Resuscitating heart transplantation: the donation after circulatory determined death donor

Simon Messer and Stephen Large*

Department of Cardiothoracic Surgery, Papworth Hospital NHS Foundation Trust, Cambridgeshire, UK

* Corresponding author. Department of Cardiothoracic Surgery, Papworth Hospital NHS Foundation Trust, Papworth Everard, Cambridgeshire CB23 3RE, UK. Tel: +44-1480-364478; fax: +44-1480-364334; e-mail: stephen.large@papworth.nhs.uk (S. Large).

Keywords: Heart transplant • Circulatory death • Machine perfusion

THE DEMAND FOR HEART TRANSPLANTATION

Despite advances in mechanical support, heart transplantation still remains the gold standard treatment for end-stage drug-resistant heart failure. It provides both excellent long-term survival and a near-normal quality of life. Unfortunately, as the number of patients eligible for heart transplantation continues to rise, the number of suitable donors after brain death (DBD) continues to fall. In the UK, this increasing disparity between demand and supply results in less than half of patients being transplanted while 43% of the waiting list are either permanently removed or die waiting for a heart transplant [1].

With the heart transplant waiting list increasing at a rapid rate (Fig. 1), attention has fallen on extended criteria donors. In Europe, it is now routine to consider those hearts from donors up to 65 years old, those with ventricular hypertrophy or those with a history of prolonged cardiac arrest. However, even after incorporating these marginal donors, there remains an increasing shortfall in meeting demand. In an attempt to push the boundaries still further, some enthusiasts, including Tolboom et al. in this edition, are looking towards the donation after circulatory determined death (DCD) donor to bridge the gap. DCD donors are patients who have sustained catastrophic brain injury but who will not proceed to brain stem death or where brain stem testing would be inappropriate. After consultation between the intensive care doctors and the family, a decision to withdraw therapy is made after it has been established that it would be futile to continue and not in the best interests of the patient.

HISTORY OF DONATION AFTER CIRCULATORY DETERMINED DEATH HEART TRANSPLANTATION

But instead of looking forward should they be looking back? It is almost 50 years since the world’s first successful heart transplant [2]. Considering the current controversies surrounding DCD heart transplantation, it is somewhat ironic that Christian and Marius Barnard transplanted the first clinical heart from a DCD donor. Success was dependent on a myocardial preservation strategy that relied on prompt reperfusion within the donor, hypothermia and continuous perfusion during implantation so minimizing ischaemia. As the brain stem testing became established following the Harvard Criteria, hearts no longer had to endure the obligatory warm ischaemic period associated with DCD donation. The elaborate methods of myocardial preservation soon became redundant in favour of the simplistic attraction of cold storage of the DBD donor heart.

ABDOMINAL DONATION AFTER CIRCULATORY DETERMINED DEATH ORGAN TRANSPLANTATION

Today, nearly half a century later, desperation has once again led us to the DCD donor. This is a direction our abdominal transplant colleagues turned to almost 10 years earlier, as they were also faced with falling numbers of DBD donors and relatively little to lose. Within the UK, DCD donation for liver and kidney transplantation is well established [3]. Over the last decade, DCD donation has increased from 1.1 to 7.9 donors per million population. DCD renal transplantation has been the major stakeholder with DCD kidney donation increasing seven-fold. The DCD liver donor now forms 25% of the national liver transplant service. Although DCD lung transplantation is still regarded to be relatively novel, outcomes have been shown to be equivalent to the DBD programme [4].

POTENTIAL OF DONATION AFTER CIRCULATORY DETERMINED DEATH HEART TRANSPLANTATION

Forecasts for DCD heart transplantation predict that if adopted, overall heart transplant activity would increase by 20% [5–7]. These conservative forecasts model on donors less than 50 years...
old, on no inotropic support and withdrawal to perfusion times of less than 30 min. In the future, these strict criteria will probably be relaxed to some extent allowing access to greater donor numbers. Within the current DCD donor pool, it is evident that there are some excellent young donor hearts that are currently being wasted due to the caveats of brain stem testing. For example, we have encountered a number of young DCD donors who, following high-speed road traffic accidents, have sustained severe traumatic brain injury. Although likely to be brain stem dead, they are unable to undergo testing due to concerns of cervical cord injury or severe lung contusion prohibiting the apnoea test.

**CLINICAL DONATION AFTER CIRCULATORY DETERMINED DEATH HEART TRANSPLANTATION**

Although we have identified both a need and a potential for DCD heart transplantation, significant obstacles exist before a successful programme can be implemented in today’s society. Although there have been several successful DCD human heart transplants performed in the past, they have all evolved strategies to reduce the ischaemic burden.

In 1967, Barnard minimized the ischaemic period both by mechanical perfusion of the donor and minimizing donor organ transport time by transplanting the recipient in the adjoining theatre. More recently in 2008, Campbell and Boucek reported three successful paediatric DCD heart transplants. Although the paediatric heart is far more tolerant to the ischaemic insult, this group undertook ante-mortem cannulation and cold perfusion within the donor, while also reducing the ‘hands off period’ from 3 min to 75 s. This work precipitated strong ethical objections and may have delayed the universal adoption of either approach. In the UK, transporting the donor to the recipient has been performed in the early days of cardiothoracic transplantation, but this was seen to excite criticism and would not be contemplated now.

Ante-mortem manipulation or cannulation of the potential UK DCD donor is not ethically acceptable, nor will the period of 5 min of observation before confirming brain death be shortened in the foreseeable future.

In order to establish a successful, universal clinical DCD heart programme, we must recognize and accept current ethical boundaries and evolve strategies to recondition and assess DCD hearts prior to transplantation. If we disregard careful assessment and selection of the DCD heart, simply relying on familiar techniques of cold storage, a programme of DCD donor heart transplantation will undoubtedly end in failure.

**EXTRACORPOREAL DONOR HEART MACHINE PERFUSION**

Over the last 50 years of heart transplantation, little investment has been made in donor heart reconditioning, preservation or functional assessment. This has inhibited progress in the development of a DCD heart transplant programme and discouraged us from pursuing the four DBD hearts currently declined on grounds of poor function or coronary disease for each donor heart currently accepted. Where are we today? Isolated perfusion of the donor heart is now possible with the TransMedics Organ Care System (OCS) (Fig. 2), the only commercial available continuous extracorporeal perfusion platform. This was originally designed to offer functional assessment but later modified to offer simpler, safer donor heart root perfusion after realizing the complexities of managing the working heart in the clinical field.

The strategy proposed by Tolboom et al. in this edition is one of extracorporeal perfusion of the DCD donor heart at the donor hospital followed by cold cardioplegic arrest and cold storage for transportation and subsequent transplantation. It is claimed that this combines the benefits of reconditioning and assessment with the logistical simplicity of cold storage during transportation. They investigate reperfusion temperature in order to optimize donor myocardial energy stores by machine perfusion. Previous studies
by this group have shown that following perfusion of DCD hearts, adenosine triphosphate (ATP) levels were significantly lower than non-ischaemic controls [10]. These authors question whether they could replenish ATP more efficiently without the myocardial energy demands associated with normothermia. Using a continuous flow Langendorff to perfuse an isolated rat heart led them to conclude that optimum recovery of DCD hearts is achieved at temperature between 25 and 30°C. Although the authors have highlighted one possible reperfusion and assessment strategy, it is unlikely to be adopted in the clinical arena as most clinicians would be reluctant to transplant a DCD heart that had a one off functional assessment some time before prolonged cold storage. We would also have such reservations.

What the authors have highlighted, however, are the possibilities that machine perfusion can offer in reconditioning donor hearts. Although some work has been undertaken in the pressure [11], temperature [12] and partial pressure of oxygen in the initial reperfusion solution, little is known of the effects of these parameters during prolonged perfusion during transportation. The optimum temperature, pH, calcium concentration, oxygen concentration, osmolarity and haematocrit are yet to be described. The role that pharmacological adjuncts such as erythropoietin [13], glyceryl trinitrate, sodium potassium exchange inhibitors [14], calcium antagonist and steroids play to attenuate the ischaemia-reperfusion insult may be important. Exciting avenues to protect and improve donor heart function have yet to be explored. These include haemofiltration, exchange transfusions and possibly stem cell therapy.

**FUNCTIONAL ASSESSMENT**

Although many of these difficulties can be overcome with planned modification of the circuit or further research into perfusate, the main obstacle is functional assessment upon the device. The difficulty of functional assessment is that the circuit volume must be large enough for the heart to pump up to 5 l a minute and be capable of an easy transition from Langendorff to working mode and back again without the risk of air embolism, over distension or loss of volume. The operator must also be skilled enough to know the familiar pitfalls of the working heart model.

In the NRP protocol, a sternotomy is performed following declaration of death. Heparin is administered and the arch vessels are clamped off to exclude cerebral blood flow in order to avoid a Cushing response. Aortic and right atrial pipes are inserted, and the donor heart re-perfused. The donor trachea is reintubated, and the donor ventilated. This permits weaning of NRP support after 90 min and permits assessment of donor heart function in a familiar way. This technique effectively transforms a DCD into a DBD heart. In our programme, DCD heart assessment is made with transoesophageal echocardiogram and a pulmonary artery flotation catheter measuring direct pressures and cardiac output. If the heart is found to be acceptable, the TransMedics OCS can...
then be primed and the perfusate optimized. Cold cardioplegia is then given before removing the heart and instrumenting upon the OCS. Problems with this technique include the need for additional blood products, the use of additional equipment and the ethics of perfusing the heart within the donor (obtained within the UK in 2012). The benefits, however, include minimizing the warm ischaemic period by on average 8 min when compared with DPP, allowing perfusion and recovery of other abdominal organs for transplantation and permitting functional assessment of the DCD heart. This approach restores control to a DCD retrieval operation and reduces the cost of priming and discarding an OCS system where the heart is deemed to have insufficient prime volume or poor function.

In summary, we are faced with a growing demand for heart transplantation in the face of declining donor heart numbers. The possibility of increasing the donor pool further by accessing the DCD donor is very welcome. Unfortunately, in order to accomplish this potential 20% increase in heart transplant activity, investment is required in machine perfusion, assessment and optimization of perfusate. This investment may be wisely spent, as successful DCD heart recovery may translate into improving those numerous DBD hearts rejected on grounds of poor function. This all has great promise for the future of heart transplantation.

Conflict of interest: none declared.

REFERENCES


