



The Voice of Transplantation in the UK

# Transplantation From Donors After Deceased Circulatory Death



Compiled by a Working Party of  
The British Transplantation Society  
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British Transplantation Society Guidelines



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# 1 INTRODUCTION

## 1.1 The Need for Guidelines

Transplantation offers patients with end-stage organ failure a cost-effective treatment that improves quality of life and increases life expectancy. Prior to the introduction of guidance defining the concept of brain death in the 1970s, all organs for transplantation were donated after circulatory death (DCD). Following the introduction of brain stem death testing, the majority of organs for transplantation were donated after brain death (DBD) or, increasingly, from living donors. However, in the UK, demand for organ transplantation has continued to rise. By 2012, the mean waiting time for deceased donor kidney transplantation had risen to over three years, while demand for other organs far outstripped the available supply with the consequence that many patients died while awaiting an organ transplant.

In an attempt to bridge the gap between supply and demand, a concerted effort has been made over the last decade to re-evaluate the use of DCD organs, and this has resulted in an increase in the number of DCD donors. Following a report from the Organ Donor Taskforce in 2008 (1), 14 initiatives were put in place with the hope of increasing organ donation by 50% over the following five years. Partly as a result, the number of DCD donors increased from 199 to 373 between 2007 and 2012, an increase of 87%. Overall, this constituted an increase of 11% of the total deceased donor activity (2).

DCD provides a valuable source of organs for transplantation and helps to address the shortfall between supply and demand. It also offers an additional donation choice for families of critically ill patients who are suffering from severe injury or illness that is incompatible with life but have not deteriorated to brain death. In this situation, DCD can facilitate both patient and family wishes at the end of life, especially when life-support is to be withdrawn. DCD has been perceived by some as an attempt to circumvent brain death criteria, but a more balanced interpretation is that it may play an important role in satisfying the wishes of the patient and/or family where DBD is not possible.

Despite some historical success with 'uncontrolled' DCD kidney programmes, only a small percentage of DCD donors in the UK are currently uncontrolled, largely because of the interventions that are necessary to maintain the viability of transplantable organs while consent/authorisation for donation is sought from the deceased's next of kin. The majority of UK DCD donations are 'controlled' Maastricht category 3. Efforts to expand donation are likely to lead to increased 'uncontrolled' DCD activity (Maastricht category 2 or even 1).

DCD donation results in fewer donated organs per donor than DBD donation (2.6 organs compared to 4). DCD donors are able to donate kidney, liver, pancreas, lung, and multiple tissues, and research in the UK is exploring the options for cardiac DCD following the successful development of such programmes in the USA (3).

Improved immunosuppression, improved organ recovery and implantation, and enhanced peri- and post-operative care mean that the outcomes from DCD organs compare favourably with those from DBD organs. Success is dependent upon establishing common practices and accepted protocols that allow the safe sharing of DCD organs and maximise the use of the DCD donor pool. Careful recipient selection and optimal donor management are pivotal to facilitate donation of as many organs as possible and it is essential that the allocation system accounts for recipient need and organ utilisation to maximise transplant benefit.

Guidelines for transplantation from deceased circulatory death donors were first published by the British Transplantation Society in 2004 under the title 'Guidelines relating to solid organ transplants from non-heart beating donors' (4). This document extends and updates the previous guidelines and aims to include recent developments in all aspects of DCD clinical practice, including outcome data for all relevant organs.

## **1.2 Process of Writing and Methodology**

The document 'Guidelines relating to solid organ transplants from non-heart beating donors' was commissioned by the BTS in 2002 to develop best practice guidance for clinicians involved in this area of transplantation. Published in January 2004 (4), the guidelines helped to establish donation and transplantation after circulatory death as an accepted part of clinical practice. With the rapid increase in the number of DCD donors over the past five years and the need to explore the use of DCD organs across all areas of transplantation, the BTS council agreed that a review and update of the original guidance was necessary.

This document has been written under the auspices of the BTS Standards Committee and has been significantly enlarged and updated in the light of new data and changing practice. An important change has been to add guidance regarding the strength of the evidence base underlying the statements of recommendation, and to ensure that the guidance has been produced in line with the BTS Clinical Practice Guideline and the recommendations of NHS Evidence (5). It has been produced with wide representation from UK colleagues and professional bodies involved in both donor and recipient management, including the BTS

Transplant Surgeons Chapter and the Intensive Care Society.

A systematic review of the relevant literature and synthesis of the available evidence was undertaken by selected clinical experts. This was followed by peer group appraisal and expert review. Draft proposals were amended by an editorial committee and appropriate levels of evidence were added to the recommendations at an Editors and Authors' meeting held in London in July 2011. Wider discussion with the transplant community was undertaken through 'face to face' consultation at a BTS consensus meeting in York in October 2011. This was attended by transplant surgeons and physicians, intensivists, Clinical Leads in Organ Donation (CL-ODs), Specialist Nurses in Organ Donation (SN-ODs), and representatives of NHS Blood and Transplant (NHSBT). The draft of the document was placed on the BTS website in March 2013 for a period of open consultation, to which patient and transplant groups were actively encouraged to contribute. The final document was posted in July 2013.

Where available, these guidelines are based upon published evidence. With the exception of descriptive studies, the evidence and recommendations have been graded for strength. A small number of conference presentations have been included where relevant. With minor exceptions where relevant results became available, the publication 'cut off' date for evidence was May 2012.

It is anticipated that these guidelines will next be revised in 2018.

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## **1.5 Disclaimer**

This document provides a guide to best practice, which inevitably evolves over time. All clinicians involved in this aspect of transplantation need to undertake clinical care on an individualised basis and keep up to date with changes in the practice of clinical medicine.

These guidelines represent the collective opinions of a number of experts in the field and do not have the force of law. They contain information/guidance for use by practitioners as a best practice tool. It follows that the guidelines should be interpreted in the spirit rather than to the letter of their contents. The opinions presented are subject to change and should not be used in isolation to define the management for any individual patient. The guidelines are not designed to be prescriptive, nor to define a standard of care.

The British Transplantation Society cannot attest to the accuracy, completeness or currency of the opinions contained herein and do not accept any responsibility or liability for any loss or damage caused to any practitioner or any third party as a result of any reliance being placed on the guidelines or as a result of any inaccurate or misleading opinion contained in the guidelines.

## **1.6 Declarations of Interest**

Editors, authors and contributors have worked to the standards detailed in the BTS Clinical Practice Guideline accessible at:

[http://www.bts.org.uk/MBR/Clinical/Guidelines/Current/Member/Clinical/Current\\_Guidelines.aspx](http://www.bts.org.uk/MBR/Clinical/Guidelines/Current/Member/Clinical/Current_Guidelines.aspx) (5).

## **1.7 Grading of Recommendations**

In these guidelines, the GRADE system has been used to rate the strength of evidence and the strength of recommendations. This approach is consistent with that adopted by KDIGO in guidance relating to renal transplantation, and also with guidelines from the European Best Practice Committee, and from the Renal Association (6,7).

For each recommendation the quality of evidence has been graded as:

- A (high)
- B (moderate)
- C (low)
- D (very low)

For each recommendation, the strength of recommendation has been indicated as one of:

- Level 1 (we recommend)
- Level 2 (we suggest)
- Not graded (where there is not enough evidence to allow formal grading)

These guidelines represent consensus opinion from experts in the field of transplantation in the United Kingdom. They represent a snapshot of the evidence available at the time of writing. It is recognised that recommendations are made even when the evidence is weak. It is felt that this is helpful to clinicians in daily practice and is similar to the approach adopted by KDIGO (6).

## **1.8 Definitions and Abbreviations**

The following definitions and abbreviations are used in this document:

CIT	Cold ischaemic time
CL-OD	Clinical lead in organ donation
CNI	Calcineurin inhibitor
DBD	Donation after brain death
DCD	Donation after circulatory death (see below for subdivisions)
DGF	Delayed graft function
ECD	Expanded (extended) criteria donor
ECMO	Extra corporeal membrane oxygenation
ED	Emergency department

ESLP	<i>Ex-situ</i> lung perfusion
EVLP	<i>Ex-vivo</i> lung perfusion
FWIT	Functional warm ischaemic time
GFR	Glomerular filtration rate
HCC	Hepatocellular carcinoma
KDIGO	Kidney Disease: Improving Global Outcomes
MELD	Model for end-stage liver disease
NHBD	Non heart beating donor/donation
NHSBT	NHS Blood and Transplant
NORS	National Organ Retrieval Service
NRP	Normothermic regional perfusion
PNF	Primary non function
SCD	Standard criteria donor
SN-OD	Specialist nurse in organ donation
WIT	Warm ischaemic time

#### Controlled DCD

Organ donation which follows circulatory arrest. This may be in the context of withdrawal or non-escalation of cardio-respiratory treatments that are considered to be no longer in a patient's best interests, or occurring in a patient already certified dead by brain stem criteria.

- Maastricht Category 3: Awaiting cardiac arrest
- Maastricht Category 4: Cardiac arrest in a brain stem dead donor

#### Uncontrolled DCD

Organ donation from a patient who has suffered an unexpected death that has been confirmed on cardio-respiratory grounds.

- Maastricht Category 1: Dead on arrival
- Maastricht Category 2: Unsuccessful resuscitation
- Maastricht Category 5: Unexpected cardiac arrest in a critically ill patient

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## 2 EXECUTIVE SUMMARY OF RECOMMENDATIONS

### Categorisation of DCD Donors

- Deceased circulatory death donors should be categorised according the Maastricht classification to aid research, communication and audit. (A1)
- The functional (or true) warm ischaemic period starts when the systolic blood pressure has a sustained (i.e. at least 2 minutes) fall below 50 mmHg and extends up to the onset of cold in situ perfusion. (B1)
- Although donor low oxygen saturation (<70%) is a concern and may well be a measure of inadequate organ perfusion and poor outcome, prospective evidence is awaited. The current recommendation is that oxygen saturation below 70% is not used as an indicator of poor outcome or as a reason for non usage, but that retrieval teams should keep a record of when oxygen saturation falls below 70% in order to allow correlation with graft outcome. (C1)

### Diagnosis of Death

- Death is irreversible and should be regarded as a state in which a patient has permanently lost the capacity for consciousness and brain stem function. (A1)
- Where cardio-respiratory criteria apply, death can be confirmed following five minutes of continuous cardio-respiratory arrest providing there is no subsequent restoration of artificial cerebral circulation. (B1)
- Where possible, circulatory arrest should be identified by the absence of pulsatile flow on a correctly functioning arterial line, or by the use of echocardiography if the expertise is available; or failing that by continuous ECG monitoring. (B1)
- DCD organ retrieval protocols should recognise the potential risks around post mortem interventions that might restore cerebral perfusion. (B1)
- The criteria for the diagnosis of death following loss of circulatory function should not be influenced by the possibility of subsequent organ retrieval. (A1)

### Law, Ethics and Donor Consent

- All healthcare professionals should be aware of the complex ethical issues that are associated with donation after circulatory death (DCD) and the transplantation of donated organs. Such professionals should be familiar with the terminology used to describe and discuss the ethics of DCD transplantation. (B1)

- Good ethical practice is integral to efforts to facilitate donation and achieve transplantation in the context of DCD. This includes decisions about allocation and consent in relation to both the organ donor and recipient. (B1)
- DCD in the United Kingdom is underpinned by definitions of death that are accepted by society. The principles of donor dignity and non-maleficence must not be compromised in efforts to facilitate donation and transplantation from DCD donors. (B1)
- Ethical principles integral to the UK controlled DCD programme must extend to any future uncontrolled DCD programme. (B1)
- The BTS Ethics committee is available for guidance and information to support practice in this complex field. (Not graded)
- The UK Donation Ethics Committee is also available to offer guidance and information in this area. (Not graded)

#### Informing the Recipient

- Providing information, both orally and in writing, for the potential transplant recipient is a requirement for consent and is the responsibility of the multi-disciplinary transplant team. This must be updated and reviewed annually and the outcome of discussions clearly documented in the patient's medical record. (B1)
- Information should be tailored to the requirements of the potential recipient, recognising that not all patients wish to receive detailed information. However, this must not preclude engagement with the transplant process. (B1)
- The risk-benefit analysis presented to the potential transplant recipient must explain the relative risk for that recipient of remaining on the transplant waiting list compared to that of receiving a DCD organ. (B1)

#### Organ Retrieval

- Treatment withdrawal should ideally be planned for a time when the donor HLA type and virology are known, and the liver and pancreas recipients are in the recipient hospitals. (C1)
- Treatment withdrawal in the operating department is associated with shorter warm ischaemic times (asystolic periods) than withdrawal on a remote intensive care unit or ward. (C1)
- The retrieval team need to be satisfied about the donor details (blood group, past medical history, illness leading to death) before treatment is withdrawn. (A1)

- Retrieval teams should be scrubbed in the operating theatre at the point of treatment withdrawal. (B1)
- Maastricht 4 donors, where death has been established previously by brain stem criteria, may be given heparin before treatment withdrawal. Death does not need to be reaffirmed once circulatory arrest has occurred. (A1)
- The specialist nurse should keep a record at regular intervals of the donor's haemodynamic parameters following treatment withdrawal. (C1)
- Death may be confirmed 5 minutes after complete circulatory arrest. There is no need for a further stand off period following this. (A1)
- For controlled donors, retrieval starts by gaining access to a large artery and vein, typically the right common iliac artery or aorta, and the IVC in the abdomen or right atrium in the chest. (Not graded)
- 20000 units heparin should be added to the first bag of ice-cold preservation solution to be perfused through the aorta. (Not graded)
- A fibrinolytic agent such as streptokinase or recombinant tissue plasminogen activator may be added to the first bag of preservation solution. (B3)
- The kidneys may be removed either individually or *en bloc*. (Not graded)
- The pancreas may be removed either *en bloc* with the liver, or following removal of the liver. (Not graded)
- Cannulae for preservation fluid should never be placed in the SMV or IMV when the pancreas is being retrieved. (B1)
- The liver should be recovered using a rapid technique which minimises liver congestion. (Not graded)
- Dual perfusion of both artery and portal vein is essential for recovery of DCD livers for transplantation. (C1)

### Viability Testing

- Viability testing has a different emphasis depending on the organ being tested. Kidneys from young controlled DCD donors who have died rapidly after withdrawal of support, undergone rapid laparotomy, aortic cannulation, perfusion and venous exsanguination will be expected to work promptly if cold ischaemia is minimised and the kidneys appear well perfused on retrieval. This is deemed to be sufficient viability testing in this case. The role of machine perfusion to 'improve' the kidney is controversial. (C2)

- For uncontrolled DCD or when perfusion of the kidneys on retrieval is poor, using parameters such as high resistance during machine perfusion or high enzyme levels within the perfusate may indicate increased cellular damage and an increased risk of primary non function but this is not universally accepted (C1)
- Viability testing for the liver and pancreas has not been fully established. (Not graded)
- Testing the graft function of warm perfused organs prior to transplantation is considered the 'gold' standard. However, warm perfusion of such organs is difficult to perform and usually impractical. (C2)
- Warm viability testing of donor lungs using *ex-vivo* lung perfusion is the exception. The test is performed by ventilating the lungs and perfusing them with Steen solution with or without added red blood cells. The ability of the ventilated lung to oxygenate the perfusate is assessed together with lung compliance, airway resistance and tidal volume via the ventilator. (B1)

#### Immunosuppression

- No definitive data suggest significant benefit from any particular immunosuppressive regimen in the context of DCD organs. (C1)
- Following DCD kidney transplantation, there is increased risk of delayed graft function due to DCD injury. Induction therapy with mono- or polyclonal antibodies may be used to reduce the risk of clinically unrecognised acute rejection prior to recovery from DCD injury. (B1)
- Induction therapy is often combined with delayed introduction or reduced intensity of calcineurin inhibition to limit the incidence and duration of delayed graft function. (C2)
- Following liver transplantation, consider renal sparing regimens with delayed CNI introduction. Induction and T cell depletion may also be considered, but risk and benefit must be balanced with choice of regimen. (C2)
- Following heart and lung transplantation, there is no evidence to use a different regimen from that used in DBD transplantation. (C1)

#### Kidney

- Individuals with advanced or end-stage chronic kidney disease, or with cortical necrosis demonstrable on biopsy should not be considered as potential kidney donors. (B1)

- The use of donors with functional warm ischaemic time >2 hr or absent blood pressure for 30 minutes should be restricted to (currently experimental) protocols which attempt to resuscitate organ viability. (B2)
- Units undertaking cold machine perfusion of DCD kidney transplants prior to implantation should collaborate to standardise the prospective collection of data to enable aggregated analyses of outcomes. (A2)
- None of the dynamic characteristics of machine perfusion, perfusate effluent biochemical analysis, or kidney transplant biopsy scoring systems - alone or in combination - have sufficient predictive value to mandate organ discard. (A2)
- Such assessment may, however, help determine when kidneys should be considered for dual transplantation. (B2)
- Long term outcomes of DCD recipients are similar to those of DBD recipients and the allocation system for DCD and DBD organs should be similar. Nevertheless, it is recognised that DCD kidneys appear to be more susceptible to cold ischaemia, and the proposed national allocation scheme should take this into account. (B2)
- The incidence of delayed graft function is increased in DCD recipients and this should be discussed with the patient prior to transplantation. (A1)
- Antibody induction therapy should be considered as part of the initial immunosuppressive regimen for recipients of DCD kidneys. (B1)
- Long-term outcomes for standard criteria donors are equivalent for DCD and DBD kidney transplants. (A1)
- Graft outcome is more closely related to whether a transplant is ECD or SCD than whether the mode of donation is DCD or DBD. (B2)
- Prospective data are required to determine whether the impact of extended criteria donation (ECD) is different in DCD and DBD donors and whether different thresholds for organ use may be required. (A1)

### Liver

- Livers transplanted from Maastricht 3 DCD donors are a useful resource and should be used where deemed safe. (B1)
- Short and medium term outcome appears inferior to livers from DBD donors, with more PNF and ischaemic cholangiopathy and a higher rate of re-transplantation. (B1)
- DCD and DBD subjects transplanted with MELD >30 or on organ-perfusion support have similar graft survival. However, there is no survival benefit when DCD livers are

transplanted in patients with MELD  $\leq$ 30 or in those not receiving organ-perfusion support. (B2)

- The incidence of biliary stricture is significantly lower when a low viscosity solution is used to cold flush the aorta. (C2)
- DCD liver use should be matched with the need of the recipients on the waiting list, with allocation to those who will have the greatest transplant benefit. (B2)
- The outcome of DCD liver transplantation is improved with short CIT, which is best kept to under 8hrs. (B1)
- A favourable outcome can be expected if an 'ideal' DCD liver is transplanted. An 'ideal' DCD liver donor is <50 years old, has a functional WIT time <20 min, a shorter CIT <10 hr, and <10% steatosis. (B1)
- Using more restrictive DCD Donor criteria including BMI <29 kg/m<sup>2</sup> and a functional WIT <20 min (SAP <50 mmHg), equivalent 1 and 3-year patient and graft survival rates can be achieved for both DCD and DBD liver transplants. (B1)
- Long FWIT is associated with an increased risk of ischaemic cholangiopathy
- Potential recipients of DCD liver grafts should be informed of the potential risk and be offered the choice to refuse such organs prior to transplant listing. (C2)
- DCD grafts are best avoided in recipients of re-transplantation (B1)
- DCD liver grafts should be ideally used in younger recipients with age <60 years. (B1)
- Factors predictive of graft failure are: age  $\geq$ 55 years, male sex, African–American race, HCV positivity, metabolic liver disorder, transplant MELD  $\geq$  35, hospitalisation at transplant, and the need for life support at transplant. Recipient predictors of mortality are age  $\geq$ 55 years, hospitalisation at transplant, and re-transplantation. (B1)
- A national audit should be performed to identify factors for non-utilisation of extended criteria donors to establish the incidence of cholangiopathy under ideal circumstances, identify more suitable risk factors, identify further subgroups of DCDs that could potentially be utilised, allow for medical interventions to be evaluated, and provide qualitative data regarding centre-specific performance. (C1)

## Pancreas

- Although DCD organs can be used for isolated pancreas transplants in pancreas transplant alone, pancreas after kidney or simultaneous pancreas kidney (SPK)

transplants, available evidence and current practice are increasingly in favour of SPK recipients. (C2)

- Pancreas transplants from DCD donors are at increased risk of reperfusion pancreatitis and thrombosis and this may be exacerbated by prolonged cold ischaemia time and higher donor BMI. The issue of donor age is poorly studied but may constitute a further risk factor. Ideal donors should be <60 years old and have BMI <30 kg/m<sup>2</sup>. (C2)
- The pancreas team should stand down after a functional warm ischaemia time (systolic BP <50 mmHg and/or oxygen saturation of 70%) of 60 minutes. (C2)
- A primary focus of any DCD pancreas transplant should be to achieve the shortest possible cold ischaemic time. (B2)
- There is little evidence regarding recipient risk factors but it is logical to assume that higher recipient BMI, age, cardiovascular morbidity, and technical surgical factors may contribute to poorer outcome. (C2)
- Reported outcomes for DCD donor pancreas transplantation are broadly similar to those of DBD donors, although considerably greater donor selection is likely to have taken place. (C2)
- Graft loss from thrombosis is twice as common in DCD as DBD pancreas transplants. Particular attention should be paid to measures to prevent thrombosis in recipients of DCD organs. A DCD organ should not be transplanted into a recipient with a history of thrombo-embolic disease unless this is monitored and treated. (C2)
- Selected transplant centres will have built up a volume of expertise with DCD extended criteria pancreas grafts and these guidelines should not restrict innovative but safe practice of pancreas transplantation. (Not graded)

### Pancreatic islets

- Selection criteria for recipients of islets from DCD donors should be the same as for DBD donors. (B2)
- Organs from DCD donors for islet isolation and transplantation should be allocated through the National Pancreas Allocation Scheme. (B2)
- The long term outcome of islet transplantation from DCD donors has been satisfactory in the UK but the cohort is small. Further audit and research is required. (C2)
- Satisfactory functional islet preparations can be routinely obtained from DCD donors. (C2)

## Lung

- The donor selection criteria for lung DCD should be the same as for DBD. (B2)
- All patients on the lung transplant waiting list have the potential to receive DCD lungs. (C1)
- DCD lungs should not be regarded as extended or marginal. Transplant outcome and quality is at least similar to DBD organs. (B1)
- Perform antegrade and retrograde flush perfusion at the time of lung retrieval. (B2)
- Pre-transplant *ex vivo* lung perfusion (EVLP) is advised in case of uncertain graft performance to safely extend donor and procedural criteria (long warm ischaemia, bad flush, clots). (B1)
- Acceptance criteria on EVLP may include measures of pulmonary compliance, vascular resistance, and gas exchange. (C2)

## Heart

- In the UK, heart transplantation from DCD donors is currently NOT standard of care. Because of a number of ethical issues, the use of DCD hearts is not currently recommended. (Not graded)

## **PART 1: GENERAL PRINCIPLES**

### **3 CATEGORISATION OF DCD DONORS & DEFINITION OF WARM ISCHAEMIC TIME**

#### **Statements of Recommendation**

- *Deceased circulatory death donors should be categorised according to the Maastricht classification to aid research, communication and audit. (B1)*
- *The functional (or true) warm ischaemic period starts when the systolic blood pressure has a sustained (i.e. at least 2 minutes) fall below 50 mmHg and extends up to the onset of cold in situ perfusion. (B1)*
- *Although donor low oxygen saturation (<70%) is a concern and may well be a measure of inadequate organ perfusion and poor outcome, prospective evidence is awaited. The current recommendation is that oxygen saturation below 70% is not used as an indicator of poor outcome or as a reason for non usage, but that retrieval teams should keep a record of when oxygen saturation falls below 70% in order to allow correlation with graft outcome.*

#### **3.1 Categorisation of DCD Donors**

Organ donation following circulatory death is classified as either 'controlled' or 'uncontrolled'. Controlled donation occurs when treatment is withdrawn on an intensive care unit (ICU) or emergency department (ED) and death follows. Uncontrolled donation refers to potential donors who suffer an unexpected cardiac arrest and are either brought into hospital dead or when death is declared in hospital following unsuccessful attempts at cardiopulmonary resuscitation (CPR). Donation after Circulatory (previously called cardiac) Death (DCD) was formerly known as Non Heart Beating Donation (NHBD).

DCD donors can be divided into categories based principally on work from the Consensus meeting held in Maastricht in 1995 (1). Classification is important both for the logistics of retrieval and analysis of the outcome following transplantation. 'DCD' has become the term of preference as it complements similar terminology such as standard criteria donors (SCD) and extended criteria donors (ECD). The term NHBD is no longer used.

The following classification is recommended:

#### Maastricht Category 1: Death occurring outside of hospital

Death is confirmed outside a hospital environment. For these individuals to be potential donors, the moment of sudden death needs to have been witnessed, the time that it occurred documented, and 'resuscitation' continued after death.

#### Maastricht Category 2: Unsuccessful resuscitation

CPR is started outside of hospital following collapse. Death is confirmed on admission to hospital.

Both Category 1 and 2 donors are also referred to as '**Uncontrolled**' **DCD donors** and usually present to the emergency department.

#### Maastricht Category 3: Awaiting cardiac arrest

Death is inevitable but brain stem death criteria are not fulfilled. These patients are cared for in many areas within hospitals, but are most commonly identified in neurosurgical and general intensive care units, coronary care units, emergency departments and medical wards.

#### Maastricht Category 4: Cardiac arrest in a brain stem dead individual

Death has been diagnosed by brain stem criteria following which the patient suffers a cardiac arrest. This may be whilst awaiting the donor team or as an intentional arrangement, depending upon the wishes of the next of kin.

Categories 3 and 4 are also referred to as '**Controlled**' **DCD donors**.

#### Maastricht Category 5: Unexpected cardiac arrest in a hospitalised patient

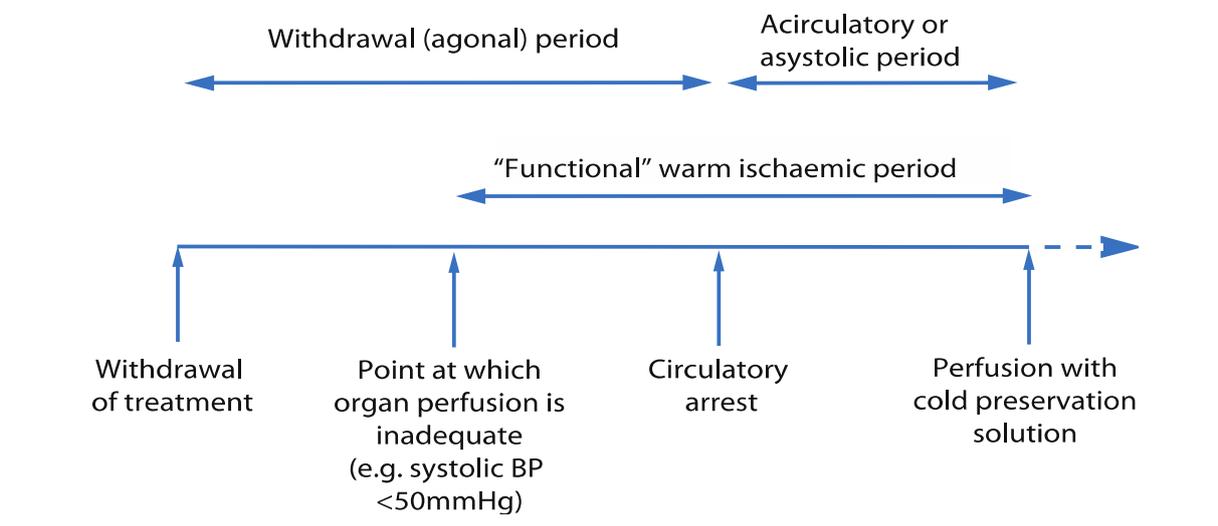
Category 5 is an 'uncontrolled' donor in a hospitalised patient so the warm ischaemic time (WIT) between cardiac arrest and organ perfusion is likely to be longer than categories 3 or 4 but shorter than categories 1 or 2.

### **3.2 Nomenclature of Time Periods**

The process of organ donation starts with treatment withdrawal, following which the patient's vital signs, in particular the blood pressure, deteriorate at varying rates until cardiac activity ceases (asystole). Following the verification of death, organ retrieval begins with perfusion of the donor with cold preservation solution. The following time periods have been defined (see figure 3.2.1):

- The **withdrawal period** (sometimes called the *agonal period*): the time from treatment withdrawal to circulatory arrest.
- The **asystolic or acirculatory warm period** (also known as the *primary warm ischaemic time*): the time from circulatory arrest to the perfusion of the organs with cold preservation solution *in situ*.
- The **functional (or true) warm ischaemic period**: starts when the systolic blood pressure has a sustained (i.e. at least 2 minutes) fall below 50 mmHg and extends up to the onset of cold *in situ* perfusion.

**Figure 3.2.1 Time points in donation following circulatory death**



Time to circulatory death after withdrawal of life-sustaining treatment in potential organ donors (2)

The functional (or true) warm ischaemic period reflects the fact that, even though a circulation exists, end organ perfusion is poor and the organs suffer a warm ischaemic insult. It is therefore appropriate to consider this warm ischaemic period when assessing likely organ damage, rather than the asystolic warm period.

A systolic blood pressure of 50 mmHg has been identified as predicting the onset of warm ischaemia, although there is little published evidence to support this. Organs from young donors are likely to tolerate hypotension far better than older donors, and organs from

patients who have a history of hypertension are likely to experience significant critical ischaemia with systolic blood pressures in excess of 50 mmHg. (3)

The time for which the haemoglobin oxygen saturation is below 70% should also be taken into account, and is used when assessing the suitability of some donor organs; however, it is not sufficiently robust for universal use as a criterion for functional WIT. NHSBT are prospectively collecting data in order to inform future clinical practice. As a result, the current recommendation is that oxygen saturation below 70% should NOT be used as an indicator of poor outcome or as a reason for non usage, but that retrieval teams should be encouraged to keep an accurate record of when the oxygen saturation falls below 70% in order that it may be correlated with graft outcome.

Organs are particularly sensitive to warm ischaemia, since metabolic processes continue but cells switch from aerobic to anaerobic metabolism. Anaerobic metabolism is heavily dependent on adenosine triphosphate (ATP) and intracellular ATP stores deplete rapidly. ATP is essential for the maintenance of membrane-associated ion exchange channels and as warm ischaemia progresses membrane integrity is lost and cellular dysfunction and cell death occur. The same processes occur during cold ischaemia, but metabolism is slowed markedly in the cold so cells and organs are able to survive for longer periods.

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## 4 DIAGNOSIS OF DEATH

### Statements of Recommendation

- *Death is irreversible and should be regarded as a state in which a patient has permanently lost the capacity for consciousness and brain stem function. (A1)*
- *Where cardio-respiratory criteria apply, death can be confirmed following five minutes of continuous cardio-respiratory arrest providing there is no subsequent restoration of artificial cerebral circulation. (B1)*
- *Where possible, circulatory arrest should be identified by the absence of pulsatile flow on a correctly functioning arterial line, or by the use of echocardiography if the expertise is available; or failing that by continuous ECG monitoring. (B1)*
- *DCD organ retrieval protocols should recognise the potential risks around post mortem interventions that might restore cerebral perfusion. (B1)*
- *The criteria for the diagnosis of death following loss of circulatory function should not be influenced by the possibility of subsequent organ retrieval. (A1)*

### 4.1 Professional Frameworks for the Diagnosis and Confirmation of Death

Death has clinical, legal and societal elements. As a consequence, although there may be international professional consensus on the biological features of what can and should be considered to be a state of death, other factors determine how these elements are assimilated into the professional and/or legal frameworks that clinicians are required to apply within a given jurisdiction. Invariably, differences emerge as country-specific criteria are developed and these become most evident when incorporated into deceased donor organ retrieval protocols. This is evidenced by the variation in waiting or observation periods from the onset of loss of vital functions to the confirmation of death across different countries (1,2).

The World Health Organisation has attempted to develop a consensus of the scientific, biological and medical aspects of death in a way that supersedes such differences and which may form the basis of more consistent and globally applicable diagnostic criteria.

Through this consensus process, it has become possible to define a number of over-arching principles:

- Death is a biological event and should be diagnosed on such a basis.
- The criteria used to diagnose death should be valid regardless of any subsequent post-mortem intervention (e.g. organ retrieval), and should preserve the integrity of the 'dead donor' rule.
- The criteria used to diagnose death should be functional rather than anatomical, i.e. not referred to as cardiac death or brain death but based upon the loss of vital organ function.
- Death is in essence a neurological event and occurs when there is a permanent loss of
  - the capacity for consciousness
  - all brain stem function

In this context, 'permanent' refers to loss of function that cannot be restored spontaneously and which will not be restored artificially. There is, of course, an inextricable link between brain and circulatory function, and for this reason it is recognised that this state can be arrived at in two ways – through permanent loss of circulatory function, or following a catastrophic brain injury.

- The criteria for the diagnosis and confirmation of death within DCD protocols will need to recognise, where relevant, the possibility of spontaneous return of the circulation as well as clinical interventions that might restore cerebral perfusion whilst the brain retains some sensitivity to the restoration of oxygenation.

#### **4.2 Biological Background to Death that Follows Permanent Loss of Circulatory Function**

Neurological and circulatory functions are inextricably linked. Death – i.e. the loss of capacity for consciousness and all brain stem function – most commonly occurs following the loss of circulatory function from which a patient should not be or cannot be resuscitated. Some authorities have used the terms 'permanent' (should not be resuscitated) and 'irreversible' (cannot be resuscitated) to distinguish between these two groups (3,4), and in this regard there are clear parallels between controlled DCD (permanent, where cardiopulmonary resuscitation might be successful but is inappropriate) and uncontrolled DCD (irreversible,

where cardiopulmonary resuscitation has been abandoned). Despite these differences, in both circumstances death can be diagnosed when

1. Asystole has occurred, **and**
2. Brain function has been lost, **and**
3. The possibility of *spontaneous* return of cardiac function has passed, **providing that**
4. There will be no subsequent intervention that restores cerebral perfusion whilst the brain remains responsive to such restoration.

The following observations are relevant to the diagnosis of death following circulatory arrest:

- All neurological function – including those of consciousness and the brain stem – and all cortical electrical EEG activity are lost within seconds of circulatory arrest, and will only return if cerebral blood flow is promptly restored. The minimum duration of circulatory arrest necessary to ensure that the brain will not respond to subsequent restoration of the circulation is unknown and likely to be influenced by multiple variables that are difficult to control, e.g. temperature, pre-existing injury, the duration of cardiac standstill and the effectiveness of cardiopulmonary resuscitation.
- With regards to spontaneous return of the circulation after the onset of asystole.
  - a. There have been no reported cases of spontaneous return of the circulation following the withdrawal of life-sustaining treatments (controlled DCD).
  - b. In patients who continue to be fully monitored after unsuccessful cardiopulmonary resuscitation has been abandoned (uncontrolled DCD), the longest reported interval between the onset of asystole and the return of the circulation is around seven minutes.
- ECG activity can persist for several minutes after the onset of mechanical asystole (i.e. complete absence of effective ventricular contraction).

### 4.3 Diagnosis of Death

There are important differences in the circumstance in which potential controlled and uncontrolled DCD donors die, particularly in terms of the likely clinical monitoring that is available, the risk of spontaneous return of the circulation, and the pitfalls in establishing

whether the loss of the circulation is permanent. Furthermore, although guidance on when to stop cardiopulmonary resuscitation or apply emergency artificial circulatory assist devices for the purpose of saving a patient's life are beyond the scope of this document, robust and objective guidance is essential to support clinicians in the decision-making that may then generate the potential for DCD.

**Table 4.3.1 Characteristics of Potential Controlled and Uncontrolled DCD Donors**

	<b>Potential Controlled DCD Donors</b>
Setting	Planned withdrawal of life-sustaining critical care treatments. Invasive arterial pressure monitoring, pulse oximetry and continuous surface ECG monitoring likely.
Permanent Asystole	Asystole best identified using correctly functioning arterial line or by transthoracic echocardiography. Reliance on an isoelectric ECG may unnecessarily extend warm ischaemic injury.  Brain function lost within seconds and no intention to institute cardiopulmonary resuscitation.  No reported cases of spontaneous return of circulation in literature.  Published recommended observation periods range from 2 to 10 minutes.
Death	Confirmed through absence of consciousness, respiration and other brain stem functions after the agreed period of observation.
Comments	Death can be confirmed after the possibility for the spontaneous return of the circulation has passed providing that interventions that risk restoration of cerebral perfusion are avoided.

	<b>Potential Uncontrolled DCD Donors</b>
Setting	Abandoned cardiopulmonary resuscitation after unexpected cardiac arrest. Monitoring likely to be limited to surface ECG, pulse oximetry, non-invasive arterial pressure monitoring and possibly end-tidal carbon dioxide. Invasive arterial pressure monitoring unlikely to be in place. Patient likely to have suffered an ill-defined but significant period of cerebral ischaemia prior to and during treatment.
Permanent Asystole	Brain function lost within seconds of cardiac standstill.  Published literature suggests a minimum observation period of seven minutes from the onset of asystole to allow the possibility of the spontaneous return of the circulation to be excluded.  Digital palpation of a central pulse may be unreliable, with asystole most commonly being identified on the basis of an isoelectric ECG. Transthoracic echocardiography or end-tidal carbon dioxide monitoring may be of assistance if available.
Death	Confirmed through absence of consciousness, respiration and other brain stem functions after the agreed period of observation, which should be a minimum of seven minutes.
Comments	Death can be confirmed after the possibility for the return of the circulation has passed providing that interventions that risk restoration of cerebral perfusion are avoided in circumstances where the brain might remain responsive to such restoration.  Clinicians should also be aware of circumstances where particular care over the decision to withdraw cardiopulmonary resuscitation should be taken, e.g.: <ul style="list-style-type: none"> <li>• Hypothermia</li> <li>• Cardiac tamponade</li> <li>• Tension pneumothorax</li> <li>• Drug intoxication</li> <li>• AutoPEEP</li> <li>• Massive pulmonary embolus</li> </ul>

#### **4.4 The Decision to Withdraw Futile Life Sustaining Treatments**

The exact definition of death has given rise to significant ethical debate, which is reflected in the variability of definition between societies (1,2). The key ethical principle is that donation should proceed only after death has been established and no prospect of spontaneous auto-resuscitation exists (5). Similarly, the decision to cease attempts at life preserving treatments should be taken in a manner independent of donation/transplantation considerations and be based purely on the concept of futility with respect to the prolongation of life. Guidance on the determination and diagnosis of death can be found in the Academy of Royal Colleges Code of Practice for the Diagnosis and Confirmation of death (2008) (4). However, there remains no statutory definition of death in the UK and the working definition 'the irreversible loss of the capacity for consciousness combined with irreversible loss of the capacity to breathe' put forward by the Department of Health seems to have been adopted as the pragmatic approach. Ethical aspects related to this area are discussed further in Chapter 5.

#### **References**

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## 5 LAW, ETHICS AND DONOR CONSENT

### Statements of Recommendation

- *All healthcare professionals should be aware of the complex ethical issues that are associated with donation after circulatory death (DCD) and transplantation of donated organs. Such professionals should be familiar with the terminology used to describe and discuss the ethics of DCD transplantation. (B1)*
- *Good ethical practice is integral to efforts to facilitate donation and achieve transplantation in the context of DCD. This includes decisions about allocation and consent in relation to both the organ donor and recipient. (B1)*
- *DCD in the United Kingdom is underpinned by definitions of death that are accepted by society. The principles of donor dignity and non-maleficence must not be compromised in efforts to facilitate donation and transplantation from DCD donors. (B1)*
- *Ethical principles integral to the UK controlled DCD programme must extend to any future uncontrolled DCD programme. (B1)*
- *The BTS Ethics committee is available for guidance and information to support practice in this complex field. (Not graded)*
- *The UK Donation Ethics Committee is also available for guidance and information. (Not graded)*

### 5.1 Ethical Considerations in DCD Transplantation

A number of key ethical principles underpin clinical practice in relation to both donors and recipients in the complex context of DCD and transplantation.

Altruism: the voluntary stated wish of the individual to make the 'gift' of donation of their organs upon death without expectation of reward.

Autonomy: the right of the individual to determine his/her own fate, including that of their organs after death.

Dignity: complex to define, but in this context reflecting the unique and precious status of the human being and the ethical requirement to treat it respectfully without inflicting harm in both life and death.

Non-maleficence: the ethical principle that healthcare professionals should not cause harm or distress to their patients.

Futility: the contentious principle that it is unethical to perform interventions which cannot benefit the individual receiving them; the controversy focusing upon what does or does not constitute benefit.

Equity: The concept of fairness or justice with respect to the way the organs donated are allocated and utilised.

This chapter aims to highlight the key areas of ethical significance in DCD practice and to offer a practical framework for managing these complex situations.

## **5.2 Patient Autonomy and the Choice to Donate**

The organ donor register (ODR) allows accurate determination of an individual's wish to donate their organs in the event of his/her death. As defined in the Human Tissue Act (2004) (1) and the Human Tissue (Scotland) Act (2006) (2), registering to become an organ donor on the ODR constitutes legal consent or authorisation for the donation of organs and tissues to proceed. This carries legal primacy over the wishes of the next of kin. However, in the 5 year period from 2005-10, in 331 (7.1%) of all cases of potential deceased donation in the UK, the next of kin had a full or partial (e.g. one or more organ) objection to donation proceeding (NHSBT, 2010). The reason for the objection to donation or withdrawal of authorisation by the next of kin is routinely discussed and documented. In the absence of their support, despite the recorded legal consent or authorisation, donation does not proceed.

The stated wish to donate is central to ethical considerations in the context of DCD transplantation. Where this is clear-cut, judgements regarding the futility of interventions - or their potential for distress/harm - must take into account the effects on the donation process and the facilitation of the donor's stated wish to donate. This wish alone may provide valid reasons to consider interventions that may otherwise be considered futile or unacceptably harmful. The UK Donation Ethics Committee (UKDEC) upholds the right of all patients requiring end of life care and in the absence of a medical contra-indication, to be given the

opportunity to donate, regardless of the environment e.g. ICU/ED. Such wishes should be facilitated and integral to the care of the dying patient (3).

### **Consent / Authorisation to Organ Donation**

As previously highlighted, consent for organ donation is legally defined by the Human Tissue Act (2004) in England, Wales and Northern Ireland and authorisation for organ donation defined by the Human Tissue (Scotland) Act (2006) (1,2). Both Human Tissue Acts define the priority of next of kin to provide authorisation or consent to organ donation in the absence of the known wishes of an individual. It is important to recognise that permission to proceed with donation may be required from Her Majesty's Coroner or Procurator Fiscal in cases of death which fall within their jurisdiction.

Once an individual's consent or authorisation is ascertained or, where this is unknown, the next of kin have indicated that they wish to proceed with donation, the Specialist Nurse in Organ Donation (SN-OD) documents the decision. As part of the consent/authorisation process, minimum core information is discussed with the next of kin, which includes:

- Which organs could be donated and how they would be used benefit to others.
- The time frames associated with the process of organ and/or tissue donation.
- Tissues and blood samples that may be taken and stored as part of the donation process e.g. HLA typing, biopsies, etc.
- The option for participation in research (e.g. organs and tissues donated solely for research, those donated for research if they are unsuitable for donation, participation in research studies to support and improve donation outcome).
- The disposal of organs that are unsuitable for transplantation or discarded following participation in a research study.
- The appearance of an individual following the donation of organs and/or tissues.
- The need for virology testing and that results may be discussed with them if a test result were found to be positive.
- The past medical and social history of the potential donor.
- Following documentation of consent/authorisation as described above, the organ donation process can start.

### **5.3 Donor Distress and Rights after Death**

Resuscitation methods such as intubation and CPR may cause pain and distress to an individual. This is usually considered ethically justifiable in attempts to save the individual's life but is less clear-cut when possible interventions are futile in terms of the potential for recovery. The Human Tissue Acts legally sanction the minimum necessary steps to preserve organs in a state which allows successful donation. The principles of non-maleficence and individual dignity suggest that only the least invasive steps are morally acceptable to preserve organs after death. Advancing technology may redefine the minimum necessary steps and the evolution of organ transplantation beyond the current range of organs and tissues might reflect an increase in this minimum. The process of donation must also respect the individual's right to continuity of care, in particular access for relatives and communication/explanation of events.

The central ethical conundrum that arises from deceased donor transplantation is whether the facilitation of a stated wish to donate provides an ethical justification for interventions which may be considered futile in live-saving terms. The autonomy of the individual who has described a wish to donate should support interventions - even those that may be painful or undignified - in order to fulfil his/her stated wish. The view that death denies the individual 'rights' in the legal sense conflicts with the legal status of the last will and testament; it is considered morally appropriate to go to some lengths to honour individual's wishes after death.

#### **The conflict between donation and dignity in death**

Controlled DCD entails a period of time during which supportive treatment, often mechanical ventilation and inotropic cardiac support, are withdrawn. The basis of such a step is the futility to continue since recovery has been deemed irreversible.

This is followed by an 'agonal' phase (see section 3.2) which varies in length when respiratory distress, movements consistent with discomfort etc. may be observed. This situation creates conflicting ethical considerations, including:

- Facilitation of the individual's autonomous wish to donate their organs (see above)
- The right (and/or desire) for a dignified death
- The societal responsibility to optimise the quality of the organ donated by the individual's altruism

Best practice must reflect these ethical standpoints and local protocols should provide appropriate guidance for staff dealing with patients and families in the context of DCD.

#### **5.4 Uncontrolled DCD donation**

Uncontrolled DCD raises some unique ethical dilemmas. The majority of these potential donors either suffer sudden cardiac arrest and are brought into hospital while undergoing CPR, or they arrest suddenly inside the hospital (Chapter 3). This situation evolves far more rapidly than DBD or controlled DCD scenarios.

##### **Early approach to the bereaved**

The rapid approach to relatives that is necessary to obtain consent or authorisation quickly is a balance between the autonomy and altruism of a person who may have discussed or documented their commitment and wish to donate and the potential additional distress that may be imposed upon newly bereaved next of kin. The experience and expertise of the UK SN-OD network is central to success in this situation. Experience suggests that an approach to relatives regarding donation following the death of their loved one is most often a comfort, and rarely the cause of additional distress (4,5). Experience from The Netherlands and Spain, where uncontrolled DCD is well established, also supports this (6). The universal acceptance of this donation pathway in the UK has yet to be confirmed.

##### **Pre-consent preservation measures**

Uncontrolled DCD donation can only proceed successfully with external preservation measures to maintain organ quality i.e. *in situ* perfusion of organs via a femoral cannula (7). These must be instigated rapidly and often before relatives are present from whom consent/authorisation can be sought.

The ODR provides a valuable resource to document the potential donor's stated wishes and expression of autonomy; altruism and/or autonomy provide the ethical basis for pre-consent preservative measures. Where the wishes of the deceased are unknown at the time of death, the insertion of a femoral cannula protects the right of the individual to donate until the next of kin can be consulted.

The legal requirement for minimum preservative measures is also ethically applicable in this situation and such measures must be withheld until death has been certified.

## **Preservation measures and the potential to restore cerebral circulation**

The potential for preservative measures to restore the cerebral circulation raises ethical concerns because it creates a grey area in which the status of the potential donor as 'truly dead' may be in question (8). If the definition of death is robust and all parties involved in DCD are unequivocally certain that the donor is dead, cerebral reperfusion may be considered morally acceptable. DBD donors may very rarely retain a cerebral blood supply despite being unequivocally dead, so cerebral perfusion *per se* is not ethically incompatible with death and donation. Protocols must reflect the need for clarity and transparency with reference to the state of death so that ethical concerns about cerebral reperfusion are adequately considered.

## **5.5 Organ Quality and Recipient Risk**

### **Allocation of DCD organs**

The unpredictability of events during the agonal phase and the risk of under-perfusion and prolonged warm ischaemia both increase the risk of poor outcomes from DCD organs, including intra-operative problems, prolonged post-operative recovery and poor long term outcomes. If the organ is transplanted into a 'higher risk' recipient, the clinical and ethical complexities are further increased

### **Balance of donor and recipient risk**

Three concepts must be considered in the process of deceased (DBD or DCD) donor organ allocation:

- Equity: all those listed for a transplant have equal opportunity to receive an organ
- Efficiency: ensures minimal waste of organs
- Utility: distribution of organs maximises benefit to recipients, "the greatest good for the most people"

With the increasing use of DCD organs and the willingness to operate on recipients who present a higher risk of graft failure and/or morbidity and mortality, the transplant community need to consider the implications of the *higher risk transplant*, rather than the donor or recipient in isolation. This can generate complex clinical and ethical scenarios. For example,

if a DCD organ is given to a low risk recipient, a graft of possibly inferior quality and shorter life span is allocated to a patient with high expectations regarding the outcome of the transplant and a longer life expectancy. Subsequent graft dysfunction may result in transplant failure, sensitisation to future potential grafts, or recipient death. For sensitised recipients who are listed for re-transplantation, the waiting time on the national transplant list is increased and many patients will not receive a subsequent transplant. One solution would be to avoid transplanting lower risk recipients with DCD organs or those from any other higher risk donor. However, such recipients would then have a clear advantage and, although it would significantly enhance the chance of a successful transplant for them, the pool of better quality organs would be limited for all other patients listed for a transplant. Such an approach would be difficult to justify as ethically acceptable.

Alternatively, if DCD organs were only allocated to higher risk recipients, it might be clinically justified on the grounds that good organs were not 'wasted' on higher risk recipients. However, it is ethically unacceptable to create a two tier system where a defined cohort of patients is at greater risk of not achieving a successful transplant from the outset. The principle of national allocation is that the scheme should not discriminate against individual groups of patients.

Patients who are listed in the national transplant list will have different expectations based upon the severity of their clinical conditions, but this does not affect their right to equivalent access to high quality treatment/organs for transplantation. Organ allocation schemes are based upon complex algorithms that take into account numerous clinical and patient factors including predicted outcome, impact of waiting times and scarcity of available organs for transplantation. The aim is to facilitate equal rights and access for all potential recipients in the context of a scarce resource. To improve the options for those with already good chances of success to the detriment of those with less good chances is ethically unacceptable.

### **Presentation of risk**

Potential recipients have the right to receive information about the risks and benefits of a more complex transplant so that they have an opportunity to understand the implications of accepting or not accepting a particular transplant in the context of other available treatment options. The patients' suitability for and consent to transplantation must be reviewed regularly to ensure that the risk-benefit analysis in the context of their medical condition has not changed and that they remain willing to proceed with a transplant from a DCD donor and/or from any other source. (See Chapter 6: Informing the Recipient).

## 5.6 Patient Choice

There are few data on patient perspectives on organ allocation. The only notable study is of 128 transplant recipients and 104 dialysis patients in which two hypothetical patients were selected for deceased donor kidney transplantation, based on eight scenarios (9). Patients in this study disagreed with several aspects of current allocation systems. Transplant allocation algorithms do not factor in individual preferences and recipients feel that they are given little information on donor characteristics. Whilst some recipients may be happy to receive a higher risk allograft to reduce waiting time on the list, others may choose to hold out for an organ with more favourable characteristics (e.g. better HLA matching from a younger donor).

To incorporate patient choice in an allocation system, Su et al developed the UNOS/CHOICE system, a proposed extension to the UNOS policy for allocation of higher risk allografts, in which patients can define the range of kidneys that would be acceptable to them for transplantation (9). If adopted, this model would ensure that organs were only offered to potential recipients who were willing to accept them. The disadvantage would be that the kidney allocation process would be more complex, and possibly difficult for recipients to understand. The integration of *donor advocates* into the preparation for deceased donation, who provide non-biased professional representation for patients' interests in the living donor process, may be a possible solution to this (1,2).

## 5.7 British Transplantation Society (BTS) Ethics committee

The Ethics Committee is a BTS sub-committee of multidisciplinary healthcare professionals practising in transplantation and its related fields. It consists of elected and appointed individuals with a specialist interest in ethical issues that are relevant to donation and transplantation. The committee encourages questions and approaches for advice or help of any kind in the area of transplantation ethics and may be contacted via [ethics@bts.org.uk](mailto:ethics@bts.org.uk) or through the officers of the BTS.

The UK Donation Ethics Committee is an analogous resource within the academy of Medical Royal Colleges. In 2011, UKDEC published 'An Ethical Framework for Controlled Donation After Circulatory Death' (3) which outlines a framework for addressing the key ethical issues in current controlled DCD practice. UKDEC may be contacted via [donationethics@aomrc.org.uk](mailto:donationethics@aomrc.org.uk)

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## 6 INFORMING THE RECIPIENT

### Statements of Recommendation

- ***Providing information, both orally and in writing, for the potential transplant recipient is a requirement for consent and is the responsibility of the multi-disciplinary transplant team. This must be updated and reviewed annually and the outcome of discussions clearly documented in the patient's medical record. (B1)***
- ***Information should be tailored to the requirements of the potential recipient, recognising that not all patients wish to receive detailed information. However, this must not preclude engagement with the transplant process. (B1)***
- ***The risk benefit analysis presented to the potential transplant recipient must explain the relative risk for that recipient of remaining on the transplant waiting list compared to that of receiving a DCD organ. (B1)***

### Perspective

Valid consent requires that the potential transplant recipient be informed of the risks and benefits of an intervention, namely transplantation using a DCD donor organ. The NHSBT and BTS have jointly produced a Guideline for Consent for Solid Organ Transplantation (1). This provides specific recommendations about the provision of information during patient consent and reflects the challenges that are unique to transplantation such as diversity of risk versus benefit depending upon organ type, recipient and donor co-morbidity, timeframes for decision making, and limited organ supply. The guideline highlights key areas for consideration to facilitate consent:

- Information to be given prior to joining the transplant waiting list
- Maintaining consent while on the waiting list
- Informing patients about risk
- Patient choice and the donor organ
- Discussions at the time of an organ offer
- Information which the recipient is entitled to know about the donor
- Information which the donor family is entitled to know about the recipient

Informing the recipient is a complex process and individual patients have different requirements for information. The method of delivery must be flexible to reflect this and is best achieved through a multi-disciplinary approach. Specialist nurses/recipient coordinators often take a lead role in providing education and support for potential recipients, but engagement across the multi-disciplinary team is vital.

A two-stage consent process is advocated in which the patient is registered on the national deceased donor transplant waiting list, followed by confirmation of consent on admission for transplantation. Best practice recommends that consent and accompanying information is updated annually for recipients who remain on the list (1).

Peer Support also provides a valuable opportunity to involve patients who have previously experienced transplantation in the support of those who are embarking upon the process. This complements the approach from healthcare professionals, encourages acceptance of chronic illness, and supports decision-making (2).

### **Specific considerations for the recipient of a DCD organ**

The key issue for any potential transplant recipient is to understand the risks and benefits of remaining on the transplant waiting list versus those of accepting a donated organ. In the context of DCD, there are organ-specific considerations relating to the type of organ that is required and the characteristics of the individual organ, and recipient considerations such as the likely length of time to wait for an alternative organ and the risk of death while waiting.

The risks involved from DCD organs, and the risks involved in waiting for a non-DCD organ, need to be individualised wherever possible, with data from the transplant unit being supplemented by national data where available. It is pertinent to note that, while the risk of receiving an organ transplant is correctly highlighted in the consent process, the risk of remaining on the transplant risk is often significantly underestimated.

### **References**

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## 7 ORGAN RETRIEVAL

### Statements of Recommendation

- *Treatment withdrawal should ideally be planned for a time when the donor HLA type and virology are known and the liver and pancreas recipients are in the recipient hospitals. (C1)*
- *Treatment withdrawal in the operating department is associated with shorter asystolic periods (warm ischaemic times) than withdrawal on a remote intensive care unit or ward. (C1)*
- *The retrieval team need to be satisfied about the donor details (blood group, past medical history, illness leading to death) before treatment is withdrawn. (A1)*
- *Retrieval teams should be scrubbed in the operating theatre at the point of treatment withdrawal. (B1)*
- *Maastricht 4 donors, where death has been established previously by brain stem criteria, may be given heparin before treatment withdrawal. Death does not need to be reaffirmed once circulatory arrest has occurred. (A1)*
- *The specialist nurse should keep a record at regular intervals of the donor's haemodynamic parameters following treatment withdrawal. (C1)*
- *Death may be confirmed five minutes after complete circulatory arrest. There is no need for a further stand off period following this. (A1)*
- *For controlled donors, retrieval starts by gaining access to a large artery and vein, typically the right common iliac artery or aorta, and the IVC in the abdomen or right atrium in the chest. (Not graded)*
- *20 000 units heparin should be added to the first two bags of ice-cold preservation solution to be perfused through the aorta. (Not graded)*
- *A fibrinolytic agent such as streptokinase or recombinant tissue plasminogen activator may be added to the first bag of preservation solution. (B3)*
- *The kidneys may be removed either individually or en bloc. (Not graded)*
- *The pancreas may be removed either en bloc with the liver, or following removal of the liver. (Not graded)*

- ***Cannulae for preservation fluid should never be placed in the SMV or IMV when the pancreas is being retrieved. (B1)***
- ***The liver should be recovered using a rapid technique which minimises liver congestion. (Not Graded)***
- ***Dual perfusion of hepatic artery and portal vein is essential for recovery of DCD livers for transplantation. (C2)***

## **7.1 The Procedure of Organ Recovery**

### **Timing of treatment withdrawal: general considerations**

The timing of treatment withdrawal in the donor should be planned with the intention of optimising the outcome of the donated organs. There are several screening tests (e.g. donor virology) and other tests (e.g. histocompatibility testing) that should be completed urgently.

Allocation of kidneys, pancreas and lungs usually require the donor human leucocyte antigen (HLA) type to be known, therefore donor blood should be sent to the nearest histocompatibility and immunology laboratory as soon as possible. Additional blood may be requested by the recipient centres ahead of withdrawal to allow a pre-emptive cross match to be performed on peripheral blood.

Once the intended recipients have been identified, it is desirable that the lung, liver and pancreas recipients are all in the recipient hospital when treatment withdrawal in the donor is planned. In the case of liver transplantation, the recipient should be ready to go to the operating room as soon as the liver has been declared useable by the retrieving centres.

### **Standard retrieval interventions**

Most controlled DCD protocols allow the retrieval laparotomy and organ perfusion with cooled crystalloid or colloid solutions as soon as death has been confirmed, although others require an additional brief period of 'stand off' (typically five minutes) after death has been diagnosed. However, additional precautions may be necessary should interventions risk restoring the supply of oxygenated blood to the brain.

### **Continued cardiopulmonary resuscitation**

Uncontrolled DCD follows an unexpected cardiac arrest in which a decision is made that continued resuscitation measures will not succeed in saving the patient's life. However, there

is generally a requirement to resume or continue circulatory support in order to prevent excessive organ ischaemia prior to organ perfusion/retrieval, and this has generated anxieties over restoring/maintaining cerebral perfusion, particularly if death has already been diagnosed. An alternative approach, that has some parallels with controlled DCD, is that cardiopulmonary support should be continued until the suitability of the patient as a potential donor has been assessed and the preparations for organ retrieval have been completed, and that only at this point should those treatments be withdrawn and death subsequently confirmed.

### **Preparations for treatment withdrawal**

To minimise warm ischaemic injury associated with the time from death to perfusion with ice-cold preservation solution, treatment withdrawal is best done in the operating theatre complex wherever possible, although there may be local constraints and family preferences that prevent this. Three contingencies need to be considered:

1. A clinician must be readily available throughout the period of withdrawal to enable prompt confirmation of death when it occurs. This clinician must not be a member of the transplant team.
2. The next of kin must be given the opportunity to be present before and during treatment withdrawal and until death is confirmed. Their privacy must be respected; a room should be available into which they may withdraw at the time of death and where they may remain undisturbed for a period of time following death. Some potential donors do not die in a manner or time frame conducive to successful organ donation.
3. If the potential donor remains alive beyond the period of time that the retrieval surgeons deem appropriate (a minimum of 3 hours), it is not suitable to keep him/her in the operating department. Since death is inevitable, the patient must be transferred to the most appropriate alternative accommodation, which may be a bed/single room on an adjacent ward or transfer back to the ICU or ward from whence he/she came. This possibility must be explained to the next of kin at the time donation is discussed

The retrieval team/s are responsible for reviewing the potential donor's hospital/medical notes to satisfy themselves that they have the correct information, in particular with respect to the donor's blood group and past medical history.

### **Mode of withdrawal of life sustaining treatment**

A decision that continued active management of a patient is futile follows confirmation by both examination and investigation that he/she has sustained a catastrophic and irreversible brain injury. At this point, formal testing of brain stem function should be performed to establish whether the criteria are fulfilled for a diagnosis of brain stem death. This recommendation is in line with those made in the Organ Donation Task Force report of 2008 (1). If some residual function remains, the supervising ICU or ED clinician may decide that there is no hope of recovery and that further treatment would be futile. If this opinion is based on the interpretation of CT or MR images of the head, a written opinion is required from the neurologist or neurosurgeon involved prior to the declaration of futility (see Diagnosis of Death, Chapter 4).

Following a diagnosis of futility, the supervising clinician will withdraw life-sustaining treatment. Typically this includes ventilatory support and inotrope infusions but may also involve extracorporeal membrane oxygenation (ECMO) support. If consent/authorisation has been given by the patient in life, or by the next of kin attending the patient at this time, organ donation may be considered.

To ensure the best transplant outcome from the donated organs, abrupt cessation of ventilation, extubation, and discontinuation of any inotropic drugs induces the shortest time to death (withdrawal period) and associated warm ischaemia to the donated organs.

While it may be desirable to administer heparin at the time of treatment withdrawal, as recommended by the American Society of Transplant Surgeons (2), this is not permitted by the Human Tissue Act 2004 or the Human Tissue (Scotland) Act 2006 (3,4). However in Maastricht category 4 controlled donors, in whom death has already been verified, it may be given. Prior cannulation in Maastricht category 3 controlled donors is also currently forbidden.

The retrieval teams must be aware of how treatment withdrawal will be performed. The manner of treatment withdrawal is for the supervising intensivists to decide and must not be dictated by the transplant team. The retrieval team must check with the recipient centre that the recipient preparations are sufficiently far advanced for treatment withdrawal to be undertaken.

### **Immediately before treatment withdrawal**

Before withdrawal of treatment, the following preparations apply:

- Retrieval teams for all the organs must be present and ‘scrubbed’ in theatre. Adequate numbers of non-scrubbed staff must be available to allow for rapid transfer of the donor from bed to operating table.
- If the donor is Maastricht type 4 and death has previously been certified by brain stem criteria, the donor can be heparinised with 20 000 units heparin immediately before treatment withdrawal. This is not permitted for type 1, 2 or 3 DCD donors. Once treatment is withdrawn in such donors there is no need to verify death: death has already been declared. The donor can be moved immediately into the operating theatre.
- The preservation fluid must be run through the giving sets, although the bags themselves must remain on ice. 20 000 units/litre of heparin must be added to each of the first two bags of preservation fluid. If both portal vein and aortic perfusion is to be undertaken, the first portal bag **must** also contain heparin.
- A doctor (usually an anaesthetist) must be available to verify death.

#### **After treatment withdrawal**

Following treatment withdrawal, the SN-OD will:

- Record serial haemodynamic measurements, i.e. pulse, blood pressure
- Measure oxygen saturations every 3 to 5 minutes +/- regular blood gases if available
- Record residual urine output from the donor

Once circulatory arrest occurs, **five minutes** must elapse without any evidence of resumption of circulation before death may be verified (5). There is no need for any further “stand off” period once death is verified.

#### **The withdrawal (agonal) phase: the relevance of time to death**

Various factors are known to predict the likelihood of death after withdrawal of life supporting treatment (6-8), but none are fool proof. The haemodynamic changes following treatment withdrawal vary, with some patients showing an immediate fall in blood pressure while others have a sustained good blood pressure for many minutes or hours before it eventually falls (9).

Many authors suggest that organs removed after a fixed withdrawal period, i.e. 30 minutes for livers, 60 minutes for kidneys, are untransplantable (10), although there is a lack

evidence to support this. Indeed there are several reports in support of longer withdrawal phases producing transplantable organs (6,11).

The most important consideration during the withdrawal phase is the perfusion of the organs; a prolonged withdrawal phase is unlikely to be harmful as long as the blood pressure is maintained and urine output continues. To address this, a threshold systolic blood pressure of 50 mmHg has been proposed below which warm ischaemic injury occurs (12). This has been adopted widely so that the **functional (or true) warm ischaemic period (FWIT)** starts when the systolic blood pressure has had a sustained (at least 2 minutes) fall below 50 mmHg (or the haemoglobin oxygen saturation below 70%) and extends up to the onset of cold *in situ* perfusion (see also Chapter 3).

The FWIT reflects the fact that, even though a circulation exists, end organ perfusion is poor and the organs suffer a warm ischaemic insult. It may be appropriate, therefore, to consider this warm ischaemic period when assessing likely organ damage, rather than solely the acirculatory (asystolic) warm period.

Evidence for this threshold blood pressure is limited, particularly for liver transplantation, and a different BP threshold may be appropriate. Moreover, the threshold may vary with age and baseline blood pressure, such that a hypertensive 60-year-old will suffer more ischaemic damage when the systolic pressure is 50 mmHg than will a young normotensive patient. The surgeon needs to take all these factors into account when evaluating the viability of the donated organs. More evidence is required before absolute thresholds can be suggested.

Pulse oximetry has also been used to inform the onset of organ hypoxia. However, a peripherally placed pulse oximeter will only reflect peripheral hypoxia. It is common for donors to become peripherally shut down as the process of dying proceeds, which reduces the accuracy of oximetry. For this reason, it has been suggested that oxygen saturation should no longer be used in the definition of FWIT. In this document, oxygen saturation has been retained as a marker of FWIT; however, this is an area that may evolve rapidly.

### **Management on confirmation of death**

Individual techniques for organ retrieval vary. The principle is to rapidly cool the organs by a combination of intra-arterial perfusion with ice-cold preservation solution and application of topical slush. Once cold, the organs need to be removed quickly but with care to ensure no inadvertent damage, particularly to anomalous vessels.

Once death is confirmed:

- The patient is transferred to the operating table.
- The chest and abdomen are rapidly cleaned with antiseptic and drapes applied.
- A midline incision is made from the suprasternal notch to the symphysis pubis. The abdomen and chest are opened.
- Venous drainage is achieved either by opening the right atrium into the left chest or by cannulating the inferior vena cava just above the confluence of the common iliac veins to allow the blood to siphon out to a receptacle. The right common iliac artery or distal aorta are identified and cannulated; ice-cold, heparinised preservation solution is flushed into the aorta. A cross clamp is placed either on the descending thoracic aorta in the chest or on the supra-coeliac aorta in the abdomen; the former is quicker if the chest is open.
- If the liver is being retrieved, the portal vein may be cannulated directly by dividing it 1 cm from the superior mesenteric vein/splenic vein confluence; when the pancreas is not being retrieved the superior or inferior mesenteric veins may be cannulated. Ice slush is then placed across the liver, between the bowel loops, in the lesser sac, behind each kidney, and in the right hemi-thorax on the dome of diaphragm above the liver. The common bile duct is then divided and flushed with cold saline, and the gall bladder fundus incised and bile washed out.
- Dissection should now wait until the organs are properly perfused and cooled. Allow at least 2 litres of preservation fluid through the organs before starting final dissection to remove them.

Caveats:

1. Cannulating the common iliac artery may prejudice its use for reconstructing the arterial supply to the pancreas so, if it is used, divide it as close to the aortic bifurcation as possible.
2. Neither the superior nor inferior mesenteric veins should be cannulated when the pancreas is being retrieved, since the venous perfusion pressure prevents perfusion of the pancreas.

Following removal of the organs, an extensive search must be made of the abdominal and thoracic contents for evidence of cancer, in particular of the colon, stomach, pancreas, oesophagus and lungs. The kidneys should also be exposed by removal of the perinephric

fat *before* cold storage, looking for tumours and checking perfusion. Any abnormal lesions should be removed and urgent histology obtained before any of the organs are implanted.

## 7.2 Preservation Solutions

A variety of preservation solutions can be used. There are no randomised controlled trials of preservation solution in DCD donors. Preservation solutions are further discussed in organ specific chapters (Chapters 8-13). However, in summary:

- Animal work from Holland suggests that UW solution (ViaSpan; SPS-1; Belzer-UW) is associated with more effective organ cooling in a pig model than Bretschneider's histidine-tryptophan-ketoglutarate (Custodiol-HTK) solution (13).
- Infusion pressure is limited by the length and diameter of the tubing, the fluid viscosity, and whether or not the bag is pressurised. The widest bore tubing should be used (e.g. operating theatre suction tubing) with wide bore cannulae (e.g. 32 Fr) and continuous pressurisation of the bag.
- Static cold storage is the most prevalent method for renal allograft preservation.

Several solutions have been designed to counteract the detrimental effects of cold ischaemia and reperfusion. A systematic review was carried out by O'Callaghan et al (14) using delayed graft function (DGF) as a primary end point. Fifteen trials with a total of 3584 kidneys were included. The key findings were as follows and are supported by registry data:

- EuroCollins was associated with a higher risk of DGF when compared in two randomised controlled trials (RCTs) to University of Wisconsin solution (UW), and when compared in two RCTs to histidine-tryptophan-ketoglutarate (HTK).
- UW was associated with an equal risk of DGF compared with Celsior in three RCTs and compared with HTK in two RCTs.
- The choice of preservation solution has an effect on the incidence of DGF, and may affect long-term outcomes.
- Both UW and HTK have lower rates of DGF than EuroCollins.
- There is no difference in the incidence of DGF with the use of Celsior, HTK and UW.

## **Heparin / fibrinolytic**

Heparin is added to prevent clots forming once preservation solution is infused; solution alone will cause clot formation. Some units consider the addition of a thrombolytic agent to be essential, although the evidence for such intervention comes from small animal and clinical trials (15-19). The effectiveness of agents such as streptokinase in the hypothermic environment is questionable, although some authors have suggested an initial warm 'pre-flush' to overcome this problem.

### **7.3 Staffing the Retrieval Procedure**

The 'stand alone' National Organ Retrieval Service (NORS) teams are responsible for retrieving organs from both DBD donors and controlled DCD donors. Because of the severe time limitations, uncontrolled donors are outside the remit of the NORS teams and centres with uncontrolled DCD programmes make their own local staffing arrangements according to the availability of members of their transplant team.

Currently there are seven abdominal and six cardiothoracic on-call NORS retrieval teams, which cover the whole of the UK. These teams are commissioned and fully funded by NHSBT. Each team includes a lead surgeon, an assistant surgeon and a scrub nurse. All the cardiothoracic and four of the abdominal teams also include a perfusionist. In addition, it is usual for two SN-ODs to attend a DCD donor, one of whom accompanies the donor family and liaises with the donor hospital staff whilst the other SN-OD accompanies the retrieval team and assists with perfusion if required.

In general, the closest available NORS team should attend the donor. If there is doubt about the suitability of a particular DCD organ for transplant, the recipient centre may send an individual to join the designated retrieval team and assess the organ *in situ* provided that this does not delay the retrieval procedure. DCD lung retrieval is still relatively novel and some centres have no experience with the procedure; lung recipient centres may retrieve themselves provided that this does not delay the donor operation and prejudice the chance of donation occurring.

In the event of a DCD kidney only donor (i.e. consent has only been granted for kidney retrieval, or all other organs have been offered but declined as unsuitable by all potential recipient centres), then the local kidney transplant team may retrieve if they are willing and able to do so without the support of a NORS team. However, if for any reason the local team

is unable or unwilling to attend the donor then the designated NORS team is obliged to retrieve.

## **7.4 Abdominal Organs: Specific Procedures**

### **Removal of the kidneys**

- The right colon is reflected upwards to expose the inferior vena cava (IVC), aorta, ureters and Gerota's fascia around the kidneys.
- The ureters are divided as distal as possible and a marker clip placed on the end of each.
- The left renal vein is divided at its confluence with the IVC leaving the IVC intact to go with the right kidney; the cut end of the left renal vein is then reflected laterally. The anterior wall of the aorta is incised in the midline through to the origin of the SMA. The posterior wall is similarly incised between the origins of the lumbar arteries. A generous amount of aorta plus underlying tissue is removed with the renal arteries; no attempt should be made to identify the arteries at this stage, although their ostia should be identified from within and care taken to ensure that they are on the patch.
- The kidneys in their pocket of perinephric fat are then held one by one and dissection continued posteriorly onto psoas to avoid damage to the arteries. Avoid pulling the kidney away from the body - intimal arterial tears are readily made, particularly in older donors.
- Alternatively *en bloc* removal of both kidneys may be performed. Both ureters are divided as they cross the iliac artery and their ends clipped and held up. The distal aorta and IVC are also held up by clips and the tissue behind the aorta, cava and ureters is divided progressively more cranially. Both kidneys come out as a bloc. This is the preferred technique for retrieval of small paediatric kidneys (under 5 years old) and may be appropriate if both kidneys are known to be going to the same recipient centre, or in rare cases of horseshoe kidney. This technique is associated with less damage to the kidneys.

### **Removal of the liver**

- The donor is placed in a supine position, quickly prepped and draped typically with a large single use light drape to save time.

- The standard retrieval procedure derives from the super-rapid technique, originally described by Casavilla et al (20).
- A midline laparotomy is performed from the sternal notch to the pubis. There is no need for diathermy in the absence of a circulation.
- The abdomen is kept open using a large self-retaining retractor handed half open (for speed of action).
- The distal ileum, caecum and small bowel is reflected superiorly, exposing the area of the aorto–iliac bifurcation and just sufficient to rapidly identify and cannulate the distal aorta or the right common iliac artery.
- Cold perfusion is started immediately by gravity with a low viscosity preservation solution (e.g. Marshall's) containing 20 000 u/l of heparin. The IVC must be vented early on to prevent congestion of the liver. This can be via the abdominal IVC or more preferably the supra-diaphragmatic IVC; easily performed by opening the diaphragm or with a thoracotomy. The abdominal IVC is preferable if the lungs are also being retrieved.
- Copious amounts of saline ice slush are then used in the abdomen and chest for topical cooling of the liver.
- A sternotomy using a Gigli or automated sternal saw can then start and a Finocchietto retractor be placed. The right atrium can be partially divided to improve venous venting and both pleura are opened to facilitate drainage into the pleural cavities where two pool suction tubes are placed to collect the effluent blood and perfusion solution. The left lung is lifted exposing the descending thoracic aorta and at this time a cross clamp can be applied. Following aortic cross clamping the perfusion fluid pressure can be increased to 200 mmHg, applied with a pressure bag to improve perfusion pressure in the aorta.
- In DCD liver retrieval, dual perfusion of the portal vein and aorta is paramount. The portal vein can be cannulated via the SMV and perfused with 1 litre of UW solution containing 20 000 u/l of heparin. The SMV is exposed at the root of the mesentery for cannulation below the head of the pancreas.
- In situations of concomitant pancreatic recovery, the portal vein needs to be directly isolated after division of the common bile duct and cannulated approximately 1 cm from the edge of the duodenum. The fundus of the gallbladder is secured with a Kelly clamp and incised over 2 cm. The gallbladder content is aspirated and the lumen

flushed with cold normal saline using a bladder syringe. The divided common bile duct is also directly flushed with cold saline using a 10 ml syringe with a Tibbs cannula.

The procedure now continues with dissection in the cold phase, which is the same as that used for a rapid retrieval in unstable DBD donors:

- The liver is retrieved first, followed by the pancreas and kidneys. One option is to retrieve the liver and pancreas *en bloc* and subsequently separate the two organs on the back bench. Although there is no clear advantage for this, it remains the preference of some NORs teams and is particularly suitable if both organs are returning to the same implanting centre since they can be split there, and not at the donor hospital.
- Many centres use a low viscosity solution through the aorta as an initial flush. The second litre is UW solution. Whichever fluid is used, the first two litres through the aorta and first litre through the portal vein should each contain 20 000 units heparin. Usually the flow of UW solution in the portal vein is slowed down after 800 ml to complete 1 litre of UW portal perfusion *in situ*. (All steps must be confirmed with the retrieving surgeon).

### **Removal of the pancreas**

- The pancreas can be removed *en bloc* with the liver, or following removal of the liver. Removal *en bloc* has the advantage of allowing identification of accessory or replaced right hepatic arteries arising from the superior mesenteric artery (SMA).
- The duodenum is Kocherised. The gastro-colic ligament divided fully to expose the body and tail of pancreas.
- The short gastric vessels are divided close to the stomach and the tail of the pancreas mobilised by using the spleen as a handle to lift it medially.
- The transverse mesocolon is divided near the colon and the small bowel divided just beyond the duodenojejunal flexure using a linear stapler; the stomach is similarly divided just before the pylorus. The small bowel mesentery is then stapled, staying away from the pancreas in order to avoid damage to the inferior pancreatico-duodenal artery.
- If the pancreas is to be removed *en bloc* with the liver it is next mobilised; if it is being removed after the liver has been removed the tail of the pancreas should now be lifted

via the spleen and the under surface of the gland dissected away from the underlying Gerota's fascia.

- The SMA is divided at the level of the aorta without an aortic patch to avoid damage to the aortic patch that is required for the kidneys.

Current practice is to use the pancreas if the warm ischaemic insult is under 30 minutes, although successful transplantation has been reported with longer times.

### **Back table preparation**

- As the organs are removed they are best placed in bowls containing saline slush to aid cooling.
- More preservation solution may be passed through the hepatic artery and portal vein, and the bile duct further washed out.
- The perinephric fat is bivalved along the lateral border of the kidney to expose the kidney parenchyma completely along its length in order to identify any tumours. If perfusion is poor, the renal artery/ies may be further perfused with preservation solution.

### **Repair of organ damage**

If damage has occurred this must be recorded on the relevant NHSBT form and the recipient surgeon notified. No attempt should be made to repair the damage at the donor hospital; this is best done by the implanting surgeon.

### **Packing for cold storage**

Following cold *in situ* perfusion, the organs are still relatively warm and must be packed in ice as soon as possible. It is best to avoid prolonged back table dissection in the donor hospital. If the pancreas and liver are removed *en bloc*, avoid splitting the bloc at the donor hospital wherever possible; it is preferable to do this when the organs are truly cold, after at least an hour in ice.

### **Uncontrolled DCD donors (Maastricht type 1 and 2)**

Under the Human Tissue Act (2004) and the Human Tissue (Scotland) Act (2006), it is lawful to take the minimum steps necessary for the purpose of preserving organs for transplantation until consent/authorisation, or lack of consent/authorisation is established

from the next of kin (3,4). Such consent/ authorisation includes being on the Organ Donor Register (ODR) (see Chapter 5).

Such minimal steps include the cannulation of the femoral vessels (HTA 2004, Part 3, Section 43; HTA Scotland 2006, Part 1, Section 13). Once the femoral vessels are cannulated, it is appropriate to perfuse the body with ice cold, heparinised preservation solution. The best catheter for such purposes is a double balloon catheter that ensures only the abdominal compartment is perfused.

### **Normothermic regional perfusion (NRP)**

Normothermic regional perfusion, also known as normothermic recirculation and normothermic ECMO (NECMO), has been pioneered in Spain and has now been adopted elsewhere in Europe, the US and Russia (21,22). At the time of writing, pilot programmes have also been established in the UK. The technique involves perfusing the abdominal organs with oxygenated blood at normal body temperature using a modified extra-corporeal membrane oxygenator (ECMO) circuit, which includes an oxygenator, heat exchanger and pump. Venous drainage is from the IVC via catheters in the right atrium, distal IVC, or femoral vein, with return of oxygenated blood either into the femoral artery, ascending thoracic aorta or distal abdominal aorta. Current guidance (2011) following a joint meeting of the Department of Health, the Intensive Care Society of Great Britain, the British Transplantation Society, and other interested parties, is to limit perfusion to the abdominal organs and specifically to exclude the coronary, carotid and subclavian arteries from the circulation e.g. through balloon occlusion of the thoracic aorta.

In addition, it has been agreed that when lungs are to be retrieved from DCD donors undergoing NRP, the lungs will be flushed *in situ* and then removed early after the initiation of NRP. The thoracic team are responsible for clamping both the supra-diaphragmatic aorta *and* the intra-pericardial IVC, and for securing complete haemostasis within the chest. They should not leave the operating theatre until any residual bleeding is controlled to the satisfaction of the abdominal team.

## 7.5 Thoracic Organs: Specific Procedures

### Removal of the lungs

#### The donor ICU team

- The retrieval team and the SN-OD are not involved in any way with the management of the donor prior to retrieval, so there is a reliance on the donor ICU team.
- Ventilator management should be with a lung-protective regimen, 5-6 ml/kg tidal volume and PEEP of 8 cmH<sub>2</sub>O.
- In an ideal situation, there will have been a bronchoscopy, with a report of the state of airway mucosa and secretions, recent ABGs and a chest X-ray within 12 hours.
- A nasogastric tube should be placed unless there is likelihood of distress to the donor.
- A suitably experienced clinician should be available throughout the process of withdrawal of treatment, and should be responsible for confirming death promptly when it occurs. This individual may agree to re-intubate the donor after death (if there has been extubation). The donor hospital team should have a robust protocol in this regard.
- The situation with regard to re-intubation by the donor hospital team must be ascertained before the retrieval team leave their base. If the donor hospital team will not re-intubate the donor, and this is often regarded as a conflict of interest, the retrieval team MUST include someone appropriately skilled.

#### The retrieval team

- Withdrawal of treatment may take place in the ED, ICU, an anaesthetic room, or an operating theatre. The team should be present in, or adjacent to the operating theatre to be used for the retrieval surgery. If withdrawal has taken place in the operating theatre and asystole has occurred, the retrieval team may be scrubbed and ready to begin 5 minutes after asystole, and verification of death.
- The local arrangements should be confirmed with the SN-OD with regard to withdrawal of treatment, the presence of the family, time to arrival in the operating room, and personnel to re-intubate. Potential difficulties with intubation should be identified at this stage.

- The retrieval surgeon should check the consent, height and weight, chest X-ray, blood group and virology of the donor and complete the National Transplant Database Form.
- A discussion should take place with the abdominal retrieval team with regard to how the surgery should be planned. If possible, discussions should also be held with the donor team about the use of the operating theatre anaesthetic machine to deliver continuous PEEP.
- After withdrawal of treatment, regular contact should be maintained with the SN-OD with regard to the haemodynamics and oxygen saturation of the donor. If cardiac arrest has not occurred within 60 minutes, the situation should be discussed with the implanting team. If the donor condition remains stable, a decision may be made to abandon the retrieval at this stage.
- The point should be noted at which systolic blood pressure falls below 50 mmHg or the oxygen saturation falls below 70%. If more than an hour passes with blood pressure and oxygen saturation at this level, there is concern about warm ischaemia and the retrieval should be abandoned.

#### After cardiac arrest

- The time of death must be noted.
- On arrival in the operating theatre, the donor should be re-intubated with a cuffed endotracheal tube; this may be preceded by a rigid bronchoscopy, depending on the skills available.
- Intra-abdominal manipulation may cause aspiration, so early protection of the airway is important.
- Thorough airway toilet should be performed as soon as possible.
- Once reintubated, atelectatic lung may be recruited with a *single* breath, perhaps 25 mmHg pressure for 40 seconds, ideally using the anaesthetic machine. CPAP should be maintained at 5 cmH<sub>2</sub>O and continuous O<sub>2</sub>, once again possibly with the theatre anaesthetic machine or an appropriate valve.
- Cyclical ventilation must not be used until the chest is open and the aorta can be clamped. The time of lung inflation should be noted. Warm ischaemia is lessened at this stage, but many teams feel that early flushing of the lungs is still important, so the chest is rapidly opened.

- The lungs should be examined for collapse, consolidation, mass lesions and pleural adhesions. If there is a suspicion of airways disease, the degree of collapse when the lungs are disconnected should be noted. This test should be done before flushing.
- The pulmonary artery should be cannulated, and the right ventricle may be opened to remove clot.
- Antegrade perfusion should be started as per the practice of the retrieval team. Many will begin with warm Perfadex<sup>®</sup>. The left atrium or atrial appendage should be widely opened and clot washed out of the pulmonary veins. At this stage, distribution of perfusate is aided by gentle cyclical or intermittent recruitment and ventilation of the lungs.
- When the antegrade perfusion is complete, the pulmonary veins should be gently cannulated for retrograde perfusion, 200-500 ml down each one, until the effluent from the pulmonary artery is clear. The lungs may be removed collapsed, although some retrieval teams may continue to ventilate. If they have been collapsed when only the trachea is intact, the lungs should be cautiously reinflated prior to storage. After removal, the lungs should again be examined.
- Information about the degree of inflation, the “collapse” test, any areas of consolidation or masses, clot in the pulmonary artery, the uniformity of flushing, and any palpable oedema will be required by the implanting team. They will decide to use the lungs outright, to place them on *ex vivo* lung perfusion (EVLP, also called *ex situ* normothermic lung perfusion), or to abandon the retrieval.
- Communication between retrieving and implanting team must be regular and complete. The decision about use of the lungs will usually require a detailed discussion between retrieving and implanting surgeon.
- If EVLP is to be used, at least 10 cm of trachea and ample LA and PA should be retrieved if possible. The lungs should be packed as for a standard retrieval, with the routine blood specimens and paperwork.

**Note:** It has been agreed that the lungs will not be reinflated until 10 minutes has elapsed since the time of death, to avoid any chance of auto-resuscitation. Similarly, cyclical ventilation should not be used until the chest is open and there is no longer any chance of brain stem activity; isolation of the cerebral circulation is recommended.

## Removal of the heart

This is an area in which there is limited experience and is briefly covered in section 13.2.

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## PART 2: ORGAN SPECIFIC DISCUSSION

### 8 KIDNEY

#### Statements of Recommendation

- *Individuals with advanced or end-stage chronic kidney disease, or with cortical necrosis demonstrable on biopsy should not be considered as potential kidney donors. (B1)*
- *The use of donors with functional warm ischaemic time >2 hr or absent blood pressure for 30 minutes should be restricted to (currently experimental) protocols which attempt to resuscitate organ viability. (B2)*
- *Units undertaking cold machine perfusion of DCD kidney transplants prior to implantation should collaborate to standardise the prospective collection of data to enable aggregated analyses of outcomes. (A2)*
- *None of perfusion pressure dynamic characteristics, perfusate effluent biochemical analysis, or kidney transplant biopsy scoring systems - alone or in combination - have sufficient predictive value to mandate organ discard. (A2)*
- *Such assessment may, however, help determine when kidneys should be considered for dual transplantation. (B2)*
- *Long term outcomes of DCD recipients are similar to those of DBD recipients and the allocation system for DCD and DBD organs should be similar. Nevertheless, it is recognised that DCD kidneys appear to be more susceptible to cold ischaemia, and the proposed national allocation scheme should take this into account. (B2)*
- *The incidence of delayed graft function is increased in DCD recipients and this should be discussed with the patient prior to transplantation. (A1)*
- *Antibody induction therapy should be used as part of the initial immunosuppressive regimen for recipients of DCD kidneys. (B1)*
- *Long-term outcomes for standard criteria donors are equivalent for DCD and DBD kidney transplants. (A1)*

- ***Graft outcome is more closely related to whether a transplant is ECD vs SCD than whether the mode of retrieval is DCD vs DBD. (B2)***
- ***Prospective data are required to determine whether the impact of expanded criteria donation (ECD) is different in DCD and DBD donors and whether different thresholds for organ use may be required. (A1)***

## **8.1 Introduction**

Kidney transplantation using DCD organs is fundamentally similar to transplantation using DBD organs, except that the organs will have suffered an additional warm ischaemic insult and may not have been subjected to the physiological and inflammatory stress associated with brain stem death.

The increased incidence of primary non function with DCD kidneys shows that irreversible injury can occur under certain circumstances, especially in the context of pre-existing or additional ischaemic damage. However, the very good medium term outcomes reported for DCD organs suggest that this DCD-associated injury may be reversible, yielding organs with essentially identical long term function to those from DBD donors.

Although the kidney is the organ for which most experience and published data are available in relation to DCD transplantation, there are complex interactions between different degrees of warm ischaemic DCD injury, cold ischaemic injury, and pre-existing damage due to hypertension, diabetes, atheromatous disease, and to other co-morbidities in kidneys from extended criteria donors (ECD). A recent, large, UK based cohort study has suggested that DCD donor kidneys are more susceptible to cold ischaemic injury, but there is no evidence that DCD ECD donor kidneys suffer from more long term graft dysfunction than equivalent DBD ECD donor kidneys (1).

Deceased donor kidney donation in the UK is currently associated with increasing numbers of both ECD and DCD donors. The complex interactions between the two make the definition of best practice in relation to DCD extremely difficult. Only careful prospective data collection will allow the resolution of important issues such as the role of machine perfusion and the predictive utility of histological or functional scoring systems in optimising clinical outcomes.

## **8.2 Donor Selection**

### **Absolute contraindications**

In addition to the general absolute contraindications to organ donation defined by NHSBT, (i.e. invasive or haematological malignancy, untreated systemic infection, prion disease, and HIV disease), obvious absolute contraindications to the use of organs for DCD kidney transplantation are:

- End-stage kidney disease (CKD stage 5, eGFR <15 ml/min)
- CKD stage 4 (eGFR 15-30 ml/min)
- Acute cortical necrosis on pre-implantation kidney biopsy

Acute kidney injury, even that requiring dialysis for the donor during the current hospital admission, is not an absolute contraindication to kidney donation. However, it is likely to increase the risk of DGF or primary non function (PNF) to a greater degree than that associated with DBD donation.

### **Relative contraindications**

Donor and retrieval factors that impact upon graft outcomes include donor age and cold ischaemic time (2,3). Additional factors such as donor hypertension and cardiovascular disease have also been shown to have an impact on DCD kidney survival, but to a lesser degree than these factors (2).

For older DCD donors (>60 years), particularly those with hypertension and/or cardiovascular death, pre-implantation biopsy may identify kidneys with substantial arterial disease or glomerulosclerosis that are likely to have poor long term outcome (4,5). Such kidneys are normally discarded, although good outcomes have been described using DBD kidneys with moderate disease when used as dual transplants into a single recipient (6). Given the comparable outcomes between DCD and DBD kidneys, a similar approach may successfully expand the DCD donor pool, but experience is limited.

Neither acute renal impairment nor haemodynamic instability during a prolonged period from withdrawal of life-sustaining treatment until cardiorespiratory arrest influence DCD kidney graft outcomes (2).

## **Warm ischaemic time**

Given the clear association between WIT and poor outcome, both in terms of PNF and subsequent graft failure, the presence or clear anticipation of prolonged warm ischaemia is a contraindication to kidney donation. Current opinion tends to view functional WIT (FWIT) - when the systolic blood pressure falls below 50 mmHg - as the critical time. Although this has not been validated in any prospective studies, it has become current 'best practice'. The absolute FWIT that affects outcome is unknown and data are currently being collected by NHSBT, but the current recommendation is a maximum of 2 hours. In the event of no blood pressure, 30 minutes appears to be an absolute upper limit of acceptable warm ischaemia, although registry analysis suggests outcomes are less good beyond 20 minutes (7,8). Data from urological surgery strongly suggest that there is effectively no lower limit below which some degree of long term functional damage is not demonstrable (9). The use of kidneys with >30 minutes of total WIT should be restricted to programmes which are undertaking measures to 'recondition' organs via *ex situ* oxygenated normothermic perfusion, with the possibility of more predictive assessment of organ quality than appears possible with static cold storage or cold perfusion technologies.

## **8.3 Organ Preservation**

### **Preservation solutions**

No definitive data currently suggest any advantage for specific preservation solutions in the context of DCD kidney transplantation (10), although animal data suggest that there may (or may not) be solution-specific effects in the context of warm ischaemia (11,12).

### **Cold machine perfusion**

The value of cold machine perfusion of kidneys prior to transplantation is uncertain, and there is currently no clear evidence to support machine perfusion in DCD kidney transplantation. A large prospective European study of DBD and DCD organs showed positive initial findings in terms of DGF and 1-year graft survival (13). In an extension of this study targeted specifically at DCD kidneys, machine perfusion was associated with a significant reduction in the incidence of DGF (54% versus 69%) but no difference in 1-year graft survival or function (14). However, these findings were contradicted by negative results from a multi-centre UK study of machine versus standard cold perfusion in DCD kidneys alone (15). Subsequent 3-year follow-up from the European study showed that

improved graft survival was restricted to DBD organs and (particularly strongly) to ECD organs, and that there was no difference in outcome between static and cold machine perfusion preservation in the DCD sub-group (16).

The apparent contradictions in these studies highlight the importance of careful definition and recording of the donor pre-morbid and agonal characteristics and preservation systems. This is essential if studies of the current, widely varied practices are to help resolve the question of when and how to undertake cold machine perfusion.

### **Ex situ normothermic machine perfusion**

The practice of *ex situ* normothermic machine perfusion offers the potential for oxygenation of the retrieved organ with the aim of limiting or even repairing ischaemic damage and has now moved into the clinical sphere (17). With increasing interest in and data from experimental models of normothermic *ex situ* perfusion of kidney, as well as other solid organ transplants (18), definitive prospective data in clinical kidney transplantation may soon become available.

### **Experimental interventions**

In addition to the maintenance of physiological parameters such as flow and oxygenation, whether by gaseous persufflation or normothermic perfusion, a broad range of active interventions are under investigation in experimental models. These include remote ischaemic preconditioning, small interfering RNAs to down-regulate apoptosis and inflammatory pathways, and a range of anti-thrombotic agents to target the vascular endothelium. As these move towards possible clinical application, similar care will be required to that suggested for the analysis of outcomes using machine perfusion (19).

## **8.4 Organ Quality Assessment**

After transplantation, kidneys may work immediately, recover after a period of impaired or absent function, or never function at all. Early function is dependent upon the underlying health of the donor as well as the ischaemic time and any damage sustained during the process of the death and organ retrieval. Because of the availability of dialysis to support initial graft dysfunction, the emphasis in kidney transplantation must be on minimising, and as far as possible eradicating, primary non function (PNF).

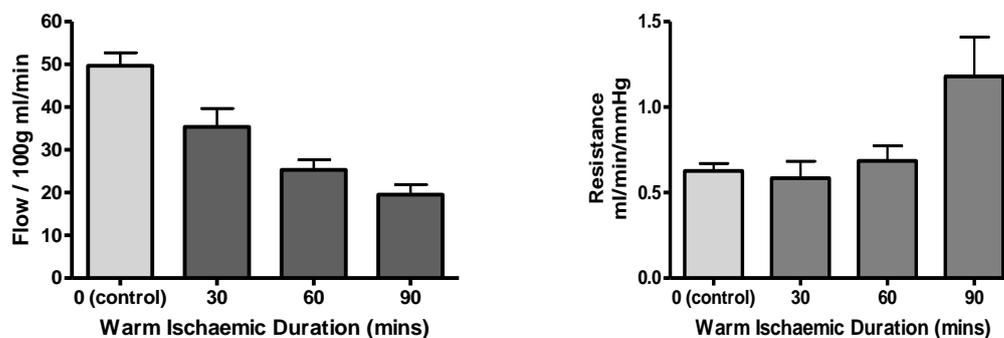
The 'ideal' kidney comes from a young, controlled DCD donor without significant co-morbidity prior to the terminal illness, with a rapid death on withdrawal of support, a quick laparotomy, aortic cannulation, perfusion and venous exsanguination, and good appearance on removal. Such kidneys will be expected to work promptly if cold ischaemia is minimised. In such patients, no viability testing is required, although the role of machine perfusion to 'improve' the kidney is debated.

### Viability assessment from perfusion parameters and biomarkers

As shown in figure 8.4.1, animal models reveal the impact of warm ischaemia on flow and resistance within the kidney, underscoring the importance of reducing WIT as far as possible to preserve graft function.

For uncontrolled DCD or kidneys with poor perfusion on retrieval, additional viability testing is often recommended. In general, low flow rates on machine perfusion or high enzyme levels within the perfusate indicate an increased level of cellular damage which may indicate an increased risk of PNF.

An example of such viability tests are those used by the Newcastle group and shown in table 8.4.1 (20).



**Figure 8.4.1** Effect of increasing WIT on flow and resistance (20).

**Table 8.4.1 Newcastle criteria for viability testing in DCD kidney transplantation**

<b>Characteristic</b>	<b>Criteria for single kidney use</b>
Flow on machine perfusion (Perfusion Flow Index)	>0.4 ml/min/mmHg/100g of tissue
Intracellular enzymes (GST) (ALT, FABP, Redox iron can also be used)	GST: <100 iu/100g of kidney/litre perfusate in standard organ recovery cassette
High GST, low donor GFR, elderly donor, diabetes, prolonged cold ischaemia	Consider dual renal transplant

In the European study of machine perfusion versus static storage which contained a mixture of DBD and DCD, enzyme levels were analysed in perfusate effluent. Although there was a correlation between higher enzymes levels and higher resistance to flow on machine perfusion for kidneys that had delayed graft function, there was no relationship with rates of primary non function. However, the DCDs in this trial were Maastricht category 3 and did not have profound ischaemic damage, reinforcing the point that viability assessment is not so critical for kidneys from this group of DCD (21).

#### **Viability assessment from biopsy parameters**

Work on assessment of organ quality from histological parameters is mainly derived from examination of ECD, rather than specifically in relation to DCD organs. Much of the data derive from studies which were specifically developed to assign organs with reduced functional capacity to dual kidney transplantation (22). Well validated scoring systems based on the 'Pirani' (22,23), Banff, and CADI (chronic allograft damage index) scores (23,24) show better predictive value for poor graft function at 1 year than clinical scoring systems alone. Composite scores combining donor hypertension and creatinine with histological scoring provide the best predictive value. Clinical assessment of these scores requires large, formalin fixed biopsy samples.

There are currently no histological markers that predict PNF as a result of excess warm ischaemia or irreversible ischaemia-reperfusion.

### **Clinical donor risk scores**

A range of increasingly complex scoring systems have been developed in an attempt to predict outcomes in relation to pre-existing donor factors. These are not specific for use in the context of DCD kidney donation. No scoring system, either alone or in combination with pump parameters or histological scoring, has yet been shown to accurately define which organs should be discarded due to an excessive risk of PNF or seriously impaired long-term graft function (1, 25).

## **8.5 Recipient Selection**

### **DCD graft outcome**

In the UK, current data suggest that recipients of DCD kidneys have similar outcomes to recipients of DBD kidneys (3). This is supported by UNOS registry data, which examined 44 035 deceased donor kidney transplant recipients, of which 1177 (3%) received a DCD kidney, and found no difference in patient or graft survival at 5 years (26).

### **Factors that may influence outcome**

NHSBT data show that increasing donor and recipient age and a cold ischaemic time of >12 hours are associated with worse outcome (3). UNOS data show that the incidence of DGF is increased in DCD recipients, ranging from 41-51% compared with 24% in DBD recipients (26,27). It is important to note that the most recent evidence suggests that ECD DCD donor kidneys are no more likely to fail early than ECD DBD donor kidneys (1).

### **Extended criteria DCD organs**

Given the progressive improvement in long term deceased kidney transplant outcomes, with 5-year graft survival approaching 90% (28), it is important to avoid exposing young patients to sensitisation from a poorly matched, poor quality organ which may fail within a short period of time. Equally, the potential for serious morbidity or death resulting from medical and/or other complications associated with DGF in older, more highly co-morbid recipients raises the question how combined ECD DCD organs, with worse outcomes associated with donor age and co-morbidity and increased risk of DGF due to DCD retrieval, may best be utilised. This is largely an ethical issue, and is discussed further in Chapter 5.

## **Recipient informed consent**

Patient survival following receipt of a DCD kidney seems to be similar to that of a patient receiving a DBD kidney. However, the increased risk of DGF and its consequences need to be discussed with the recipient (see also Chapter 6).

## **8.6 Immunosuppression**

Kidneys retrieved from DCD donors will inevitably have suffered warm ischaemic damage and will be at increased risk of both PNF and DGF.

Widely favoured strategies to reduce the incidence of DGF and the risk of clinically silent rejection occurring during periods of DGF include the use of induction therapies to reduce the risk of rejection and the avoidance or delay in introduction of calcineurin inhibitors (CNIs).

### **Use and choice of induction therapy**

It is reasonable to assume that the benefits shown for induction therapy in non-DCD transplantation can be extrapolated to DCD transplantation (29,30). Given the high rates of DGF associated with the use of DCD organs, the reduced early rejection rate associated with induction therapy is particularly desirable.

Retrospective cohort studies from Japan and Spain show reduced rates of DGF when antibody induction therapy has been used in DCD transplantation (31,32). In the UK, a prospective, randomised trial compared IL-2 receptor monoclonal antibody blockade (Daclizumab) combined with delayed introduction of Tacrolimus when the creatinine had fallen to  $<350 \mu\text{mol/L}$  (or following biopsy-proven rejection) with initial Tacrolimus therapy without antibody induction. This showed a significant reduction in DGF in the group treated with Daclizumab and delayed Tacrolimus. However, this reduction only occurred in a sub-group of machine-perfused organs and there was no significant difference in the primary end point, which was graft function at three months (33). Larger studies in non-DCD populations have failed to show any benefit, either in terms of DGF or other outcomes, from delayed CNI introduction (34,35).

A common practice in North America is to use IL-2 receptor monoclonal antibody blockade (with Basiliximab being the only agent currently available) in transplant recipients perceived as being at low immunological risk. In high-risk recipients, such as the recipients of DCD organs, the preferred regimen is to use lymphocyte depleting induction with polyclonal anti-

T cell agents such as thymoglobulin, or the monoclonal Alemtuzumab. There is an extensive literature comparing different induction regimens used in this way but the number of grafts at high risk due to DCD organ origin is small in comparison with other markers of risk such as African-American race, high levels of sensitisation, long cold ischaemia time, and previous graft loss. It is therefore difficult to extrapolate the reported superiority of anti-thymocyte globulin over Basiliximab (36) or the equivalence of Alemtuzumab and thymoglobulin (37) into the arena of DCD transplantation.

### **Choice of CNI**

The majority of the recipients of DCD kidneys reported in the literature have received Ciclosporin. There are few data comparing the use of Ciclosporin and Tacrolimus in this context and the optimal immunosuppressive strategy remains to be established.

### **Other aspects of initial care**

Systemic heparinisation is sometimes used, particularly if there is no immediate graft function or the donor is Maastricht category 1, 2, 4 or 5, although there is little evidence to support this.

In addition, if the donor is from one of the above categories, prophylactic antibiotic cover, including anaerobic prophylaxis, is often administered for three days after transplantation, although evidence for this practice is lacking.

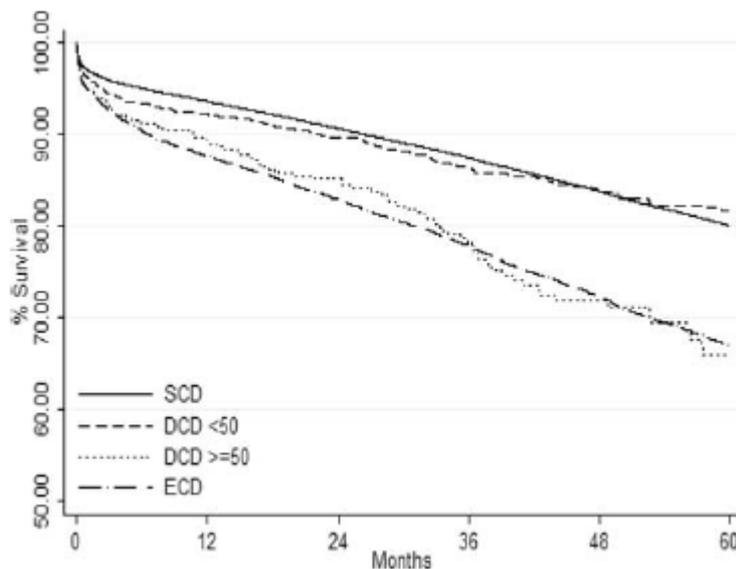
It is not clear whether recipients of kidneys from DCD donors experience excessive rejection, but rejection is certainly more difficult to diagnose in the presence of DGF. In the presence of DGF, weekly graft biopsy is therefore recommended to exclude clinically silent rejection or therapy-related toxicity (38). The histological appearances of the graft, particularly of the blood vessels, are often atypical, with vascular changes that can mimic 'vascular rejection' being common.

A Health Technology Appraisal on Immunosuppressive Therapy Post Renal Transplantation published in 2004 by The National Institute of Clinical Excellence (NICE) did not consider recipients of DCD kidneys, and the recommendations should therefore not be applied to this group (39).

## 8.7 Outcome

It is difficult to summarise the outcome after DCD kidney transplantation as many reports are from single centres, and the donor source in these is variable. In certain countries (e.g. Spain and France), DCD transplantation only occurs from uncontrolled donors. Specific centres in Spain and France utilise extra-corporeal membrane oxygenation, whilst others in France use a cold storage approach. In some countries (e.g. Japan), brain death is recognised but donors are managed as Maastricht 4 and cardiac death is awaited without withdrawal of treatment, so the donors become partly uncontrolled. Until recently in the UK, a significant proportion of DCD was uncontrolled, but this practice is now rare. The Dutch experience is also principally in controlled donors.

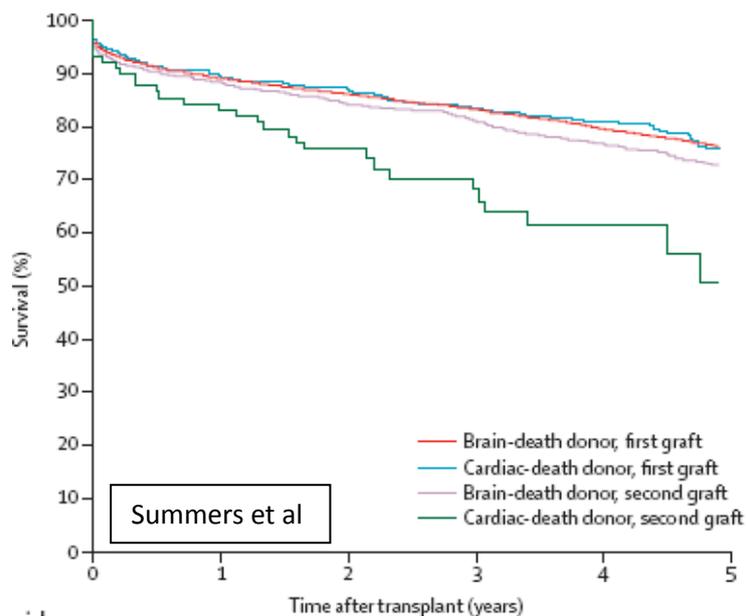
The above recognised, a variety of published data now support the view that overall graft outcome after transplantation is primarily determined by the quality of the donor rather than the mode of donation (figures 8.7.2 and 8.7.3). Thus, graft outcome is more closely related to whether a transplant is ECD vs SCD than whether the mode of retrieval is DCD vs DBD (2,40-44).



**Figure 8.7.2** Graft survival following kidney transplantation from different donor types (44).

As well as graft survival, graft function is also similar. GFR is initially poorer because of the high incidence of DGF in DCD, but is equivalent after 3 months. At 3 years post-transplantation, the median GFR following DCD is 45 ml/min/1.73m<sup>2</sup> and following DBD is 46 ml/min/1.73m<sup>2</sup> (3).

DCD kidneys are more prone to the detrimental effects of cold ischaemia than DBD kidneys, as confirmed by a recent UK cohort study (1). The proposed national allocation scheme should take this into account and ensure a policy that minimises CIT.



**Figure 8.7.3** Graft survival following kidney transplantation from different donor types (3).

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Statements of Recommendation

- *Livers transplanted from Maastricht 3 DCD donors are a useful resource and should be used where deemed safe. (B1)*
- *Short and medium term outcome appears inferior to livers from DBD donors with more PNF and ischaemic cholangiopathy, and a higher rate of re-transplantation. (B1)*
- *DCD and DBD subjects transplanted with MELD >30 or on organ-perfusion support have similar graft survival. However, there is no survival benefit when DCD livers are transplanted in patients with MELD ≤30 or in those not receiving organ-perfusion support. (B2)*
- *The incidence of biliary stricture is significantly lower when a low viscosity solution is used to cold flush the aorta. (C2)*
- *DCD liver use should be matched with the need of the recipients on the waiting list, with allocation to those who will have the greatest transplant benefit. (B2)*
- *The outcome of DCD liver transplantation is improved with short CIT, which is best kept to under 8hrs. (B1)*
- *A favourable outcome can be expected if an 'ideal' DCD liver is transplanted. An 'ideal' DCD liver donor is <50 years old, has a functional WIT time <20 min, a shorter CIT <10 hr, and <10% steatosis. (B1)*
- *Using more restrictive DCD Donor criteria including BMI <29 kg/m<sup>2</sup> and a functional WIT <20 min (SAP <50 mmHg), equivalent 1 and 3-year patient and graft survival rates can be achieved for both DCD and DBD liver transplants. (B1)*
- *Long FWIT is associated with an increased risk of ischaemic cholangiopathy*
- *Potential recipients of DCD liver grafts should be informed of the potential risk and be offered the choice to refuse such organs prior to transplant listing. (C2)*
- *DCD grafts are best avoided in recipients of re-transplantation (B1)*
- *DCD liver grafts should be ideally used in younger recipients with age <60 years. (B1)*

- ***Factors predictive of graft failure are: age ≥55 years, male sex, African–American race, HCV positivity, metabolic liver disorder, transplant MELD ≥ 35, hospitalisation at transplant, and the need for life support at transplant. Recipient predictors of mortality are age ≥55 years, hospitalisation at transplant, and re-transplantation. (B1)***
- ***A national audit should be performed to identify factors for non-utilisation of extended criteria donors to establish the incidence of cholangiopathy under ideal circumstances, identify more suitable risk factors, identify further subgroups of DCDs that could potentially be utilised, allow for medical interventions to be evaluated, and provide qualitative data regarding centre-specific performance. (C1)***

## **9.1 Introduction**

The burden of chronic liver disease continues to grow worldwide and the UK is no exception. Consequently, the indications for liver transplantation continue to expand with increasing numbers of patients listed (52% increase over the last 4 years in the UK) but a continuing shortage of donor livers (1). The liver transplant waiting list mortality in the UK is currently 8-22%, comprising patients who die waiting for a transplant or are removed from the list because they become too ill.

Besides the national campaigns to increase donor numbers, strategies for increasing the liver donor pool include a UK wide split liver program and expansion of the use of DCD organs. The long term outcome for liver transplantation from DCD donors has been considered inferior to organs from DBD donors (2,3). However, recent reports suggest comparable outcomes for DBD and DCD livers after transplantation (4,5). It is also becoming apparent that the outcome of DCD livers depends on a number of donor and recipient factors and technical factors in relation to the organ retrieval and implantation (6).

## **9.2 Donor Selection**

There are now numerous single centre series (7-11) and large registry analyses (12-15) which confirm that advanced donor age is associated with an increased risk of recipient complications: specifically, ischaemic cholangiopathy, graft loss and mortality, with the donor reference age being 40-45 years. Increasing donor weight/BMI is also associated with

increased risk of graft loss (15) and recipient mortality (6), especially in combination with prolonged ischaemic times. Donor BMI <30 kg/m<sup>2</sup> or an absolute donor weight <100 kg is preferable.

Peri-extubation hemodynamics in the donor also seem to have an influence. Three single institution studies (15-17) and one multi-centre study (18) provide evidence for peri-extubation hypotension and/or hypoxia as risk factors for poor outcome, but the exact values (BP and tissue oxygenation) at which irrecoverable liver/biliary injury occurs are still unclear. An increased risk of ischaemic cholangiopathy is associated with a prolonged period of FWIT. A mean arterial pressure of 50 mmHg for no more than 20 minutes is suggested, although a higher risk of graft failure (composite end-point) is seen with a WIT of as low as 15 minutes (18).

With respect to primary WIT, both an early study from King's College (17) and a more recent study (the largest single centre report on DCD liver transplantation) (10) report increasing duration of WIT being associated with recipient complications, specifically for ischaemic cholangiopathy and graft failure. Primary functional WIT of less than 20 minutes (9,13,16,17) and time to perfusion from donor asystole of less than 10 minutes are preferred (10). Increasing cold ischaemia time (CIT) is also a significant factor for risk of biliary complications including ischaemic cholangiopathy (6,9), graft failure (16), and recipient mortality (14); the exact CIT cut-off is between 6-8 hours (8,9,16).

### **Absolute contraindications**

In addition to the general absolute contraindications to organ donation defined by NHSBT (i.e. invasive or haematological malignancy, untreated systemic infection, prion disease and HIV disease), obvious absolute contraindications to the use of organs for DCD liver transplantation are:

- End-stage liver disease (CLD, cirrhosis and portal hypertension)
- Acute liver failure (drug, viral)
- Moderate and severe steatosis (>30% fat)
- Acute liver injury that is not improving

The DCD donor can be categorised in two ways. Firstly, by the criteria used in DBD selection, i.e. 'good' livers for transplantation:

- Age <50 years
- Normal liver function

- <5 days on ICU
- Fat content <30%
- Absence of high dose pressor support
- Absence of active infection

The second categorisation is restricted to DCDs. Within the DCD donor group there are those that can be regarded as 'ideal' and those that are 'marginal' (ECD).

The *ideal* DCD donor profile includes:

- Age <50 years
- Weight <100 kg
- ICU stay <5 days
- WIT <20 minutes
- Cold ischaemia time <8 hours, no steatosis (<15%)

The *marginal (ECD) DCD* donor profile includes:

- Age >50 years
- Weight >100 kg
- ICU stay >5 days
- WIT >20 minutes (up to 30 minutes)
- CIT >8 hours (up to 12 hours)
- Steatosis >15%

**Table 9.2.1**    **Categorisation of DCD liver donors**

	<b>Ideal DCD</b>	<b>Marginal (ECD) DCD</b>
Age (y)	<50	>50
Weight (kg)	<100	>100
ICU stay (days)	< 5	>5
Warm ischaemia time (min)	≤ 20	20-30
Cold ischaemia time (min)	≤ 8	>8-12
Steatosis (%)	≤15	>15
Recommendation	All potential liver donors fulfilling these criteria should be used	These grafts should be used selectively

### 9.3    **Organ Preservation**

Effective washout of the DCD liver microvasculature during retrieval is essential for optimal preservation. If the blood remnants in the liver are not completely washed out of the microcirculation, perfusion of the biliary tree and graft viability may be compromised. Low viscosity preservation solutions (e.g. HTK, Marshall's) are believed to do this more effectively than high viscosity solutions (e.g. UW).

As non pressurised *in situ* aortic perfusion has been shown to be inadequate in delivering physiological pressures in the hepatic artery, high pressure *in situ* 120 mmHg (Marshall Solution) or 200 mmHg (UW solution) and *ex situ* perfusion 120 mmHg (UW Solution) has been suggested to improve perfusion of the hepatic arterial tree, therefore more effectively flushing the microcirculation of the bile ducts. The incidence of biliary strictures may be lower when a low viscosity solution is used to cold flush the aorta in comparison with when a high-viscosity solution is used. (These data are from a series of DBD patients and results can only be extrapolated to the DCD situation) (19).

Type of flush fluid: A retrospective study analysing UNOS data has suggested that the use of HTK to flush and store livers after retrieval from DCD donors is associated with a poorer

outcome compared to the use of UW solution (20). Therefore, using a low viscosity flush for the arterial perfusion (such as Marshall's solution) and a more viscous flush for portal perfusion (such as UW) seems an attractive combination (17,19).

Operative technique: King's College Hospital, London recommend decompressing the inferior vena cava prior to starting the aortic flush to avoid detrimental congestion of the liver, which is always present following circulatory collapse (17).

In DBD transplantation, pressurised aortic flush (19) and pressurised back-table flush (21) decrease the risk of ischaemic and other biliary complications. However, this has not been investigated in studies of DCD transplantation.

#### **9.4 Organ Quality Assessment**

There are currently no clearly defined measures of graft quality. Other than the suggested clinical ECD criteria such as advanced age (>65 years), serum sodium >155 mmol/l, prolonged ICU stay (>4 days with ventilatory support), donor serum creatinine >106 µmol/l, BMI >30 kg/m<sup>2</sup>, positive serology, carcinoma outside the liver, high vasopressor support and split-grafts, macrovesicular steatosis (>40%) is probably the best measure of poor quality especially when combined with a prolonged FWIT and CIT >12 hours.

Steatosis, especially macrosteatosis, is an established risk factor for primary non function and graft dysfunction. Hepatic steatosis is more common in donors of advanced age, as well as in those with a history of obesity, dyslipidemia, metabolic disorders, or diabetes. Severely fatty livers are more susceptible to warm and cold ischaemia reperfusion injury. In contrast to macrovesicular steatosis, livers with predominantly microvesicular steatosis show less injury and allograft survival rates are similar to those in nonsteatotic grafts. Extrapolating from the DBD experience, hepatic allografts with moderate macrovesicular steatosis (30-60%) can be used selectively in critical situations; mild macrovesicular steatosis (<30%) is relatively safe, and severe steatosis (>60%) increases the risk of PNF. As macroscopic evaluation is unreliable in the appraisal of the severity of steatosis, microscopic evaluation before transplantation is recommended in cases where significant steatosis is suspected. The percentage of steatosis should be determined by liver biopsy before transplantation. Current practice is such that the majority of steatotic DCD grafts are declined.

## 9.5 Recipient Selection

As experience increases worldwide, more studies are attempting to address the factors that can predict adverse outcomes after DCD liver transplantation. Although there is now a clearer understanding of some of the donor factors, there is still a lack of high level evidence relating to both donor and recipient factors that may affect outcome. In 2006, Mateo et al (12) analysed the outcome of 367 DCD liver transplants performed in the US between Jan 1996 and Dec 2003. Several recipient risk factors were identified as being associated with DCD graft loss. These included recipients:

- Age >60 years
- Transplanted while on life support
- With a long ICU stay prior to transplantation
- Needing re-transplantation
- Dialysis dependent prior to transplantation
- With severe renal dysfunction (creatinine at transplant  $\geq 177 \mu\text{mol/l}$ ).

A more recent review of the Scientific Registry of Transplant Recipient (SRTR) database identified 1567 recipients of DCD liver transplantation between Sept 2001 and April 2009 (14). In this analysis, recipient factors predicting graft failure included some common factors such as:

- Age (<18 or >55 years)
- ICU admission prior to transplantation
- The presence of life support

Other identified adverse recipient factors included:

- Female sex
- African American decent
- Transplanted with metabolic disorders
- MELD score >35
- Positive Hepatitis C virus serology

Predictors of mortality included age >55 years, re-transplantation, and ICU stay at the time of transplantation. Analysis of the same registry over a shorter period of time identified recipient hepatocellular carcinoma (HCC) as a factor that significantly amplified mortality risk (14). However, most patients with HCC on the transplant list tend to have a lower MELD score and, with the exception of age, are consequently less likely to have the other

recognised adverse recipient risk factors. As a result, there is a tendency to use DCD grafts in fit HCC patients and this may lead to bias. It is generally accepted that the use of ECD DBD or DCD grafts in fit patients with HCC is a good use of this resource.

### **Organ allocation**

The current allocation system for DBD liver grafts in the UK is a centre-based system with grafts allocated according to need and transplant benefit. Following a consensus meeting in March 2012, it was agreed that a national allocation system should instead be implemented. The final decision about the best way to allocate DCD grafts is still awaited, but most centres favour regional allocation in order to keep CIT as short as possible and to ensure the best outcome.

In the USA, Mateo et al developed a classification of DCD liver grafts as low-risk or high risk, depending on whether the FWIT was  $\leq 30$  min and CIT was  $\leq 10$  hr (12). They also grouped recipients into low or high risk groups based on a recipient cumulative relative risk (RCRR 1-5.17, i.e. no risk to maximum risk) using age, medical condition at transplantation, re-graft status, dialysis received, and serum creatinine. When low risk recipients received low risk DCD liver grafts, their graft survival rates at 1 and 3 years were comparable to those of the DBD group. A further analysis of the same data has suggested similar results from similar matching, but with an emphasis on donor age  $< 45$  years (13).

Based on these analyses, this group has suggested an algorithm for selecting potential recipients for a DCD liver graft (13), but this needs external validation before implementation in routine clinical practice.

### **9.6 Immunosuppression**

Although there are no data to support an optimal immunosuppressive regimen for DCD liver transplantation, consideration should be given to renal sparing regimens with delayed CNI introduction. Induction immunosuppression and T cell depletion may also be considered, but risk and benefit must be balanced in any choice of regimen.

With regards to HCV, intense immunosuppression often promotes HCV recurrence and the need for treatment of acute cellular rejection (with pulse dosed corticosteroids) leads to increased HCV RNA values, decreased graft survival and increased overall mortality (22,23).

The concept that a particular CNI may impact the natural history of HCV in liver transplant patients is controversial (24). Although overall survival is similar regardless of the CNI use, preliminary data suggest that ciclosporin-based immunosuppressive regimens, when used in conjunction with interferon-alpha and ribavirin to treat HCV, may lead to a greater likelihood of virological response to therapy, possibly through greater T cell regulatory inhibition (25). Further confirmatory studies are required.

## 9.7 Outcome

In 2009, of the 646 deceased organ donors, 110 were DCD donors from whom livers were recovered, and 76 of these livers were transplanted. This increased to 97 in 2010. However, studies have shown that the graft survival of DCD livers is inferior to that of DBD donor livers (7,12,26-28), with one study estimating a relative risk of graft failure of 1.85 times higher in DCD recipients (27). The incidence of PNF using DCD livers has ranged from 0-5.5%, while biliary complication rates have been reported to be higher compared with DBD allografts (13-37% vs 1-20%) (5,7,15). The majority of studies on DCD outcomes have come from reviews of national databases such as the UNOS database (12,27,28), the Scientific Registry of Transplant Recipients (SRTR) database, and the UK transplant registry, or single-centre studies that have reported on relatively small numbers of patients (5,7,15,17,29,30). There are no widely accepted DCD donor parameters predictive of good outcomes that could guide surgeons on whether or not to use or discard a DCD liver. In addition, it is unclear and controversial as to which patients would benefit the most from the use of these allografts (12,27).

Recently, Jay et al (14) compared 1113 DCD and 42 254 DBD recipients from the SRTR database transplanted between 1996 and 2007. Patient survival was examined using Kaplan-Meier analysis and Cox regression. DCD recipients had worse patient survival than DBD recipients ( $p < 0.001$ ). One and three year survival was 82% and 71% for DCD compared to 86% and 77% for DBD recipients. Moreover, DCD recipients required re-transplantation more frequently (DCD 14.7% vs DBD 6.8%,  $p < 0.001$ ), and survival after re-transplantation was markedly worse than survival after primary transplantation irrespective of graft type. Amplification of mortality risk was observed when DCD was combined with a CIT  $> 12$  hours (HR 1.81), shared organs (HR 1.69), recipient hepatocellular carcinoma (HR 1.80), recipient age  $> 60$  years (HR 1.92), and recipient renal insufficiency (HR 1.82).

In addition, the Pittsburgh experience of DCD liver transplant outcome was recently reported (9). 141 patients who underwent DCD liver transplantation between 1993 and 2007 were

compared to a matched cohort of 282 patients who received DBD livers. Patient survival was similar, but 1, 5 and 10-year graft survival was significantly lower in DCD (69%, 56%, 44%) vs DBD (82%, 73%, 63%) recipients ( $p < 0.0001$ ). Primary non function and biliary complications were more common in DCD patients, accounting for 67% of early graft failure. Donor WIT  $> 20$  minutes, CIT  $> 8$  hours, and donor age  $> 60$  years were associated with poorer DCD outcomes. There was a lack of survival benefit in DCD livers used in patients with MELD  $\leq 30$  or those not on organ support, as graft survival was significantly lower compared to DBD patients. However, DCD and DBD subjects transplanted with MELD  $> 30$  or on organ support had similar graft survival, suggesting a potentially greater benefit of DCD livers in critically ill patients. The attrition in DCD grafts occurred early within the first year after transplant and was due to a high incidence of PNF/DGF and biliary complications, which also led to a higher re-transplantation rate in the DCD group. Of note, the survival curves of both cohorts became parallel after the first year, suggesting that interventions to decrease the occurrence of these complications will significantly improve the survival of these grafts. PNF/DGF were the leading causes of early graft failure in the DCD group, accounting for 50% of the cases, and by multivariate analyses were found to be associated with the transplantation of male donor livers to female recipients and with recipients  $> 60$  years or with a BMI  $> 30$  kg/m<sup>2</sup>. CIT  $\leq 8$  hours was associated with a much lower incidence of PNF, though this did not reach statistical significance because of low patient numbers.

By contrast, using restrictive criteria (Maastricht 3 DCD donors aged  $< 55$  years with a BMI  $< 29$  kg/m<sup>2</sup>, donor WIT  $< 30$  min and hypotensive episodes  $< 15$  min), a multi-centre Dutch study produced 1 and 3-year patient survival rates which were similar for DCD (85 and 80%) and DBD (86.3 and 80.8%) transplants ( $p = 0.763$ ), and equivalent graft survival rates (74% and 68% vs 80.4% and 74.5%;  $p = 0.212$ ) (4). Of concern, the 3-year cumulative percentage of surviving grafts developing non-anastomotic biliary strictures was 31% after DCD and 9.7% after DBD transplantation ( $p < 0.001$ ). The re-transplantation rate was similar overall ( $p = 0.081$ ), but that for biliary strictures was higher in the DCD group ( $p < 0.001$ ). Risk factors for 1-year graft loss after DBD liver transplantation were transplant centre, recipient WIT and donors with severe head trauma. After DCD liver transplantation, they were transplant centre, donor WIT and CIT. As previously reported, use of DCD grafts was a risk factor for non-anastomotic biliary strictures.

The preoperative identification of factors associated with poor outcomes in DCD liver transplantation remains an important challenge. The period between extubation and asystole may help predict graft function. Less liver damage may occur if the donor progresses quickly to cardiac death, as opposed to maintaining a circulation in the presence

of significant hypoxia or hypotension. Consistent with this, restrictions on recovery are now imposed by most UK centres based on donor time to death and the duration of hypoxia or hypotension. This FWIT starts when the systolic blood pressure has a sustained (i.e. at least 2 min) fall below 50 mmHg (or the haemoglobin oxygen saturation falls below 70%) and extends up to the onset of cold *in situ* perfusion. The duration of the FWIT is the important determinant of outcome. The recent document 'Donation After Circulatory Death' published by a steering group on behalf of the British Transplantation Society and Intensive Care Society (31) suggested that the stand-down time from the onset of functional warm ischaemia for DCD liver transplantation was 30 minutes (although 20 minutes is ideal), and that age was an important factor.

Similarly, the 2006 Report of the National Conference on Donation after Cardiac Death in the US recommended recovering livers for transplantation if the time from extubation to cold perfusion was less than 30 minutes (32). These recommendations are based on animal models which show that increasing this time from extubation to organ recovery decreases survival (33,34).

A retrospective examination of the New England Organ Bank DCD database concentrated on donor factors including vital signs after withdrawal of support (18). The outcome of DCD liver transplantation was based on a composite endpoint chosen to represent a failed graft which included any transplant-related death, primary non function, graft loss within 1 year, or diffuse intra-hepatic biliary abnormalities (requiring re-transplantation). Data on 37 transplanted livers demonstrated that the donors tended to be young (average age  $34.3 \pm 13.2$  years) and thin (average BMI  $25.1 \pm 5.8$  kg/m<sup>2</sup>). The average time from extubation to asystole was  $17.6 \pm 8.7$  min and the average time from extubation to flush was  $28.6 \pm 8.8$  min. Recipient MELD scores averaged  $22.8 \pm 7.5$ . Mean follow-up was  $416 \pm 328$  days. One-year patient and graft survival rates were 81.1% and 78.9% respectively. A total of 14 (37.8%) recipients reached the composite endpoint of death, graft loss within 1 year, or diffuse intra-hepatic biliary abnormalities. Recipients who reached the primary endpoint tended to have received livers from donors who were older, exhibited longer profound hypotension in the post-extubation period, and had slightly longer CIT. To determine clinically relevant parameters for predicting the primary endpoint, receiver operating characteristic analysis on donor and recipient parameters were performed, including donor age, CIT, time from extubation to asystole, time from extubation to flush, time with oxygen saturation less than 50% to flush, and time from systolic BP <50 mmHg to flush. The best predictive test was time from systolic BP <50 mmHg to flush (area under curve 0.652), and the next best was donor age (area under curve 0.589).

A meta-analysis examined the risks of biliary complications, particularly ischaemic cholangiopathy, after DCD compared with DBD liver transplantation (35). Eleven retrospective cohort studies were reviewed, involving 489 DCD and 4455 DBD recipients. DCD recipients had a 2.4-fold increased risk of biliary complications and a 10.8-fold increased risk of ischaemic cholangiopathy. Ischaemic cholangiopathy was present in 16% of DCD compared with 3% of DBD recipients. DCD recipients also experienced higher odds of 1-year patient mortality (OR 1.6) and graft failure (OR 2.1). In addition, a single centre experience of DCD compared to DBD liver transplantation showed following multivariate analysis that CIT >8 hours (HR 2.46; p=0.05) and donor age >40 years (HR 2.90; p<0.01) significantly increased the risk of ischaemic cholangiopathy (8).

A favourable outcome can be expected if an 'ideal' DCD liver is transplanted. An 'ideal' DCD donor is <50 years old (8), has a shorter WIT than 30 min (14,15,18), has a CIT <10 hours (32) and has <15% steatosis. Although Mateo et al (12) speculated that recipient MELD scores in candidates who received DCD livers would be a predictive prognostic factor, most other data have shown no relationship between the recipient MELD and prognosis and a more robust algorithm needs to be developed to best match DCD donor livers with recipients awaiting transplantation. However, the expected lifetime of a liver transplant candidate offered a DCD liver should be compared with the expected lifetime of that candidate if they were to turn down the DCD offer and continue to wait for a DBD liver. That is to say, even if graft and/or patient survival is lower with a DCD liver, it may be better than dying on the waiting list.

Considering the current shortage of donor organs, every liver transplant candidate should be informed at the time of evaluation that the choice in the UK is frequently not between a marginal (including DCD) liver and a standard liver, but between a marginal (DCD) liver or no liver at all. Until an algorithm for the use of the DCD donor is determined, recommendations by transplant teams and decisions by liver transplant candidates should be predicated on full disclosure of the known risks and potential benefits of DCD liver transplantation (5).

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Statements of Recommendation

- *Although DCD organs can be used for isolated pancreas transplants in pancreas transplant alone or pancreas after kidney, available evidence and current practice are increasingly in favour of their use for simultaneous pancreas and kidney (SPK) transplantation. (C2)*
- *Pancreas transplants from DCD donors are at increased risk of reperfusion pancreatitis and thrombosis and this may be exacerbated by prolonged cold ischaemia time and higher donor body mass index. The contribution of donor age to the incidence of reperfusion pancreatitis/thrombosis in DCD organs is poorly studied but may constitute a further risk factor. Ideal donors should be <60 years old and have BMI <30 kg/m<sup>2</sup>. (C2)*
- *The pancreas team should stand down after a functional warm ischaemia time (systolic BP <50 mmHg and oxygen saturation of 70%) of 60 minutes. (C2)*
- *A primary focus of any DCD pancreas transplant should be to achieve the minimum cold ischaemic time. (B2)*
- *There is little evidence regarding recipient risk factors but it is logical to assume that higher recipient BMI, age, cardiovascular morbidity, and technical surgical factors may contribute to poorer outcome. (C2)*
- *Reported outcomes for DCD donor pancreas transplantation are broadly similar to those from DBD donors, although considerably greater donor selection is likely to have taken place. (C2)*
- *Graft loss from thrombosis is twice as common in DCD as DBD pancreas transplants. Particular attention should be paid to measures to prevent thrombosis in recipients of DCD organs. A DCD organ should not be transplanted into a recipient with a history of thrombo-embolic disease unless this is monitored and treated. (C2)*
- *Selected transplant centres will have built up a volume of expertise with DCD extended criteria and these guidelines should not restrict innovative but safe practice of pancreas transplantation. (Not graded)*

## 10.1 Donor Selection

The selection of DCD donors for pancreas transplantation is more restrictive than that for DBD donors. A recent review of the UK experience of 134 DCD pancreas transplants compared to 875 contemporaneous DBD grafts reported that DCD donors tended to be younger (median age 28 vs 37 years,  $p < 0.001$ ), had a lower BMI (23 vs 24  $\text{kg/m}^2$ ,  $p = 0.04$ ), and were less commonly due to cerebrovascular cause of death (33 vs 60%,  $p < 0.0001$ ) (1). The median cold ischaemic time was similar in both DCD and DBD transplants (750 vs. 752 min), although achieving such cold ischaemia may be more challenging in DCD transplantation due to the shorter lead time available to complete recipient selection, travel to the recipient centre, and cross-match before organ retrieval.

Numbers transplanted do not allow a rigorous analysis of factors affecting donor selection, but the following broad comments reflect current experience and practice in the UK.

### Age

Hitherto unpublished analysis of the UK transplant registry data suggest that donor age is a significant factor contributing to transplant outcome for DBD pancreata in the UK. Numbers do not allow extensive analysis of data for DCD transplants, but the effect is likely to be the same. Current criteria are to consider all potential donors up to the age of 60 years.

### Body mass index

A low donor BMI ( $< 28 \text{ kg/m}^2$ ) is preferred, but potential donors with higher BMI should still be referred and organs should be retrieved when the donor BMI is  $\leq 30 \text{ kg/m}^2$ . Pancreata from donors with a BMI  $> 30 \text{ kg/m}^2$  should be referred for consideration of islet transplantation.

### Waiting time

A functional warm ischaemic time, from the point at which the systolic pressure is  $\leq 50 \text{ mmHg}$  for 30 minutes, is a reasonable indication to abandon pancreas retrieval. Otherwise, a donor in whom the blood pressure is stable and physiological may still yield a transplantable pancreas some time after treatment withdrawal. In general, the retrieval team should be prepared to retrieve the pancreas for up to 3 hours following the withdrawal of support. The decision to stand down sooner should be made on the basis of the blood pressure profile and other donor criteria. Donors with a withdrawal period over 60 minutes have been used successfully (1,2).

### Inotropes

Although high doses of inotropes are widely agreed to be detrimental, there is no good evidence on which to base national criteria. Inotrope levels should not, therefore, be used to exclude the referral of DCDs for pancreas retrieval.

### Amylase and glucose levels

There is no good evidence that the level of either amylase or glucose has prognostic significance and these should not be used to exclude either the referral or the transplantation of DCD pancreata.

### Steatosis and fibrosis

These factors are largely subjective and difficult to quantify, and the precise significance of differing degrees of steatosis or fibrosis are uncertain. For these reasons, retrieval should proceed unless the changes are gross. It is important that the transplanting surgeon should be able to speak to the retrieving surgeon to discuss the quality of the donor organs.

### Caution

Suggested donor criteria for pancreas transplantation are shown in table 10.2.1. However, this is an evolving field. It is important to note that transplanting centres in the UK will have built up a volume of expertise with extended DCD criteria, and these criteria should not restrict innovative but safe practice of pancreas transplantation.

**Table 10.2.1 Donor criteria for pancreas transplantation**

	<b>Ideal DCD</b>	<b>Marginal (ECD) DCD</b>
Age (year)	<45	45-60
BMI (kg/m <sup>2</sup> )	<28	28-30
WIT (min)	≤ 30	>30
CIT (hr)	≤ 9	>9
Steatosis	None	Mild-moderate
Recommendation	All potential pancreas donors fulfilling these criteria should be used	These grafts should be used selectively

## 10.2 Organ Preservation

### Warm ischaemia time

The endocrine function of the pancreas appears to tolerate warm ischaemia relatively well, but the complication of reperfusion pancreatitis has serious implications in terms of both morbidity and graft survival and this is probably (in part) related to the duration of warm ischaemia. A WIT less than 30 minutes is preferred (ideal), but organs with WIT of more than 30 minutes should be considered.

### In situ perfusion and preservation

*In situ* perfusion for pancreas donors should be via the aorta only (with additional perfusion of the liver via the portal vein being instituted by opening the portal vein without impeding venous drainage from the pancreas). UW solution is the preferred preservation solution both for the initial flush and preservation.

### Thrombolysis

The evidence for the benefit of an initial streptokinase flush comes from DCD kidney retrieval. There is no equivalent evidence in DCD pancreas transplantation. A national trial of the use of streptokinase in DCD donation is under consideration.

### Cold ischaemia time

As with other organs, there is good evidence that cold ischaemia is detrimental to the outcome of pancreas transplantation in proportion to its duration. UK data suggest that a CIT of >12 hours in DBD pancreas transplantation is associated with a significantly increased risk of graft loss; it is likely that a shorter CIT (such as 9 hours) will be more appropriate when transplanting a DCD pancreas.

## 10.3 Organ Quality Assessment

There is no 'standard' of quality assessment. Assessment is largely based on a visual inspection and clinical experience. In general, a quality assessment can be made by looking at the quality of perfusion of the gland and duodenum, as well as the amount of fat infiltration, and by feeling the texture of the gland for fibrosis. These observations should be considered alongside the donor characteristics and the haemodynamics and duration of the withdrawal period.

## **10.4 Recipient Selection**

There is relatively little reported experience of DCD pancreas transplantation to guide recipient selection (see also section 10.6). While it is possible that the recipients of DCD pancreas transplants are selected more rigorously than those receiving DBD transplants, analysis of national databases does not show significant differences in recipient characteristics between the two groups. Therefore, the indications for DCD pancreas transplantation are no different to those for pancreas transplantation in general, and are summarised in the National Protocol for Assessment of Kidney and Pancreas Transplant Patients at [http://www.organdonation.nhs.uk/about\\_transplants/organ\\_allocation/pancreas/](http://www.organdonation.nhs.uk/about_transplants/organ_allocation/pancreas/). However the UK data do suggest a poorer outcome when the DCD pancreas is transplanted alone rather than with a kidney (1).

### **Organ allocation**

As with other organs, there is good evidence that cold ischaemia is detrimental to the outcome of pancreas transplantation in proportion to its duration. The implication is that, as at present, DCD organs should be transplanted locally rather than transported for use in sensitised patients. Current allocation arrangements in the UK are summarised on the NHSBT website at [http://www.organdonation.nhs.uk/about\\_transplants/organ\\_allocation/pancreas/](http://www.organdonation.nhs.uk/about_transplants/organ_allocation/pancreas/). The current scheme aims to minimise the distance the pancreas travels to a recipient centre.

UK data suggest that the outcome of SPK transplantation using DCD organs is better than that of isolated pancreas transplantation and this is therefore the preferred way of using these organs (1).

Recent proposals for changing the allocation of DCD kidneys will enable a DCD kidney to be preferentially offered with a DCD pancreas.

## **10.5 Immunosuppression**

There are no data that indicate an optimal immunosuppressive regimen for a DCD pancreas. The immunosuppressive requirements of pancreas transplantation appear to be greater than those of kidney transplantation, but otherwise consideration of a kidney-friendly protocol seems appropriate, with an induction agent such as Daclizumab or Alemtuzumab followed by mycophenolate and an initial low dose tacrolimus regimen

## 10.6 Outcome

Pancreatic transplantation from DCD donors comprises only a small percentage of the total number of pancreatic transplants, although there have been an increasing number performed in recent years, especially in the UK (3). Worldwide, there have been fewer than 300 DCD pancreas transplants in the last 25 years.

Most of the published outcome data come from the USA and the UK. These suggest that outcomes from DCD transplantation are broadly comparable to those of DBD pancreata transplanted together with a kidney (SPK). The results of pancreas alone transplantation are worse than those of combined SPK transplantation, with DCD pancreas alone transplantation being non-significantly worse than that of DBD transplantation (1).

The US experience of 57 transplants (47 SPK, 10 solitary pancreas) from controlled (Maastricht 3) DCD donors between 1993 and 2003 was collated from the UNOS registry in 2006 (4). Over this period, there were 4038 DBD pancreas transplants. Patient, kidney and pancreas graft survival from DBD and DCD donors were equivalent at 1, 3 and 5 years after transplantation (Table 10.6.1). Early graft loss due to vascular thrombosis was higher with DCD donors (12.8 vs 6.1%), although 37 of the 57 DCD transplants were performed at one centre, where no vascular thromboses were experienced.

A separate publication from Wisconsin summarised their experience of 37 transplants also performed between 1993 and 2003 (5); these patients probably formed the bulk of the US experience summarised in the 2006 paper.

In one US centre, four DCD donors were treated using an extracorporeal perfusion circuit with heparinisation and cannulation of the femoral vessels prior to treatment withdrawal. These donors were perfused with oxygenated blood and cooled to 22°C. The four pancreata were transplanted as part of a combined pancreas and kidney transplant, with immediate function of both pancreas and kidney in each case and all grafts surviving over 2 years at the time of reporting (6).

**Table 10.6.1 Outcome of DCD pancreas transplantation in the USA, 1993-2003**

Transplant	Survival	n	% Survival	
			One year	Three year
<b>Donors after brain death</b>				
SPK	Pancreas graft	2431	86	77
	Patient	2431	96	89
	Kidney graft	2431	92	82
Isolated pancreas	Pancreas graft	1607	81	62
	Patient		100	72
<b>Donors after cardiac death</b>				
SPK	Pancreas graft	47	85	80
	Patient	47	98	93
	Kidney graft	47	96	83
Isolated pancreas	Pancreas graft	10	90	45
	Patient	10	95	88

The above studies demonstrate roughly comparable outcomes of pancreas transplantation with DBD and DCD donor organs. However, they share the inevitable methodological shortcomings of retrospective reviews and cannot provide adequate information about donor or recipient selection criteria, warm or cold ischaemia limits, and other donor or recipient factors that may have an impact on outcome. It is also recognised that the US deceased donor pool is younger and has a lower rate of cerebrovascular death compared with deceased donors in the UK.

In the UK, a review for NHSBT's Pancreas Advisory Group in 2010 showed that the outcomes of DCD pancreas transplantation were broadly similar to the US data and to

transplants from DBD donors, although the numbers were small (Table 10.6.2) (7). Of note, 1 year pancreas survival was substantially less for isolated pancreas transplantation in comparison to SPK transplantation (76 vs 86%), although small numbers meant that this difference was not statistically significant. This was almost exclusively due to a higher rate of graft thrombosis in one centre following DCD donor isolated pancreas transplantation (12 vs 2% from the largest centre). Given this, particular attention should be paid to measures to prevent thrombosis in recipients of DCD organs. A DCD organ should not be transplanted into a recipient with a history of thrombo-embolic disease unless the coagulopathy is corrected and closely monitored.

**Table 10.6.2 Pancreas transplant outcomes at one year in the UK (6)**

<b>Transplant</b>	<b>Organ</b>	<b>n</b>	<b>% survival</b>	<b>95% confidence intervals</b>
<b>Donors after brain death 1/4/07 to 31/3/09</b>				
SPK	Pancreas graft	294	88	83-91
	Patient	296	96	93-98
	Kidney graft	302	93	90-95
Isolated pancreas	Pancreas graft	55	76	62-85
	Patient	56	94	83-98
<b>Donors after circulatory death 1/4/05 to 31/3/09</b>				
SPK	Pancreas graft	36	86	69-94
	Patient	36	94	79-99
	Kidney graft	38	95	80-99
Isolated pancreas	Pancreas graft	33	76	57-87
	Patient	33	97	79-99

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## 11 PANCREATIC ISLETS

### Statements of Recommendation

- ***Selection criteria for recipients of islets from DCD donors should be the same as for DBD donors. (B2)***
- ***Organs from DCD donors for islet isolation and transplantation should be allocated through the National Pancreas Allocation Scheme. (B2)***
- ***The long term outcome of islet transplantation from DCD donors has been satisfactory in the UK but the cohort is small. Further audit and research are required. (C2)***
- ***Satisfactory functional islet preparations can be routinely obtained from DCD donors. (C2)***

### 11.1 Donor Selection

There is very limited clinical experience of islet transplantation from DCD donation and limited information as to what constitutes the ideal donor for islet transplants procured from a DCD pancreas.

Given the above, ideal donor criteria have to be extrapolated from the ideal DBD donor as recommended by the National Clinical Guideline islet transplant program. Young donors yield fewer islets after islet isolation because of the effect of collagenase on the pancreatic extracellular matrix (1,2). The smaller the donor weight, the smaller the donor pancreas and thus fewer islets are isolated for transplantation (3-9). Obese non-diabetic donors are excellent for islet isolation because of a higher beta cell mass. Human islets are very intolerant to prolonged periods of both warm and cold ischaemia and this is crucial to successful islet transplantation (10).

The following summarises the current criteria for donor selection in the UK:

#### ***Optimal (ideal)***

Age 18-45 yr

Weight 50-100 kg

BMI 21-35 kg/m<sup>2</sup>

Cold ischaemia <8 hr

Warm ischaemia <5 min

***Marginal (ECD)***

Age 16-18 or 45-65 yr

Weight 40-50 or >100 kg

BMI < 21 or >35 kg/m<sup>2</sup>

Cold ischaemia 8-16 hr

FWIT 5-30 min

Previous extensive abdominal surgery

***Absolute contra-indications***

Age >65 yr

BMI >40 kg/m<sup>2</sup>

Cold ischaemia > 16 hr

FWIT >30 min (systolic BP <50 mmHg, SpO<sub>2</sub> <70%)

Diabetes mellitus

Evidence of pancreatic disease (e.g. chronic pancreatitis)

Pancreatic duct transection/traumatic capsular damage

Positive for HCV, HIV, HBV

Variant CJD

Untreated systemic infection

Evidence of intravenous drug use

Malignancy, myeloma, lymphoma, leukaemia

Invasive cancer in the last 3 years, excluding non-melanoma skin cancer and primary brain tumour

**11.2 Organ Preservation**

Human islets are very intolerant to prolonged periods of both warm and cold ischaemia. It is important that pancreas retrieval for islet transplantation is performed to the same high standard as for whole pancreas transplantation, cooling the donor organs as rapidly as possible during the retrieval process.

### **11.3 Organ Quality Assessment**

The same quality criteria apply as described in section 10.3.

### **11.4 Recipient Selection**

Selection of recipients of islets from DCD donors should be as for those from DBD donors:

- Insulin sensitive patients with Type I diabetes and normal renal function who experience recurrent severe hypoglycaemia despite optimised specialist management.
- Insulin sensitive patients with a renal allograft who are unable to maintain HbA1c <7.0% (53 mmol/mmol) despite optimised specialist management.

There is no evidence that particular subsets of these patients benefit from DCD organs, and those waiting for prolonged periods for second infusions are automatically given priority through the National Pancreas Allocation Scheme.

#### **Allocation**

Organs for islet isolation and transplantation should be allocated through the National Pancreas Allocation Scheme. Current allocation arrangements in the UK may be found on the NHSBT website [http://www.organdonation.nhs.uk/about\\_transplants/organ\\_allocation/pancreas/](http://www.organdonation.nhs.uk/about_transplants/organ_allocation/pancreas/)

### **11.5 Immunosuppression**

There are no data to indicate an optimal immunosuppressive regimen for DCD islet transplantation. The current practice for the small number performed in the UK includes an induction agent such as Daclizumab or Alemtuzumab, followed by mycophenolate and an initial low dose tacrolimus regimen

### **11.6 Outcome**

The first islet transplant from a DCD donor was described in 2003 (11) and since then the majority of the clinical outcome data originate from Japan (5,8,12).

DCD islet preparations can be obtained that are comparable to preparations from DBD donors and the early clinical outcomes (restoration of hypoglycaemic unawareness) are similar. Although insulin independence from a single islet infusion from a DCD donor has been described, the Japanese data only describe 3/64 patients achieving insulin independence, which is significantly lower than would be expected from DBD islet preparations.

There are no good data on long term outcomes of islet transplants from DCD donors and only a small number have been carried out in the UK, but data from the King's group have demonstrated that satisfactory functional islet preparations can be routinely obtained from DCD donors (13).

Factors that appear to predict good clinical outcomes are FWIT <25 minutes, short CIT, and donor age <55 years.

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## 12 LUNG

### Statements of Recommendation

- *The donor selection criteria for lung DCD should be the same as for DBD. (B2)*
- *All patients on the lung transplant waiting list have the potential to receive DCD lungs. (C1)*
- *DCD lungs should not be regarded as extended or marginal. Transplant quality and outcome is at least similar to DBD organs. (B1)*
- *Perform antegrade and retrograde flush perfusion at the time of lung retrieval. (B2)*
- *Pre-transplant ex vivo lung perfusion (EVLP) is advised in case of uncertain graft performance to safely extend donor and procedural criteria (long warm ischaemia, bad flush, clots). (B1)*
- *Acceptance criteria on EVLP may include measures of pulmonary compliance, vascular resistance, and gas exchange. (C2)*

### 12.1 Donor Selection

All DCD organ donors age <65 years who do not have any of the contraindications listed below are suitable to donate lungs:

- Chest trauma with extensive bilateral lung contusions
- Convincing radiological evidence of bilateral pneumonic consolidation
- Pre-existing structural lung changes (e.g. emphysema or multiple large bullae)
- Previous complex intra-pleural thoracic surgery or dense adhesions prohibiting safe procurement
- Systemic arterial  $PO_2$  <30 kPa on 100%  $FiO_2$  and 5 cmH<sub>2</sub>O PEEP, or equivalent  $FiO_2:PaO_2$  within 12 hours
- Bronchoscopy (if available) showing inflammation/soiling of the airway, *and* recurrent secretions in the distal airway after adequate toilet
- Sustained peak airway pressure >30 cmH<sub>2</sub>O

All UK centres are currently participating in DEVELOP-UK, a trial of the efficacy of *ex-vivo* lung perfusion in marginal lungs, or lungs (such as after DCD donation) where an objective assessment cannot be made. The entry criteria of lungs into the study have therefore become adopted as the national standard.

The decision with regard to *ex-vivo* lung perfusion (EVLP) is taken by the implanting centre, not by the offering SN-OD or the retrieving centre. If EVLP is not being considered, the following are also required:

- The proposed transplant satisfies the criteria as for standard DBD donor lungs (if information available)
- DCD donor from Maastricht Category 2, 3, or 4
- Systemic arterial PO<sub>2</sub> >40 kPa on 100% FiO<sub>2</sub> and 8 cmH<sub>2</sub>O PEEP, or equivalent FiO<sub>2</sub>:PaO<sub>2</sub> within previous 12 hours
- Functional warm ischaemic time (FWIT) <30 minutes (FWIT starts when donor systolic BP <50 mmHg and/or O<sub>2</sub> saturation <70%)
- Withdrawal of life support (WLS) time <120 minutes

The following are the criteria by which a DCD lung can be entered into the EVLP arm of the study:

*Any one or more of the following:*

- FWIT >30 minutes and <60 minutes for DCD donors
- Chest X-ray findings prohibitive to standard transplantation
- Systemic arterial PO<sub>2</sub> <35-40 kPa and/or selective PV gas <30 kPa on 100% FiO<sub>2</sub> and 8 cmH<sub>2</sub>O PEEP
- History of aspiration with bronchoscopic inflammation/soiling of the airway, or recurrent but not prohibitive secretions in the distal airway after adequate bronchial toilet
- Difficult to recruit atelectasis
- Sustained peak airway pressure >30 cmH<sub>2</sub>O
- Unsatisfactory deflation test on disconnecting endotracheal tube
- Unsatisfactory palpation of the lungs identifying undetermined masses, nodules or gross oedema
- Deterioration or cardiac arrest in the donor prior to retrieval such that uncertainty over assessment remains
- Unsatisfactory inspection of the lung after administration of the preservation flush and

procurement

- Logistical reasons that will extend donor lung ischaemic time >10-12 hr

### Information on Referral

'Organ Donation after Circulatory Death: a Consensus Statement from the British Transplantation Society and Intensive Care Society' (1) specified that "Donor assessment and recipient identification rely in part on a series of blood tests. It is both acceptable and lawful for samples of blood to be taken from the donor to allow these various tests to be carried out (including FBC, U&E, LFT, blood gases, virology screening, HLA-typing, and blood group) and this should be done as soon as possible to minimise delays. It is vital that all blood samples are correctly and fully labelled, particularly if they are to be sent for analysis in laboratories other than those of the donor hospital".

For lung donation, the following additional donor information should be available at the time of offer:

- Age
  - Sex
  - Height
  - Blood group
  - HLA Tissue Type\*
  - Serological result for HIV, HBV, HCV\*
- \*or the time that this information will be available

The following information should be provided to determine the likelihood of death occurring:

- Primary diagnosis and past medical history
- The use and dose of inotropes
- Presence of a gag reflex
- Presence of a cough reflex
- Respiratory rate when disconnected from the ventilator
- The fraction of inspired oxygen (FiO<sub>2</sub>)
- Arterial oxygen saturation and pH
- Ventilation mode
- Planned time of withdrawal of treatment
- Planned mode of withdrawal of treatment - i.e. extubation, reduction of inotropes

The following should be available, but with varying detail:

- Arterial blood gases, ideally on 100% and PEEP 5 cmH<sub>2</sub>O. Not all ICUs will report this, but the ABG and FiO<sub>2</sub> of the last blood gas, within less than 12 hours of retrieval, should be available.
- Chest X-ray within 24 hours of retrieval. The chest X-ray report should be available (on the basis of which some of the contraindications may be identified, i.e. extensive bilateral lower lobe consolidation).
- Bronchoscopy. The consensus document states “bronchoscopy to assess the potential for lung donation may be appropriate, if it does not cause the patient distress”. This needs specific discussion with the patient’s family. Bronchoscopy should be requested as a routine, although there is no obligation for the ICU to carry it out. There is no need for gram staining of tracheal or central airway secretions.

## 12.2 Organ Preservation

The lungs are antegradely flushed with supplemented (3.6% THAM 3.3 ml, 0.6 ml CaCl ± 2.5 ml prostacyclin /litre) Perfadex<sup>®</sup>, the first litre at room temperature, the rest at 4°C. A minimum volume of 60 ml/kg is given. The lungs are gently ventilated to maximise distribution of the perfusate.

After the antegrade dose, 200 ml will be given down each pulmonary vein as a final retrograde flush. This can be given *in situ* or on the back table.

For lungs destined for EVLP, an adequate portion of main pulmonary artery (PA), left atrial cuff and particularly at least 4 cm of trachea will be taken by the retrieval surgeon. A piece of aorta will be required to extend a deficient main PA (divided in close proximity to the bifurcation) to allow for successful cannulation and bilateral perfusion

## 12.3 Organ Quality Assessment

Testing the graft function of warm perfused organs prior to transplantation is considered the ‘gold standard’. However, warm perfusion of most donated organs is difficult to perform and usually impractical. Warm viability testing of donor lungs using *ex situ* lung perfusion is the exception. The test is performed by ventilating the lungs and perfusing them with Steen solution +/- added red blood cells. The ability of the ventilated lung to oxygenate the

perfusate is assessed together with lung compliance, airway resistance and tidal volume via the ventilator.

## **12.4 Recipient Selection**

There are now internationally used acceptance criteria for listing lung transplant patients (2).

All recipients on the lung transplant waiting list have the potential to receive DCD lungs. Most centres in the UK have included 'DCD donor' in their list of categories for which specific consent is obtained, but do not regard it as implying any additional risk.

### **Allocation**

Time is of the essence, and organs may be lost because of delays in allocation. The consensus document (1) states: "At present most organs are offered to transplant centres sequentially rather than simultaneously. This can result in considerable delays that place an intolerable and unnecessary burden on referring units and donor families. Simultaneous offering to all relevant centres would reduce these delays significantly, and must be addressed by NHSBT as a matter of urgency".

The simplest routine is to use the current zones (on the basis that all teams can retrieve and assess DCD lungs). The zonal centre has primacy of use, but a **provisional** offer is made by NHSBT Duty Office to all the other 4 centres **at 5 minute intervals**, using the regular offering sequence.

If the zonal centre turns down the organ, the current agreement is that, as long as there is no contraindication, the decision to proceed falls on the accepting centre

## **12.5 Immunosuppression**

There is currently no evidence to suggest that there should be any difference in the immunosuppression protocol for DCD vs DBD lung transplantation.

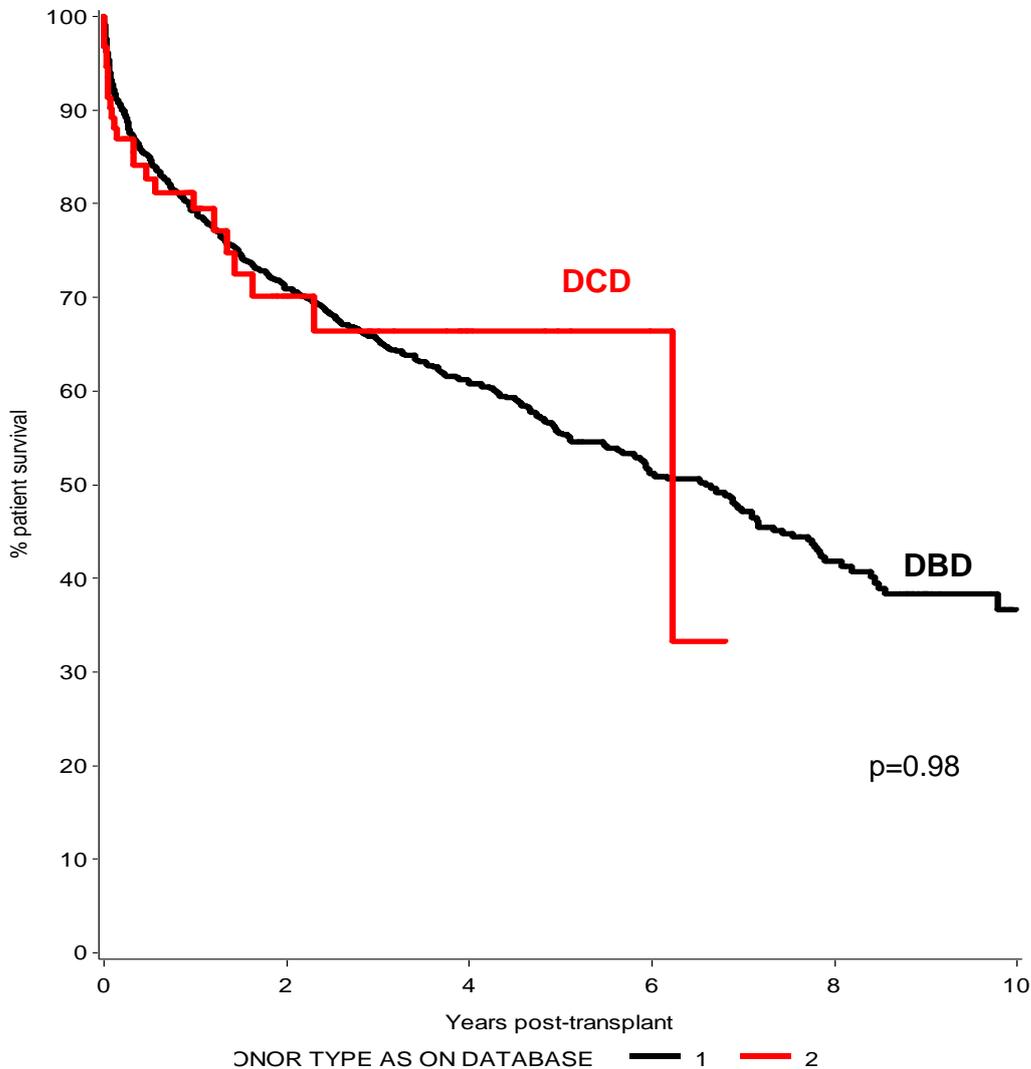
## 12.6 Outcome

Since the first published results in the modern era (3), there have been institutional reports of lung transplantation after retrieval from Category 3 donors from a number of centres around the world. These include series from Melbourne (4), Toronto (5), St Louis (6), and Leuven (7). Early US data was summarised by Mason (8). In general, outcomes were at least as good as contemporaneous transplants from DBD donors, although there may be an element of publication bias. Comparisons made include 30 day and one year mortality, and in some of the papers, the incidence of primary graft dysfunction, acute rejection and early obliterative bronchiolitis. In no series was there a higher morbidity or mortality (9).

The use of EVLP after DCD lung donation has been recently reported in both abstracts and in one landmark paper (10), again with excellent results. A further update has confirmed excellent outcomes with this treatment (11).

UK data have recently been collected on the first 100 lung transplants from DCD donors, dating from 2003. These represented 7% of the lung transplants done in this era, rising to 14% of transplants performed in the past three years. The outcomes from DBD and DCD transplantation were identical over this era, with a one-year survival of 79% (Figure 12.6.1).

**Figure 12.6.1 Patient survival following adult lung only transplants, January 2002 to October 2012, by donor type**



### **Category 2 DCD Lung Donation**

One of the earliest DCD reports was the case report of Steen describing EVLP for the evaluation of lungs from a Category 2 donor, and the subsequent successful transplant (12). Subsequently, the early Spanish experience with Category 2 donors was reported. Outcomes were perceptibly less good than for DBD lungs, and especially for DCD lungs from Category 3 donors, although the evaluation technique may have been suboptimal. More recently, the Madrid group have been using EVLP for Category 2 donors and in a series of six, report 100% patient survival with no primary graft dysfunction.

In conclusion, and in contrast with some other organs, the results of transplantation with lungs from Category 3 donors are excellent. The published data are quite scanty, however, and there are no randomised trials. EVLP will further expand this activity, and is probably important or even essential for Category 1 and 2 donors.

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## 13 HEART

### Statement of Recommendation

- ***In the UK, heart transplantation from DCD donors is currently NOT standard of care. Because of a number of ethical issues, the use of DCD hearts is not currently recommended. Once these are resolved this guideline will be updated. (Not graded)***

Transplantation of the heart from a DCD donor is established in the US (1) but to date has not been performed in the UK. The principle of DCD heart transplantation is the same as any other transplant – the heart is removed, its blood supply restored (via the coronary arteries) and resumption of function is anticipated. The following relates to the US experience.

#### 13.1 Donor Selection

The donor selection criteria for DCD cardiac transplantation are as for any other cardiac donor.

#### 13.2 Organ Retrieval

It is believed that the DCD heart requires prompt resumption of a blood supply to avoid irrecoverable myocardial loss. With this in mind two approaches have been proposed in the adult donor:

1. To perfuse within the donor by Extra Corporeal Membrane Oxygenation (ECMO) support, with exclusion of the cerebral circulation by cross clamping the aortic arch vessels. ECMO is constructed by aortic and right atrial cannulation after 30 000 u heparin has been injected directly into the right atrium and massaged around the circulation, but only after the aortic arch vessel clamp has been placed. The DCD donor heart is prevented from beating by hyperkalaemia (serum potassium level around 10 mmol/l) or the placement of a fibrillator within the pericardial cavity.
2. To take the DCD heart and immediately place it onto an *ex situ* normothermic perfusion device (normothermic retrograde aortic perfusion with 25% blood-bank

blood, 10 ml 20% mannitol and the remaining volume made up of Gelofusin<sup>®</sup>). The device offers left atrial perfusion for the beating heart, so permitting assessment of left ventricular function

### **13.3 Organ Preservation**

Prompt re-perfusion of the heart should be undertaken with warm blood-based perfusate (see above) for 1 hour followed by isolation and perfusion with cold St Thomas' solution. The heart should be removed in standard fashion and transported in 2 litres of cold (4 °C) normal saline.

This is an evolving field, and it is possible that different approaches to organ preservation and perfusion will be adopted in clinical trials.

### **13.4 Organ Quality Assessment**

No accepted parameters have been established. These will be agreed by participating units when ethical approval has been obtained and research protocols agreed.

### **13.5 Recipient Selection**

The approach should either be through:

- Acceptance that the DCD heart is a good donor heart and so is offered to the most deserving, previously consented and best matched recipient on the waiting list, or
- Allocation to a group of carefully consented patients with drug-resistant and severe heart failure who are not eligible for heart transplantation because of minor co-morbidity, but who would be prepared to accept a DCD heart as an alternative to not receiving an organ at all.

These approaches would both require a secondary DCD heart recipient waiting list.

#### **Allocation**

Time is of the essence in transplanting these organs. In practice, DCD organs will not be moved between centres for the foreseeable future. If DCD cardiac transplantation becomes established in the UK, a future issue to consider will be the national access to such organs.

### **13.6 Immunosuppression**

There is no reason to assume that the DCD heart will require a different immunosuppressive programme than that established for DBD donor heart transplantation:

Induction therapy: RATG

Maintenance therapy: CNI, prednisolone and mycophenolate

### **13.7 Outcome**

The audit outcomes of DCD heart transplantation will be those of current DBD donor heart transplant programme:

- Ventilation time
- Support (Pharmaceutical: beta agonists, alpha agonist, phosphodiesterase inhibitor infusion; Mechanical: IABP, ECMO and VAD)
- Duration of stay on ICU
- Duration of stay in hospital
- Ventricular function pre discharge and at 1 year (echocardiography)
- 30 day mortality (peri-operative)
- 90 day mortality
- 1 year mortality
- Freedom from acute rejection (1 month, 3 monthly right ventricular biopsy)
- Freedom from acute infection (bacterial, protozoal, viral, and particularly CMV)
- Freedom from chronic rejection (coronary angiography at 12 months and yearly intervals)

### **Reference**

1. Boucek MM, Mashburn C, Dunn SM, et al. Pediatric heart transplantation after declaration of cardiocirculatory death. N Eng J Med 2008; 359: 709-14

## 14 PAEDIATRIC DCD TRANSPLANTATION

Although DCD paediatric donors may constitute a small percentage of the entire paediatric donor pool, DCD donation should be considered for any child, and their family, who are facing end-of-life issues. It is essential that transplant and donor teams work with colleagues who are comfortable with this type of donation in caring and working for with those families who request donation (1).

There is great potential for DCD donation to increase organ availability for children. For example, Koogler et al (2) showed that with routine requesting within the paediatric age group, the potential for DCD donors to increase organ donation in their institution would be 42%.

Plans are currently being finalised for a UK paediatric DCD kidney allocation system, planned to start in April 2014.

Renal and liver grafts from paediatric DCD donors have graft function and transplant recipient survival rates comparable with organs recovered from SCD donors (3). A recent review of the limited UK data on DCD donors in paediatric renal transplantation has suggested that better outcomes are obtained from younger donors (up to 40 years of age) and shorter functional warm ischaemia times (up to 60 minutes).

Lungs from DCD donors are being recovered and transplanted with good success, and four hearts from paediatric DCD donors have been transplanted with good success (personal communication, NHSBT).

Families of children are more willing to agree to donation than families of adult patients (1,4). Parents and guardians want to be asked about organ donation, including DCD, and parents make no distinction between cardiac and neurologic death (5,6).

In the UK currently, NHSBT figures show that the consent rate for potential DCD donors aged 18-24 years is 58%, but the paediatric age group (0-17 years) still has the lowest consent/authorisation rate for both potential DBD and DCD donors (59% and 37%, respectively).

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