unilateral nephrectomy in a healthy person (i.e., without hypertension, obesity or diabetes) is not associated with an increased risk of kidney disease in the long term.

The long-term effects of kidney donation have been thoroughly investigated in several studies [18-21]. Studies show that donors have a lower incidence of medical disability and sick leave, as well as a higher life expectancy, than age-matched controls.

The incidence of hypertension is similar to or slightly higher than that of the general population and more often detected in older donors, as would be expected. Therefore, close monitoring is necessary so that hypertension may be detected early, and appropriate treatment may be introduced at the earliest date to prevent complications.

In older donors or in those who have a GFR in the lower normal range, a slight elevation of creatinine might be observed after the donation. It is possible that donation poses a particularly increased risk in older subjects [22]. In a limited number of cases, end-stage renal disease has been observed in donors; however, a number of studies report that its incidence is significantly lower than in the general population [18].

However, the majority of studies on long-term risk do have limitations since the follow-up periods are, in general, too short to evaluate lifetime risk. Furthermore, it might be questioned whether the control groups used are truly relevant, since they inherently include individuals who would not be eligible for kidney donation.

A recent study in Norway, with very long follow-up period, compared donors with a cohort from a large observational population study in which the subjects would be eligible as donors. The results showed a greatly increased lifetime risk of ESRD and an absolute increase in cardiovascular death of 2% over a 24.9-year follow-up period. The increased risk of ESRD might be related to hereditary factors since the majority of donors are genetically related. The risk of mortality is very moderate and occurs late in life, illustrated by the fact that the survival curves only began to separate beyond 10 years of follow up. These results do not justify changing current guidelines and should be further evaluated in future studies; however, the findings do underscore the importance of regular donor follow-up and well-functioning donor registries [23].

2. SECTION 2. LIVER DONATION

Living-donor liver transplantation (LDLT) was first conceived to provide a solution for the lack of appropriate donors for children, whose waiting list mortality rate was 30-40% [24-26].

The first successful transplant of this kind was performed in Australia [27] and the first pilot experience was carried out by Broelsch in Chicago [28]; however, liver transplantation in children from living donors was largely developed in Japan because, due to the country's particular cultural beliefs, brain death is not accepted as confirmation of a person's death [29]. Outcomes confirm the efficacy of this alternative, which renders good survival rates and has eliminated waiting list mortality.

Until 1993, all living-donor liver transplants were performed with the left liver lobe or segments 2 and 3 of the left lobe. This technique was also used for adult recipients in the United States but was abandoned because the liver mass in the left lobe was insufficient to cover the needs of adult patients. The right lobe of the liver, which represents around 60% of its total mass, was the solution to this problem.

The first right-lobe liver transplant from a living donor took place in Japan in 1993 [30], followed by the first in the United States in 1997 [31]. If the initial liver mass is sufficient, the liver's enormous regenerative capacity determines rapid growth in both the donor and the recipient. The initial success of this technique, combined with the lack of deceased donors, has led to an increasing interest worldwide in living-donor liver transplantation in adults. More recently, thanks to advances in knowledge about what is known as the "small-for-size" syndrome, LDLT using the left liver as a graft is gaining increasing importance, both in eastern and western countries.

2.1 Advantages of living donor liver transplantation

Liver transplantation is the only valid therapy for patients with end-stage liver disease [32].Thanks to improvements in surgical techniques and advances in both the post-operative management of these patients and immunosuppressive therapies, survival rates of over 82% are currently obtained one year after transplantation [33]. As a result, there has been a significant widespread increase in the demand for liver transplants worldwide, essentially due to the incidence of chronic liver disease caused by the hepatitis C virus and hepatocellular carcinoma, which is an indication for transplantation in selected patients.

In general, patients considered to be candidates for LDLT must previously have met the requirements for inclusion on the transplant waiting list. Although this policy is controversial, LDLT provides the possibility of extending the classic indications for liver transplantation, as in the case of older recipients or hepatocellular carcinoma, beyond the Milan criteria [34]. There are other diseases with poor outcomes after liver transplantation, such as cholangiocarcinoma [35] whose indication is only contemplated within the framework of controlled studies [36].

Nowadays, most waiting lists for liver transplantation are sorted using the MELD (Model for End- Stage Liver Disease) score, an objective system based on the calculation of three analytical parameters: serum bilirubin, INR (International Normalised Ratio) and serum creatinine [37]. This distribution system was introduced in the United States in February 2002, with the objective of reducing waiting list mortality in order to give priority to patients whose conditions were worse due to their liver disease, regardless of how long they had been on the waiting list.

According to this score, waiting list patients with intermediate MELD scores are the best candidates for LDLT, as they are less likely to receive a transplant from a deceased donor unless their clinical status worsens. This is an additional benefit in organ distribution, as it has been shown that the outcome of LDLT is worse in patients with higher MELD scores [38] and conversely, no clear benefit has been shown from transplantation in patients with MELD scores under 15 [39].

Once a patient is on the waiting list, they can be offered the possibility of LDLT in centres where the procedure is performed. To determine which recipients would most benefit from these procedures, besides the MELD score, consideration must also be given to the reduction in waiting list time and, in cases of hepatocellular carcinoma, the possibility of scheduling the procedure before the disease progresses. Some additional advantages are the possibility of effectively preparing the patients for the procedure and of scheduling the best time to perform the transplant (e.g., HCV patients, who are administered antiviral treatment beforehand).

Furthermore, in the case of LDLT, cold ischaemia time of the graft is generally less than 60 minutes, far less than with grafts from deceased donors, which reduces the possibility of graft dysfunction. This is also reinforced by the fact that the physiological changes associated with brain death, which are potentially detrimental and influence graft quality, are absent in grafts from living donors [40].

According to the United Network for Organ Sharing (UNOS) [41], to date there have been 4,909 LDLTs in adult recipients in the United States. The probability of graft survival (82.5 after one year, 72.2 after 3 years and 65.9 after 5 years) and patient survival (90.1 after one year, 82.5 after 3 years and 77.7 after 5 years) is similar to that currently obtained with grafts from deceased donors. An analysis of the experience in Europe up to 2011 reveals that 4,809 LDLTs were performed (information from the European Liver Transplant Registry, ELTR) [42], with an overall graft survival of 80%, 74%, and 69% at 1, 3 and 5 years, respectively.

2.2 Specific clinical evaluation of living liver donors

Assessment of possible donors starts when the transplant recipient and their family voluntarily request further information about living donation after the process has been mentioned to them. The minimum requirements for acceptance as a donor may vary from country to country, or even between different hospitals. In general terms, the criteria include being aged 18 to 55, having a blood group identical to or compatible with that of the recipient, and an apparently normal state of health with no associated diseases. However, applicability of the procedure is low, with fewer than one third of recipients having potential donors, and a rate of 14%-25% finally undergoing LDLT [43-45].

The assessment process is not carried out by the transplant patient's own doctors, but an independent team which includes hepatologists, surgeons and psychologists.

One of the most important factors when determining donor suitability is estimated liver volume, because if insufficient, it could have disastrous consequences for the recipient. Insufficient graft volume could lead to initial malfunction and loss, with the appearance of what is known as the "small-for-size" syndrome [46-50]. This syndrome is characterized by sustained cholestasis, abundant ascites, and coagulopathy. The development of extrahepatic complications and sepsis can lead to the death of the patient.

Through the use of computer programmes, both computerised axial tomography and magnetic resonance imaging are capable of calculating the volume of all or part of the liver with a high level of reliability [51,53]. Their utility is evident, since they calculate the total liver volume of the potential donor and the residual amount of liver parenchyma after resection of the right lobe, which is the one generally used for an adult recipient.

The acceptable liver volume for transplant to guarantee adequate postoperative function is considered to be 0.8-1% of the recipient's weight [47,48,54-56]. Due to its larger volume, the right lobe therefore has to be used for transplant into adult recipients.

Another consideration, besides the size of the graft, is that the severity of the recipient's disease also influences postoperative graft function and survival [56]. Patients with worse clinical conditions need larger grafts.

Knowledge of the hepatic vascular and biliary anatomy before obtaining the graft is very important to guarantee the success and safety of the surgery for both donor and recipient. The introduction of helical axial tomography and new MRI models has provided the possibility of a minimally-aggressive detailed vascular and biliary study of the liver [44,57]. Both tests are equally effective for evaluating the vascular distribution of the liver, but MRI is also capable of effectively evaluating the liver's biliary anatomy, so it is currently the gold standard in the assessment of potential donors [53].

The division of the portal vein into its right and left branches presents variations in approximately 20% of all donors. Although the existence of a three-way division is not a contraindication, it must be taken into account when it comes to vein resection (Figure 3). The need for several portal anastomoses, with or without the use of grafts, increases the risk of postoperative thrombosis.

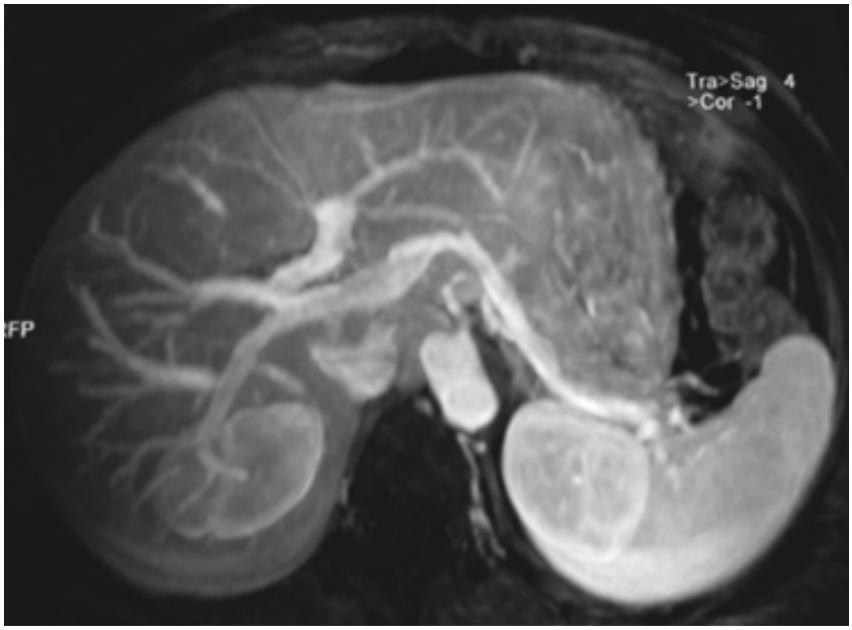

Figure 3. MRI of a donor, showing the existence of three-way portal branching. The anterior right portal branch originates from the left portal vein.

A complex arterial anatomy in the right lobe, such as multiple arteries, can be a reason for rejecting a donor, as there is a high risk of arterial thrombosis of the graft. If necessary, angiography can be used to study the hepatic vascular tree [58].

The distribution of veins in the liver can also present variations. If the lumen of these veins is larger than 5 mm, they must be anastomosed to the vena cava, either directly or using vascular grafts, to prevent them from compromising the graft's vascular drainage. Insufficient venous drainage and subsequent vascular graft congestion may lead to malfunction of the graft [59].

The bile duct is the structure with the largest number of anatomical variations, although this is not usually a contraindication for donation. However, the reconstruction of the graft's biliary drainage system often gives rise to complications, although in most cases this does not compromise its viability [60]. MRI-cholangiography is a non-invasive test which has been found to be effective for preoperative evaluation of biliary anatomy [53,61].

2.3 Living donor hepatectomy

Right hemiliver donation

The surgical procedure in the donor consists of a right hepatectomy (segments 5, 6, 7 and 8) and it is advisable for the operation to be performed by two surgeons with considerable experience in liver surgery [62]. A J-shaped or right subcostal incision is made. Once the laparotomy has been performed, a complete and thorough examination is made of the abdominal cavity and the liver is mobilised by resecting its ligaments. Before starting to resect the hepatic parenchyma, the right portal artery and vein are temporarily clamped to delimit the parenchymal dividing line, performing an ultrasound scan to visualise the middle hepatic vein and define the resection line, to the right of this vein, which remains in the left lobe of the liver. Resection and cauterization of the liver parenchyma is then performed, and intraparenchymal vessels larger than 3 mm are either tied or sutured. The right lobe of the liver is now completely separated, with its vascular structures remaining intact until the last moment, when the graft is removed (Figure 4). The presence of accessory right hepatic drainage veins in the middle hepatic vein may lead to a certain amount of venous congestion when they are tied. This reduces its functional volume, so reconstruction must be considered according to the volume of the graft and the anatomy of the venous system.

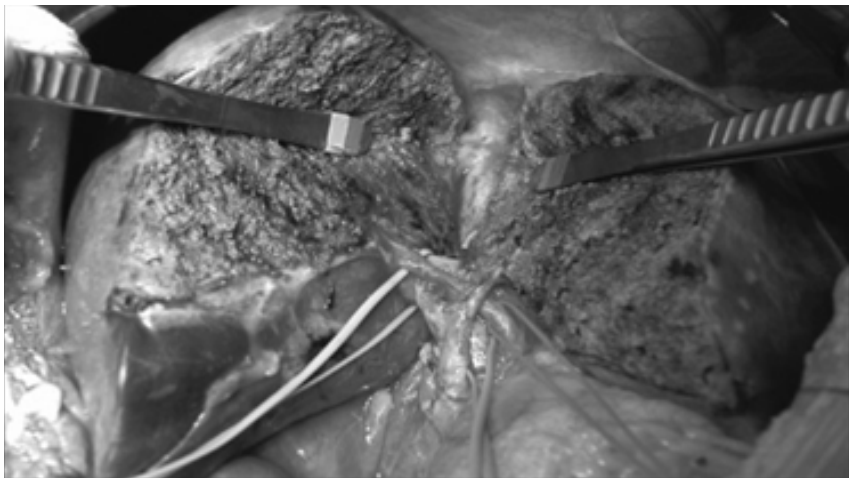

Figure 4. Image of the end of liver resection. The complete separation of the right and left hepatic lobes can be seen, with the vascular structures remaining intact.

Before removing the graft, the vascular structures are dissected and cut, starting with the right hepatic artery, always taking care not to compromise the contralateral structures. The vascular and biliary structures remaining in the donor are haemostatically sutured, and a final cholangiogram is advisable to detect possible leaks in the liver surface and verify the correct morphology of the remaining bile duct. After ensuring adequate haemostasis, the correct position of the left lobe of the liver is verified in order to guarantee correct portal patency.

After the graft is removed, it is perfused with a cold preservation solution through the portal vein and hepatic artery, and stored at 4ºC until it is implanted. It is important to assess the anatomical structures and any need for repair. In cases of multiple right bile ducts, it is usual to perform ductoplasty.

Left hemiliver donation

Although still not the gold standard in western countries, there is a growing trend to use the donor's left liver as a graft, since this involves less risk for the donor, as well as being a slightly less demanding procedure.

The surgical procedure for removing the left hemiliver as a graft for transplantation consists of a standard left hepatectomy (segments 2, 3 and 4). The surgical steps of the procedure are similar to those used in right-lobe donation. First, the vascular and biliary anatomy is evaluated intraoperatively and compared to the preoperative findings. Then, liver transection is performed leaving the middle hepatic vein in the donor side. The process of cooling and perfusing the graft is identical to that described above for the right graft.

2.4 Immediate and long-term consequences of living liver donation

The surgical procedure for right-lobe liver donation is not risk-free. The actual incidence of complications, however, is difficult to define due to a lack of uniformity in data collection. The absence of standardization in donor assessment and surgical procedure, as well as variations in the expertise and technical skills of different groups, make it difficult to evaluate the risks for donors. In 2006, seven patients were reported as having died from causes directly related to hepatectomy in the United States and Europe, representing a 0.15% mortality rate [63]. There were another two reported cases of donors who committed suicide 22 and 23 months after donation. The psychological tests performed in these two cases before donation were normal, so it is difficult to determine whether or not their deaths were related to the donation process. If we include these two cases, the mortality rate rises to 0.2% [63].

The morbidity involved with this operation varies according to the different series published, with highly variable incidence rates (Table 1). A review of published studies including 409 donors and 12 sites showed that the incidence of complications can range from 0% to 67%, with a mean rate of 31% [64]. The most common complications in living donors are related to biliary system problems. Biliary fistulas can lead to collections developing adjacent to the resection line, usually resolving with conservative treatment, but sometimes requiring percutaneous drainage. Stenosis of the remaining biliary system in the donor is less common, with an incidence rate of around 1%, again occasionally requiring surgery [65].

Table 1. Right hepatectomy morbidity in living donors in different published series and Hospital Clinic de Barcelona outcomes (SHV: suprahepatic vein)

Author	Year	*n*	Morbidity
Marcos	2000	40	17.5%
Fan	2000	22	23%
Grewal	2001	11	9%
Trotter	2001	24	32%
Miller	2001	52	34%
Pomfret	2001	15	67%
Beavers	2001	14	64%
Bak	2001	41	22%
Ghobrial	2002	20	20%
Malagó	2003	74	40.5%
H. Clinic	2006	51	41.2%
Global: 21 (41.2%)*	**Complications H. Clinic (*n* = 51)**		
Surgical: 19 (37.2%)	Biliary leak		8 (15.7%)
	Abdominal collection		7 (14%)
	Wound infection		1 (2%)
	Eventration		1 (2%)
	SHV thrombosis		1 (2%)
	Portal stenosis		1 (2%)
Medical: 14 (27.4%)	Fever		5 (10%)
	Pneumonia		3 (6%)
	Pleural effusion		1 (2%)
	Urine infection		2 (4%)
	Peripheral phlebitis		1 (2%)
	Horner syndrome		1 (2%)

CONCLUSIONS

Living kidney donation:

» Renal transplantation is a lifesaving procedure, and it is well documented that the utilisation of grafts from live donors offers significantly better graft and patient survival compared with deceased-donor kidneys.

» The general principle is that the donor should always be left with his/her best kidney if there are side differences. When both kidneys are evaluated as equal, the kidney imposing the lowest surgical risk on the recipient should be chosen.

» The risk of mortality with living donor nephrectomy is very low. Similarly, unilateral nephrectomy in a healthy person is not associated with any increased risk of kidney disease in the long term.

Living liver donation:

» LDLT provides the possibility of increasing the classic indications for liver transplantation, as in the case of older recipients or hepatocellular carcinoma, increasing the total pool of donors and reducing the waiting list.

» Applicability of living donor liver donation is low, with only less than one third of recipients having potential donors, and a rate of 14%-25% finally undergoing LDLT.

» The probability of graft survival and patient survival in LDLT is similar to that currently obtained with grafts from deceased donors.

» One of the most important factors when determining donor suitability is estimated liver volume. Due to its larger volume, the right lobe is preferred for use in transplants to adult recipients. LDLT using a left graft has an increased risk of postoperative complications for the recipient, the most feared being “small-for-size” syndrome.

» The mortality rate of living donor hepatectomy reaches 0.2%. The morbidity involved with this operation can range from 0% to 67%, with a mean rate of 31%.

» The most common complications for living liver donors are related to biliary system problems.

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LIST OF ABBREVIATIONS

ABBREVIATION	MEANING
AD	actual donors
ADH	anti-diuretic hormone
ADPKD	autosomal dominant polycystic kidney disease
AHT	arterial hypertension
ALI	acute lung injury
ALS	advanced life support
anti-HBc	antibody to hepatitis B core antigen
ARAS	ascending reticular activating system
ARDS	acute respiratory distress syndrome
ATP	adenosine triphosphate
BD	brainstem death
BMI	body mass index
BNP	brain natriuretic peptide
BP	blood pressure
CA	cardiac arrest
c-DCD	controlled donation after circulatory death
CIT	cold ischaemia time
CMV	cytomegalovirus
CNS	central nervous system
COPD	chronic obstructive pulmonary disease
CPAP	continuous positive airway pressure
CPR	cardiopulmonary resuscitation
CS	cold storage
CVA	cerebrovascular accident
DAA	direct acting antivirals
DBD	donation after brainstem death
DCD	donation after circulatory death (also, previously, donation after cardiac death)
DCDD	donation after circulatory determination of death
DDAVP	desmopressin
DGF	delayed graft function
DI	diabetes insipidus
DPP	direct procurement and perfusion
EBV	Epstein-Barr virus
ECD	expanded/extended criteria donor
ECG	electrocardiogram
ECMO	extracorporeal membrane oxygenation

ED . . . . . emergency department
EEG . . . . . electroencephalogram
eGFR . . . . . estmated glomerular filtration rate
ELIPSY . . . . . European Living Donor Psychosocial Follow-up Project
ELTR . . . . . European Liver Transplant Registry
ESHP . . . . . *ex situ* heart perfusion
ESICM . . . . . European Society of Intensive Care Medicine
ESRD . . . . . end-stage renal disease
ET . . . . . endothelin
EULID . . . . . European Living Donation and Public Health Project
EVLP . . . . . *ex vivo* lung perfusion
FEV_1 . . . . . forced expiratory volume in one second
FiO_2 . . . . . fraction of inspired oxygen
FSG . . . . . finger stick glucose
FWIT . . . . . functional warm ischaemic time
GCS . . . . . Glasgow coma scale
GFR . . . . . glomerular filtration rate
GGT . . . . . gamma-glutamyl transferase
HAV . . . . . hepatitis A virus
HBP . . . . . hight blood pressure
HBV . . . . . hepatitis B virus
Hct . . . . . haematocrit
HCV . . . . . hepatitis C virus
HES . . . . . hydroxyethyl starch
HIV . . . . . human immunodeficiency virus
HLA . . . . . human leukocyte antigens
HMP . . . . . hypothermic machine perfusion
HOC . . . . . hyperosmolar citrate
HP . . . . . hypothermic perfusion
HPPM . . . . . hypothermic pulsatile perfusion machine
HTLV . . . . . human T-lymphotropic virus
ICU . . . . . intensive care unit
IDDM . . . . . insulin-dependent diabetes mellitus
INR . . . . . international normalised ratio
IP . . . . . *in situ* perfusion
IRI . . . . . ischaemia-reperfusion injury
KT . . . . . kidney transplant
LBP . . . . . low blood pressure
LDKT . . . . . living donor kidney transplantation
LDLT . . . . . living donor liver transplantation
LST . . . . . life-sustaining therapy

LT . . . . . liver transplantation
LVEF . . . . . left ventricular ejection fraction
MAP . . . . . mean arterial pressure
MELD . . . . . model for end-stage liver disease
MP . . . . . methylprednisolone
MSM . . . . . men who have sex with men
Na K ATPase . . . . . sodium potassium pump
NAT . . . . . Nucleic Acid Amplification Test
NAT . . . . . Nucleic Acid Testing
NEOB . . . . . New England Organ Bank
NHBD . . . . . non-heart-beating donor
NMP . . . . . normothermic machine perfusion
NO . . . . . nitirc oxide
NRP . . . . . normothermic regional perfusion
NT . . . . . normothermic perfusion
ONT . . . . . Spanish National Transplant Organisation
OPO . . . . . Organ Procurement Organization
OR . . . . . operating room
OSO . . . . . organ sharing office
OTD . . . . . organ and tissue donor
PAK . . . . . pancreas after kidney transplant
PARA . . . . . panel-reactive antibodies
PCR . . . . . polymerase chain reaction
PCT . . . . . person-centred therapy
PDRI . . . . . pancreas donor risk index
PEEP . . . . . positive end-expiratory pressure
PEF . . . . . peak expiratory flow
PELD . . . . . paediatric end stage liver disease
PGD . . . . . primary graft dysfunction
PLR . . . . . pupillart light reflex
pmp . . . . . per million population
PNF . . . . . primary non-function
PP . . . . . pulsatile perfusion
PT . . . . . prothrombin time
PTT . . . . . partial thromboplastin time
ROSC . . . . . return of spontaneous circulation
RR . . . . . renal resistance
SAP . . . . . systolic arterial pressure
SBP . . . . . systolic blood pressure
SCD . . . . . standard criteria donor
SCP . . . . . simple cold preservation

SPK . . . . . simulaneous pancreas and kidney transplant
SvO_2 . . . . . venous oxygen saturation
T3 . . . . . triiodothyronine
TBC . . . . . total body cooling
TC . . . . . transplant coordinator
TCD . . . . . transcranial Doppler
TPHA . . . . . *Treponema pallidum* haemagglutination assay
TPM . . . . . transplant procurement manager
TRH . . . . . thyrotropin-releasing hormone
TV . . . . . tidal volume
t-WIT . . . . . total warm ischaemia time
u-DCD . . . . . uncontrolled donation after circulatory death
UNOS . . . . . United Network for Organ Sharing
US . . . . . ultrasound
UW . . . . . University of Wisconsin solution
WHO . . . . . World Health Organization
WI . . . . . warm ischaemia
WIT . . . . . warm ischaemia time
WLST . . . . . withdrawal of life-sustaining therapies