

**Functional restoration, transportation and  
transplantation of human hearts from donation  
after circulatory death (DCD) organ donors**

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## Background

Heart transplantation is a well-established treatment option and remains the gold standard therapy for patients suffering from end stage heart failure. However, the supply of donor hearts far out weighs the demand for this precious resource. This leads to increased waiting list mortalities, which range from 10 to 20%. Despite initiatives to increase the consent rate and implementation of UK scouting for early donor management, the number of heart transplantation has remained under 150 per year. This is due to multi-factorial reasons and the main factor is a change in donor demographics. The UK standard DBD (Donation after Brain Death) donors are older, have multiple co-morbidities and in most cases they are considered marginal. The other reason is an increase in number of DCD (Donation after Circulatory Death) donors. In contrast to heart transplantation, the other solid organ programs are thriving due to the use of organs from DCD donors. Currently hearts are retrieved only from DBD donors, as there are concerns over the period of ischaemia after circulatory death affecting the myocardial function that may affect the post-transplant outcome in the recipient.

Heart transplantation from DCD donors has been proven possible. The first human heart transplantation performed in 1967 came from a DCD donor, as brain death was not established at that time. Large animal experiments have shown that heart transplantation is feasible if the warm ischaemic time is under 30 minutes. Recently, Sydney had first demonstrated performing successful heart transplantation from DCD donors. Following this Papworth

hospital, Cambridge and Harefield hospital, London have successfully performed series of heart transplants from DCD donors.

Restoring the function of the DCD heart remains a main challenge and on average the DCD heart suffers a minimum of 15 to 20 minutes of warm ischaemia after circulatory death. In order to restore function, reduce myocardial injury, supply the energy stores and maintain homeostasis continuous warm perfusion is required. Papworth hospital model used normothermic regional perfusion (NRP) in their DCD program to restore the function, re-assess its suitability for transplantation. In addition further ischaemia by cold storage is avoided by transporting the heart in a continuously perfused and beating mode.

The commercially available TransMedics Organ Care System (OCS) (Transmedics Inc., Boston, USA) is a CE marked device and has been used by Sydney, Papworth and Harefield to transport hearts from donor hospitals. The heart function is further assessed during transport by direct visualization and lactate profiles. Nearly a dozen of heart transplantations have been performed world wide from DCD donors using OCS device with or without using NRP.

Wythenshawe hospital serves the North West region in the UK has a population of over 6.5 million. North West of the UK has the highest incidence of heart disease. On gap analysis, over 18 suitable DCD donors in the region were identified who would have been a suitable for heart transplantation during the last 3 years. This can potentially increase the Wythenshawe heart transplant activity by 20%.

**Objectives**

1. Our aim is to restore function, assess the suitability for transplantation of hearts from DCD donors by using normothermic regional perfusion (NRP)
2. Suitable heart is procured and transported in perfused, beating mode using TransMedics OCS system
3. Transplant the hearts on to suitable recipient who have given prior well informed consent

We will be using the Papworth hospital protocol for functional restoration and assessment. This protocol has gone through UK ethics committee and has been approved by NRG and NHS-BT. As this procedure is now well established internationally, local ethics approval is not required however, a trust approval, as a new service development is required.

### **Donor selection**

Donors will be recruited from the intensive care units within Wythenshawe retrieval zone and only Maastricht category 3 donors will be considered

### **Donor Inclusion Criteria**

Maastricht Category 3 DCD donors
Age 16-40 years inclusive
Consent obtained from next of kin/ organ donor register

### **Donor Exclusion Criteria**

Previous cardiac surgery
Previous midline sternotomy
Known valvular heart disease
Known coronary heart disease
Known congenital heart disease
Previous myocardial infarct
Insulin dependent diabetes
Massive inotropic or vasopressor support
Active malignancy
Hepatitis B, Hepatitis C, HIV disease
Primary Intra-cerebral lymphoma
All secondary intracerebral tumours
Melanoma
CJD and TB
West Nile Virus
Encephalitis

### **NORS team approval**

The protocol will go through National organ retrieval service (NRG) and will also go through Cardiothoracic Transplant Advisory Group (CTAG). Detailed discussion will take place between the Leeds-Manchester abdominal NORS teams regarding the use of NRP. Clinical leads in Manchester and Leeds are already aware of this new development and have given full support. Following discussion with NRG, local CLODS will be contacted to get support for this service development. Both North West and Yorkshire SNOD teams will be involved and lead SNOD from each team has already been identified. Initial screening and relevant consent will be obtained by the SNODs.

### **Contact details**

Following identification of a suitable donor the SNOD should contact the recipient transplant coordinator in Wythenshawe hospital on 0161-998-7070.

### **DCD Retrieval Team**

The team will include

- Mr. R. V. Venkateswaran and (or) Mr. James Barnard-Consultant
- Consultant Cardiothoracic Anesthetist
- Cardiothoracic transplant fellow
- SNOR-Retrieval nurse
- Perfusionist for NRP and OCS set up
- Scrub nurse

Consultant cardiothoracic transplant surgeon will discuss the protocol and conduct of the retrieval to the NORS teams in donor hospital

## **Equipment**

Wythenshawe team will coordinate and all required equipment and personnel will come from UHSM. There will be no expense to donor hospital involved.

## **Funding**

The New Start charity-Wythenshawe hospital transplant charity has funded the OCS machine and the consumables towards the transportation part of this project.

## **Donor hospitals**

All hospitals within Wythenshawe retrieval zone will be included. Initially, the 3 major neurosurgical units-Salford, Preston and Liverpool in addition to UHSM will form Phase-1. The rest of the donor hospitals will form Phase-2 (Appendix-1).

## **DCD Heart Retrieval**

No ante mortem interventions are required for DCD heart retrieval. Withdrawal of life sustaining treatments will be undertaken in the anesthetic room by the intensive care team. If it is not local practice to withdraw in the anesthetic room then it may need further negotiation in regard to the practicalities of minimizing the ischaemic time during transfer to theatre. It is now accepted that functional warm ischaemia begins when systolic blood pressure falls below 50mmHg. A time of 30 minutes of functional warm ischaemia will be tolerated before standing down. The DCD heart team will stand by for a total of 3 hours.

Death will be declared by the intensivist as set out by the Code of Practice for the diagnosis and confirmation of death (Academy of Medical Royal Colleges). The donor will then be transferred to the operating room where they will be prepared for surgery (Appendix-2).

### **DCD Heart Retrieval with NRP**

A median sternotomy will be performed and the pericardium opened. The arch vessels will be clamped and 20,000 units of heparin will be injected into the right atrium and 10,000 units into the pulmonary artery. An arterial pipe will be inserted into the distal ascending aorta and a two stage venous pipe will be inserted into the right atrium. Normothermic regional perfusion will then begin. The trachea will then be reintubated and the lungs ventilated with the following ventilation parameters, PEEP 10, tidal volume 7ml/kg maintaining 100% FiO<sub>2</sub>. Dopamine will commence at 5µg.kg.min<sup>-1</sup> and Vasopressin at 4 unit/hr. After normothermic regional perfusion has been established the abdominal surgeons will begin their warm dissection as for a DBD donor. Following thirty minutes, the donor will be weaned from ECMO and a Swan Ganz catheter and a trans oesophageal echo probe will be inserted. The TransMedics OCS will be primed with donor blood. The perfusate biochemistry will be optimized and calcium will be corrected to 1.1mmol/L and potassium to 5mmol/L. The abdominal organs will be retrieved in the usual manner as for a DBD donor.

In relation to the heart, the inferior vena cava will be transected above the diaphragm and the left heart vented. A cross clamp will then be placed across the aorta and 500mls of St Thomas crystalloid cardioplegia supplemented

with 50mg GTN and 2,500 units of Erythropoietin will be delivered to the aortic root.

If the lungs are to be retrieved, the heart will be removed in standard fashion leaving a left atrial cuff. Again, in order to reduce the warm ischemic period of the heart, the lungs will be flushed antegrade with Perfadex solution containing 500 mcg Prostacyclin once the heart once the heart has been removed. A standard retrograde pneumoplegia flush will then follow.

### **Recipient Operation**

#### **Recipient**

All patients on the Wythenshawe Hospital heart transplant waiting list who meet the inclusion and exclusion criteria for DCD heart transplantation will be given a patient information letter (Appendix 3). After meeting with a member of the transplant team, consented patients will be identified as potential recipients of DCD hearts. This will not exclude them from the standard heart transplant waiting list.

#### **Recipient Inclusion Criteria**

Patient on the active heart transplant waiting list at Wythenshawe Hospital
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#### **Recipient Exclusion Criteria**

Redo-sternotomy
Congenital Heart Disease
Moderately high trans pulmonary Gradient (PVR >3.0)
Travel Distance > 3 hours
HeartWare or Heartmate-2 Ventricular Assist Device
High antibody titre

**Recipient Implant**

The recipient will have an arterial line and venflon placed prior to the donor heart arriving. Following inspection of the donor heart on the OCS by the lead surgeon the recipient will then undergo general anaesthesia, central line insertion and Swan Ganz sheath insertion. Sternotomy and explant of the native heart will be performed in standard fashion.

The donor heart will then receive 1litre of cold St Thomas's cardioplegia supplemented with 100mg GTN and 5000 units of Erythropoietin into the aortic root before being disconnected from the OCS and prepared on the back table in ice-cold saline. The heart will be implanted using standard bicaval technique. Once the left atrium, back wall of IVC, back wall of pulmonary artery and aortic anastomosis have been completed the aortic root will be deaired and the cross clamp released. The remaining anastomoses will be undertaken with the cross clamp off minimising warm ischaemic time. Following a minimum of 60 minutes of reperfusion, the recipient will be weaned from cardiopulmonary bypass. If the recipient is unable to be weaned from cardiopulmonary bypass, a low threshold to convert to central extra corporeal membrane oxygenation will be adopted (Appendix-4).

**Evaluation**

We aim to transplant five DCD hearts using NRP. Transplant outcomes will be that of standard DBD heart transplants.

**External review**

Mr. Steven Large, consultant cardiac surgeon, Papworth hospital, Cambridge will act as an external auditor and advisor. He worked hard to get the NRP approved by the UK ethics committee and has been involved in the first successful DCD heart transplantation in the Europe. The team in Papworth lead by him has resuscitated over dozen donor hearts and has successfully transplanted over 8 hearts from DCD donors. We will be using exactly same protocol developed by Mr. Large et al.

## Appendix 1

### Donor Hospitals in Wythenshawe Retrieval Zone

#### Phase-1

1. Wythenshawe hospital, Manchester
2. Salford Royal NHS Foundation trust-Salford
3. Lancashire Teaching Hospitals NHS Foundation trust-Preston
4. The Walton Centre-Liverpool

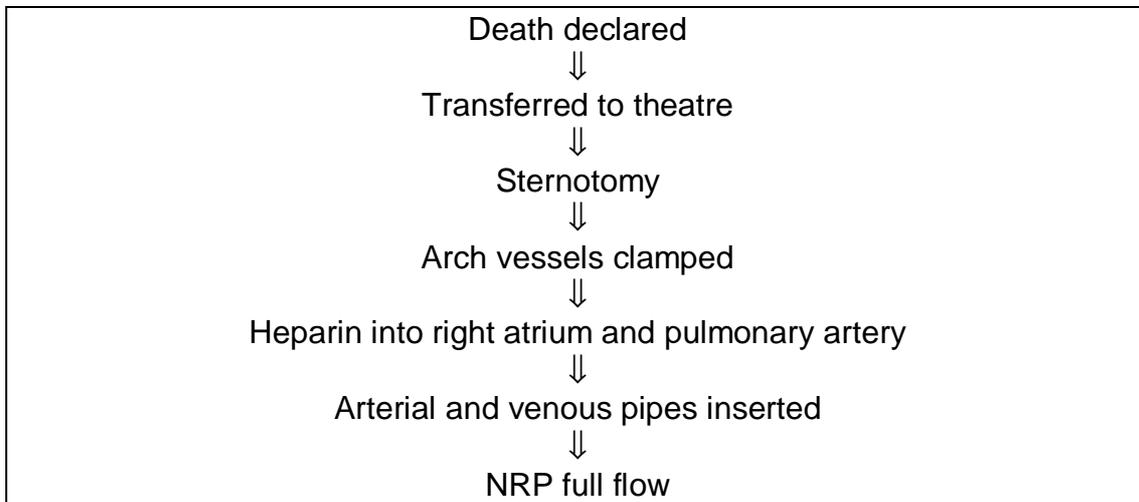
#### Phase-2

All other hospitals in Wythenshawe hospital retrieval and allocation zone will be recruited as phase-2.

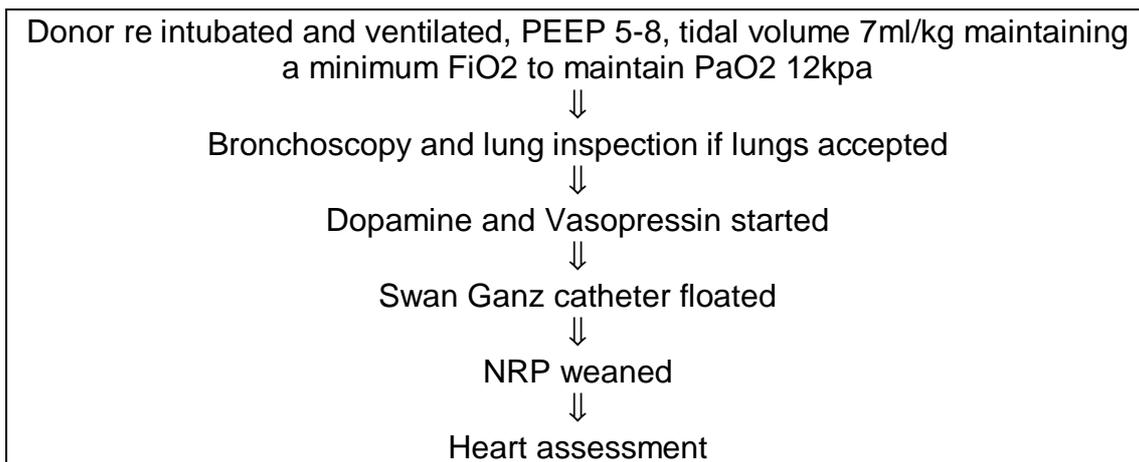
Hospitals in our extended donor retrieval zone where the allocation of organs is not to Wythenshawe may be considered after discussion with the allocation centre.

## Appendix 2: Flow Diagram of NRP Retrieval

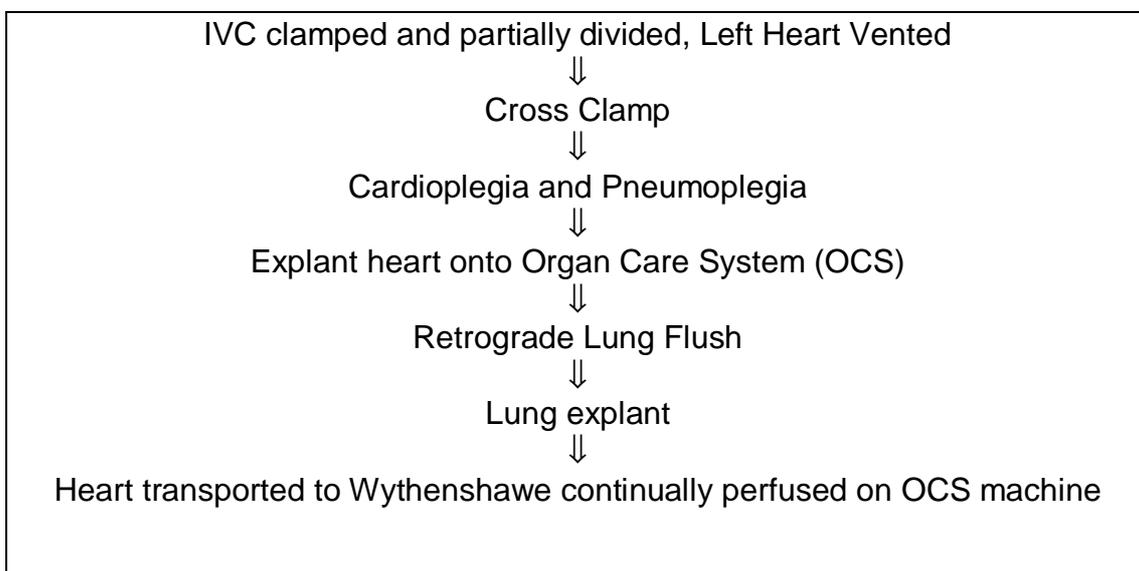
### Restoration of function



### Assessment



### Transportation



## **Appendix 3: Recipient Patient Information Leaflet**

### **Heart Transplantation from Donation After Circulatory**

#### **Determined Death (DCD) Donors**

Heart transplantation is an excellent treatment for patients with end stage heart failure prolonging and improving quality of life. Unfortunately there are many patients waiting for a heart transplant and there is a shortage of suitable donors. This gap between supply and demand can result in prolonged waiting times of more than 3 years for some patients. During this period, it is inevitable that some patients will die (10-20%), whilst others will deteriorate to a stage where they are too unwell to survive the transplant operation and subsequently, will be taken off the waiting list or have a ventricular assist device inserted. Although we are trying to increase the number of donors, statistics show that the waiting list continues to grow by more than 10% each year.

One possible way to increase the number of donor hearts is by using a different group of donors, called Donation After Circulatory Determined Death (DCD) donors. We would be grateful if you could take the time to read the following patient information leaflet in regard to DCD heart donation.

#### **Donation after Brain Death**

Currently, hearts are transplanted from Donation after Brain Death donors (DBD). These are patients who have sustained a severe brain injury and after extensive neurological testing, are shown to have no meaningful brain function. These patients are classified as "brain stem dead". Once certified as

brain stem dead, the donor is then taken to the operating room where the heart is assessed by a surgeon whilst it is still beating. Hearts that are deemed to be suitable after assessment are then arrested by administering a cold solution to protect the heart and transported back to Wythenshawe in ice ready to be transplanted

### **Donation After Circulatory Death**

DCD donation occurs when the patient has sustained a severe brain injury from which they will not recover and the patient is being kept alive by artificial means including ventilators and supportive drugs. The patient is not classified as brain stem dead but they have no hope of recovery. The decision to withdraw care is made between the relatives and doctors looking after the patient.

If the family is interested in organ donation and the decision to withdraw has been made, the patient is taken to a quiet room near the operating room where the ventilator and other machines will be turned off with the family in attendance.

Once treatment has been withdrawn, the patient's heart may stop. After 5 minutes of the heart stopping, the doctor looking after the patient will pronounce the patient dead. The donor will then be quickly transferred to the operating room where the heart will be restarted using a special procedure. The heart will then be assessed in the usual manner.

After the heart has been removed, it will be placed on a special machine called the TransMedics Organ Care System (OCS). This is a portable machine which pumps blood to the coronary arteries of the heart restoring

function. Once the heart is beating again the surgeon to determine whether it is suitable for transplantation will assess it. The machine, with the heart beating continually, will then be transported back to Wythenshawe to the awaiting recipient.

**What are the disadvantages?**

During DCD donation there is a very short time period of approximately 15 minutes where the heart is without a blood supply. When blood flow is restored to the heart on the OCS machine, the heart may be temporarily impaired or “stunned”. We know through years of experience of patients suffering from heart attacks that the human heart can tolerate a brief period of no blood flow and fully recover.

**What are the advantages?**

DCD heart transplantation is a new avenue to increase the donor pool available for heart transplantation. This will increase the chances of receiving a suitable donor heart. When any technique is introduced in transplantation we want to do it cautiously and as safely as possible. We will therefore only be using younger adult DCD donor hearts in comparison to the DBD donors.

**Has it been done before?**

The world's first successful heart transplant by Christian Barnard in 1967 was from a DCD donor, as brain stem testing had not been recognised at that point. Following the introduction of brain stem testing in the late 1970's, all heart transplants were taken from DBD donors as the donation process was

simpler and assessment of the heart was more reliable. Hearts also no longer had to endure the short period of no blood flow.

Recently in 2007, doctors in Colorado, United States, successfully transplanted four extremely sick children with DCD hearts. These children did very well and were discharged home after 3 weeks.

Between July and October 2014, surgeons in Sydney, Australia have successfully transplanted 3 adult patients with DCD hearts using the TransMedics Organ Care System. This paved the way for more widespread use of DCD hearts for adult heart transplants.

**Do any other organs get transplanted from DCD donors?**

Yes. For the last 10 or more years, kidneys, livers and lungs are routinely transplanted from DCD donors.

**If I choose to have a DCD heart will I be taken off the normal transplant waiting list?**

No. If you choose to consider receiving a DCD donor heart, you will be on both lists, maximizing your chance of a transplant.

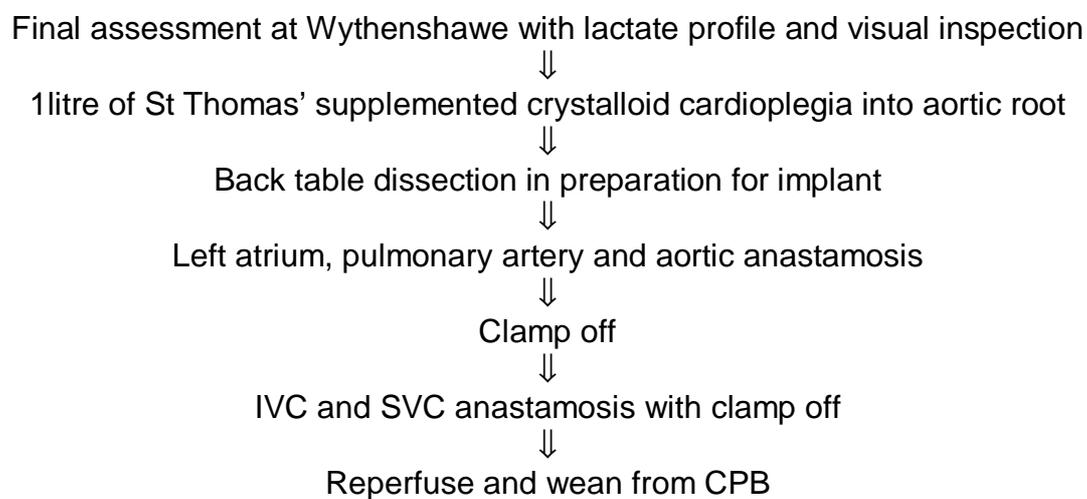
**Will my treatment be any different if I decide to have a DCD donor heart?**

No. It will be same team of surgeons and doctors that will be assessing the organ, undertaking the operation and looking after you following the operation. It is important that you understand that all the risk and complications associated with heart transplantation that you have been previously

counseled about in regard to DBD transplantation apply to DCD heart transplantation.

We understand that this may be a difficult decision for you to make. Please discuss it with your friends and relatives. Likewise, if there is anything you are unsure about or require further clarification, please call and speak to the Transplant Coordination team or make an appointment with the doctor

## Appendix 4: Flow Diagram of DCD Heart Transplant



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