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The Donation after Circulatory Death Donor can be a Source of Organs for Cardiac Transplantation

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Abstract

Objectives: The donation after circulatory death (DCD) donor is an increasing source of organs for transplantation. Currently cardiac donation from DCD donors is precluded due to concerns that circulatory arrest in the organ donor would result in ischemic myocardial injury. We have recently resuscitated a human DCD heart in-vivo using extracorporeal perfusion. Through a retrospective analysis of DCD organ donors procured for liver and kidney transplantation, we sought to determine what proportion may have been suitable for cardiac donation based on their past medical history and pre-terminal cardiovascular status.

Methods: Demographic data was obtained from individual hospital notes and standard donor information files. In order to assess their suitability for cardiac donation we carefully analyzed their cardiovascular status. In particular we reviewed hemodynamic parameters, the requirement for inotropic support and whether there was any past medical history of cardiovascular disease.

Results: Between May 1st 2003 and March 1st 2007, 67 DCD donors were consented for liver and kidney donation. Eleven DCD donors would have been excluded on the basis of a history of cardiac disease, eight of whom suffered a recent myocardial infarction. An additional three donors were considered to be hemodynamically unstable. The remaining 80% (53/67) had normal cardiac function and no history of cardiac disease.

Conclusions: Eighty-percent of DCD donors in our series may have been suitable for cardiac donation, based on their past history and cardiovascular status prior to donation. The use of hearts from DCD donors may allow for a significant expansion of the donor pool.

Keywords: Heart transplantation; Donation after circulatory death donor

Introduction

The number of heart transplants performed worldwide is declining annually [1-3]. The conventional source of donor hearts, the brain-stem dead cadaveric heart-beating donor. is decreasing. Advances in neurosurgical treatment of patients with severe head injury and intracranial haemorrhage (ICH) mean that the increase in intracranial pressure (ICH) which previously precipitated ischemic brain-stem death can now be retarded or alleviated. The donation after circulatory death (DCD) donor is being increasingly used for transplantation. Successful renal, hepatic and pulmonary transplantation using non-heart beating donors has been reported [4-8]. With respect to cardiac donation it has been assumed that the heart would suffer overwhelming ischemic damage as a result of warm ischemia associated with non-heart beating donation. The Maastricht criteria were devised to classify non-heart beating donors according to whether cardiac arrest occurs under controlled or uncontrolled circumstances [9]. Category I & II suffer either an out of hospital or in-hospital uncontrolled cardiac arrest. In this group warm ischemic times are longer and organs may be irreversibly damaged. Category III donors suffer a cardiac arrest in a controlled setting following the elective withdrawal of supportive therapy. In these circumstances the duration of warm ischemia can be minimized, limiting organ injury. We have recently demonstrated recovery of cardiac function in human controlled DCD donors. This was achieved through in-vivo coronary reperfusion 23 minutes after asystole using an extracorporeal circuit. The resuscitated heart was subsequently able to independently support the circulation of the donor [10]. Our regional program for non-heart beating kidney donation is one of the largest in the world [7]. We retrospectively analyzed DCD donors who were procured for renal and hepatic transplantation to ascertain whether cardiac donation from this group may have been suitable based on their pre-terminal cardiovascular status and co-morbidities.

Methods

We performed a retrospective review of DCD organ donors procured in our region for renal and liver transplantation. Demographic data was obtained from individual hospital notes and standard donor information files compiled by our transplant coordinators. In order to assess their suitability for cardiac donation we carefully assessed their cardiovascular status prior to non-heart beating donation. In particular we reviewed hemodynamic parameters, the requirement for inotropic support and whether there was any past medical history of cardiovascular disease. In a proportion of DCD donors the time period between withdrawal of therapy and asystole is very prolonged. Organs are not procured from these donors due to concerns over organ damage due to hyoperfusion and hypoxia. These donors were also included in the analysis. Baseline characteristics were presented as means +/- standard devation (SD) or medians with interquartile ranges (IOR) for normally and non-normally distributed measures

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respectively. Statistical analyses were performed on S Plus version 6.0 (Insightful, Washington, USA).

Results

Between May 1st 2003 and March 1st 2007, 67 DCD donors were consented to donate organs for liver and kidney transplantation at Addenbrookes Hospital (Cambridge, United Kingdom). 64% (43/67) proceeded to donate organs for transplantation. The remaining 36% (24/67) had a prolonged time to asystole and for this reason it was decided not to procure organs from these donors. Mean donor age was 48 +/- 15 years. Sixty-six percent of donors were male (44/67). Baseline demographics of all DCD donors are listed in Table 1. The commonest causes of donor death were ICH and traumatic head injury. Causes of donor death and their relative proportions are outlined in Table 2. The median interval between admission to hospital and organ donation was 4 (1-11) days. Fluid balance, electrolyte status and renal function were normal (Table 1).

After extubation and withdrawal of supportive therapy the median time to cardiac arrest was 7 (0-23) minutes. Following asystole, a stand-off period was observed for confirmation of death prior to the procurement procedure. Once this had elapsed a laparotomy incision was performed. The abdominal aorta and inferior vena cava (IVC) were cannulated to allow cold perfusion for organ preservation. The mean time interval between asystole and establishment of cold perfusion was 16 +/- 15 minutes. This represents the total warm ischemic time that all organs were exposed to as a consequence of the non-heart beating donation process.

Specific attention was directed towards evaluating whether this donor population would be suitable for cardiac donation. Standard hemodynamic parameters were assessed to determine whether prevailing cardiac function was adequate for consideration of transplantation. The average mean arterial pressure (MAP) was 92 +/- 17 mm Hg. Only two donors (3%; 2/67) were hypotensive at the time of assessment with a MAP less than 60 mm Hg. Mean CVP was 10 +/- 4 mm Hg. The average heart rate was 81 +/- 24 beats per minute (bpm) and all donors were in sinus rhythm. Inotropic support was required in 25% (17/67), in the majority of donors the only vasoactive agent used was noradrenaline (15/17). Four donors were treated with dopamine and only a single donor received an adrenaline infusion for cardiovascular support. Only 4% (3/67) of donors were receiving more than one inotrope, in these instances this was a combination of dopamine and noradrenaline.

The frequency of risk factors for cardiovascular disease amongst the donor group was determined and is documented in Table 3. A history of cardiac disease was present in 16% (11/67), eight of these donors suffered a myocardial infarction (MI) immediately prior to the hospital admission leading to donation. In fact, in 6 of these donors MI was the cause of out of hospital cardiac arrest leading to hypoxic brain injury. Of the remaining 3 donors with a past history of cardiac disease, 2 had suffered MI in the past One had underwent previous coronary artery bypass grafting and the other had been implanted with an internal cardioverter-defibrillator for recurrent ventricular tachycardia. A history of hypertension was present in 18% (12/67). Only one donor was diabetic and a substantial proportion of donors were current smokers (40%, 27/67).

Discussion

In the face of a declining number of organs for cardiac transplantation it is imperative to develop strategies to expand the

DCD donors	
Number	**67**
Donated organs, n (%)	44 (64)
Did not donate, n (%)	23 (36)
Age, yrs (SD)	48 (14)
Male sex, n (%)	44 (64)
Height, m (SD)	1.75 (0.1)
Weight, kg (SD)	81 (14)
History of trauma, n (%)	21 (31)
Hospital stay, d (IQR)	4 (1 - 11)
Duration of ventilation, hrs (SD)	168 (214)
Fluid balance, L (SD)	0.6 (2.9)
Serum Na, mmol/L (SD)	145 (7.)
Serum K, mmol/L (SD)	4 (0.5)
Plasma Urea, mmol/L (SD)	5.6 (2.8)
Serum creatinine, mmol (SD)	78 (41)
Plasma glucose, mmol (SD)	7 (2)
Hemoglobin, g/dl (SD)	11 (2.2)
Blood transfusion, n (%)	13 (19)
White cell count, (SD)	14 (6.1)
Temperature	36.8 (1.7)
Withdrawal of support to asystole, mins (IQR)	7 (0-23)
Asystole to cold perfusion, mins (SD) (***Total warm ischemic time)***	16 (5)

Table 1: DCD donor demographic data.

Cause of death	**No. (%)**
Intracranial haemorrhage *Subarachnoid hemorrhage*	30 (45) *15/30*
Traumatic head injury *Road traffic accident*	18 (27) *14/18*
Hypoxic brain injury from cardiac arrest	8 (11)
Myocardial infarction	8 (11)
Brain tumor	4 (6)
Other	4 (6)
Ischemic stroke	3 (4)
Meningitis	1 (2)

*Some DCD donors had multiple contributing causes of death

Table 2: Causes of death for DCD donors.

DCD donors	
Number	**67**
Mean arterial blood pressure, mm Hg (SD)	93 (17)
Inotropic support, n (%) *Noradrenaline* *Dopamine* *Adrenaline* Multiple inotropes, n (%)	17 (25) *15/17* *4/17* *1/17* 3 (4)
History of cardiac disease, n (%)	11 (16)
Cardiorespiratory arrest, n (%)	16 (23)
Recent myocardial infarction, n (%)	8 (11)
Hypertension, n (%)	12 (18)
Diabetes, n (%)	1 (1.5)
Smoking history, n (%)	27 (40)

Table 3: Cardiovascular status and risk factors.

donor pool. As mentioned previously the number of heart transplants from brainstem dead heart-beating cadaveric donors is decreasing [1-3]. The DCD donor is an established source of organs for renal, liver and lung transplantation. The first heart transplant performed in 1967 by Dr. Christiaan Barnard used a heart from a DCD donor. The donor was a 25-year old female who had been involved in a road traffic accident. Her heart had stopped and Dr. Barnard and his team resuscitated the organ by placing her onto cardiopulmonary bypass (CPB) [11]. Four decades later we have employed a similar strategy to resuscitate the heart of a DCD donor 23 minutes after asystole. CPB was established through cannulation of the ascending aorta and right atrium. The heart spontaneously reverted into sinus rhythm within 5 minutes of coronary reperfusion. After 2 hours CPB was weaned and the resuscitated heart was able to independently support a limited circulation from which the aortic arch vessels had been excluded [10]. It has largely been presumed that cardiac donation from DCD donors would not be feasible due to warm ischemic injury incurred by the myocardium. Successful resuscitation and transplantation of DCD hearts has been demonstrated in animal models [11-13]. Our resuscitation of a human DCD heart further serves to confirm that DCD donor can be an important source of organs for heart transplantation.

The number of DCD donors procured for kidney and liver transplantation is increasing worldwide [14,15]. In the United Kingdom there was a 44% increase in the number of DCD donors in 2006 from the previous year [16]. Current estimates suggest that as many as 1200 DCD donors in the United Kingdom are suitable for multi-organ donation. The DCD donor is not as established a source of organ donation as the brain-stem dead heart-beating donor. Consequently, there is less knowledge with regards to their cause of death, associated co-morbidities, native organ function and physiology prior to donation. Through analysis of a large cohort of DCD donors our aim was to elucidate this information, with particular emphasis on determining whether there were any absolute or relative contra-indications to cardiac donation. The predominant cause of death was cerebral trauma and ICH. The donor population was not young with a mean age of 48, and the majority of donors were male. Prior to procurement DCD donors spent an average of a week receiving hospital treatment for their presenting condition. They were mechanically ventilated for the majority of this time. Fluid balance and electrolyte status was normal. A small proportion of donors required blood transfusion.

Fifteen percent of donors had a history of cardiovascular disease, with 11% having been diagnosed with MI at the time of hospital admission. Several of these donors had an out of hospital cardiac arrest and were resuscitated at the scene prior to hospital transfer. Although myocardial infarction was the cause of cardiac arrest in these donors, cardio-respiratory arrest in the absence of MI also occurred in another 11%. Therefore in total, just over one-fifth of all DCD donors suffered cardio-respiratory arrest either immediately before or during their hospital admission. In a previous report we have documented that the use of hearts resuscitated after a period of cardiac arrest in the brain-stem dead organ donor, does not impact on either early or long-term recipient outcome following heart transplantation [17]. Two donors in our current series had a past history of MI, one of whom had required coronary artery bypass surgery. A history of hypertension was present in 18%, one donor was a diabetic and 40% were current smokers.

On the basis of their cardiovascular history we believe 11 donors would have been excluded from consideration of cardiac donation, predominantly due to recent or past MI and ischemic heart disease. At the time of assessment for non-heart beating donation only two patients were hypotensive with a MAP less than 60 mm Hg. The first was a 44 year old male who had recently been resuscitated from a 30 minute cardiorespiratory arrest, following which he remained hypotensive. The systolic blood pressure was 76 mm of Hg and no inotropes or vasoactive agents had been commenced in this patient. His urine output remained excellent and he proceeded to donate his left kidney. The second donor was a 60 year old male diagnosed with subarachnoid haemorrhage. He also required resuscitation in the intensive care unit following an episode of ventricular tachycardia during which he lost cardiac output. Following resuscitation he remained hypotensive with a MAP of 35 mm Hg. As his renal function had been satisfactory prior to his cardiac arrest, consent for donation was organised. He was immediately taken to the operating theatre for renal procurement and both kidneys were transplanted. The remaining 65 donors were all hemodynamically stable, the average MAP for the entire group was 93 +/- 16 mm Hg. Twenty-five percent (17/67) of donors were receiving inotropes at the time of assessment for donation. In approximately 90% (15/17), noradrenaline was the only inotrope used, primarily for support of blood pressure. Four donors were also receiving dopamine, 3 of whom were also on noradrenaline. A single donor was started on an adrenaline infusion for cardiovascular support, this donor was confirmed to have poor left ventricular function on trans-thoracic echocardiography. He was a 65 year old male and suffered an ICH following clipping of a left middle cerebral artery aneurysm. This donor did not proceed to donate any organs as the process was abandoned on the request of his next of kin. In our opinion a further three donors would have been excluded on the basis of their hemodynamic status. Therefore, after careful evaluation a total of 14 patients (20%, 14/67) consented for DCD donation would have been deemed unsuitable for consideration of cardiac donation. This would be on the basis of a past history of cardiac disease and inadequate cardiac function at time of assessment.

Once it is confirmed by treating physicians that a patient is suitable for controlled non-heart beating donation, consent for the procedure is taken from next of kin. Subsequently supportive therapy is withdrawn. Of the 67 patients consented for non-heart beating donation, 64% (43/67) proceeded to donate organs. Thirty-two percent (22/67) of donors had a very prolonged time to cardiac arrest and therefore organs were not procured. The decision not to procure organs in this circumstance is based on concerns that organs may accumulate substantial injury during this period as the DCD donor is inevitably hypotensive and hypoxic for long periods while cardiac arrest is awaited. In the remaining two donors the donation process was halted on request of the donor family. After supportive therapy is withdrawn circulatory arrest is awaited, in our series the median time interval between withdrawal of therapy and circulatory arrest was 7 minutes. Time from support removal to circulatory arrest exceeded 30 minutes in only 16% of the 43 DCD donors who went on to donate organs. After cardiac arrest a mandatory stand-off period is observed for confirmation of death. Once this period has elapsed the donor is transferred to the operating theatre and organs are procured. Current techniques for preservation of non-heart beating organs rely primarily on cold perfusion of organs. This is achieved following laparotomy by rapid cannulation of the abdominal aorta and inferior vena cava and infusion of cold solution into the aorta. The mean time interval between circulatory arrest and establishment of cold perfusion, including the mandatory stand-off period was 16 +/- 5 minutes. This represents the duration of warm ischemia endured by organs procured from DCD donors.

Our strategy for cardiac resuscitation involved cannulation of the

ascending aorta and right atrium through a median sternotomy [17]. This allowed coronary and visceral reperfusion of the DCD donor with normothermic oxygenated blood using an extracorporeal circuit. The donor was fully anticoagulated with an injection of heparin (300 iu/kg) directly into the right ventricle followed by internal cardiac massage to allow circulation. Measurement of the activated coagulation time following this manoeuvre confirmed satisfactory anticoagulation for extracorporeal perfusion. In our preliminary experience with this perfusion strategy we have been able to achieve central cannulation in the same time period as abdominal transplant surgeons have taken to cannulate the abdominal vessels for cold perfusion. We believe that the warm ischemic duration observed in this series of 16 minutes, will be similar to the time period required for us to establish reperfusion of the coronary circulation following circulatory arrest in the DCD donor. Eighty-percent of the DCD donors analyzed in our series would potentially have been suitable for cardiac donation. This finding, in tandem with our demonstration that the DCD heart can be resuscitated in-vivo, suggests that the DCD donor is a source of organs for heart transplantation. The full realization of this resource may have a profound impact upon cardiac transplantation through a significant and immediate expansion of the donor pool.

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