Journal of Clinical & Experimental Cardiology

Ali et al., J Clin Exp Cardiolog 2013, S9
DOI: 10.4172/2155-9880.S9-006

Research Article Open Access

Ethicality of Heart Transplantation from Donation after Circulatory Death Donors

Ayyaz A Ali[1]*, Christopher White[2], Darren Freed[2], Ziad Ali[3] and Stephen Large[1]

[1]Papworth Hospital, Cambridge, UK
[2]University of Manitoba, Winnipeg, Manitoba, Canada
[3]Columbia University Medical Center, New York, NY, USA

Introduction

Although society has largely accepted and embraced the practice of organ transplantation, the donation of organs continues to pose difficult ethical conundrums. Donation after circulatory death (DCD) organ donation is considered by many to be an ethically precarious domain. However, organ procurement from DCD donors has contributed towards a significant increase in solid organ transplantation, its importance being underlined by the fact that 1/3rd of transplants performed in the United Kingdom are now undertaken using organs obtained from DCD donors [1]. Historically, the transplantation of organs procured after cardiac arrest was instrumental in pioneering transplantation. The initial heart and liver transplants were performed using organs removed after death of the donor [2,3]. Prior to definition of criteria for brainstem death (BSD), cardiac arrest and loss of circulation were considered essential for confirmation of donor death. The practice of DCD organ donation has raised many ethical concerns and continues to have detractors. Loss of cardiac output and cessation of circulation are the principal requirements for certification of death in the DCD donor. The ethicality of resuscitating the heart in DCD donors has been questioned. It is suggested by some that "cardiac death" should be an irreversible occurrence. Once established it is argued that resuscitation of the heart by any means would potentially negate the diagnosis of death due to recovery of heart beat and restoration of circulation within the donor. The terminal event that precedes the decision to withdraw therapy in the majority of DCD donors is usually severe neurological injury. However, neurologic testing in these donors does not identify irreversible loss of brain-stem function. Consequently, conventional heart-beating cadaveric donation is not an option. The lack of a clear definition of death contributes towards further confusion.

In a recent clinical case of human DCD heart resuscitation, we utilized an extracorporeal perfusion circuit to deliver oxygenated blood to the donor after circulatory arrest [4]. The commonest protocol for DCD organ procurement relies on the rapid infusion of cold preservation solution into the donor circulation with the aim of initiating organ protection and preservation through cooling of organs. More recently, the use of extracorporeal membrane oxygenation (ECMO to reperfuse the donor with normothermic oxygenated blood has also been undertaken on the basis that warm blood perfusion may be a physiologically more appropriate means for organ resuscitation and preservation [5,6]. Currently, this practice is limited to the procurement of the kidneys and liver. The majority of retrieval teams who undertake ECMO reperfusion of the DCD donor have achieved this through cannulation of peripheral vessels, most commonly the femoral artery and vein. Institution of ECMO leads to retrograde perfusion of the abdominal viscera. During the early experience with ECMO in DCD donors, cardiac resuscitation was observed upon reperfusion. As this was deemed unnecessary, specific measures were undertaken to depress cardiac activity including the establishment of systemic hyperkalemia to produce cardiac arrest. The deployment and inflation of intra-aortic balloon catheters for occlusion of the descending aorta was another means of preventing coronary reperfusion, whilst maintaining perfusion of transplantable abdominal organs [7,8]. There remain several important ethical issues relating to DCD heart resuscitation which require discussion and debate:

1. The appropriateness of restoration of circulation and recovery of heart beat within the donor for purposes of organ resuscitation and evaluation of function
2. The ethicality of pre-treatment of the donor prior to withdrawal of support to facilitate the organ retrieval and procurement process (i.e. systemic heparinization, insertion of vascular catheters for delivery of preservation solutions)
3. The optimal site for reperfusion of organs (in-vivo perfusion using ECMO vs. ex-vivo machine perfusion of explanted organs)

Institution of an Artificial Circulation After Declaration of Death

After circulatory arrest in the DCD donor a period of time is allowed to elapse whilst the donor has no cardiac output and hence no circulation. The purpose of observing this stand-off period is for the absolute confirmation of absence of respiratory effort in association with no effective cardiac activity. The duration of the stand-off period varies. The Advisory Committee for DCD organ donation in the U.K. and the Institute for Medicine in the United States recommend a 5 minute waiting time prior to commencing with organ retrieval [9]. In other centres the period of observation has been reported to be 2 minutes or less. In the recent successful description of paediatric cardiac transplantation from DCD pediatric donors, only a 90 second absence of carotid pulsation was observed prior to commencing with cardiac preservation and procurement [10]. Boucek et al., who reported this series, argued that the purpose of the observation period is to ensure that auto resuscitation of the donor heart does not occur. They cite that the longest interval between cardiac arrest and auto resuscitation reported in the literature is 90 seconds. Consequently, they felt it was justified to certify death at this time point. A similar stance was taken by those involved with DCD organ retrieval at the University of Pittsburgh who observed a 2 minute waiting period [11].

***Corresponding author:** Ayyaz Ali, 10 Sandringham Drive, Stockport, Cheshire, United Kingdom, Tel: + 44 0161 432 0225; E-mail: ayyaz75@gmail.com

Received March 15, 2013; **Accepted** May 03, 2013; **Published** May 06, 2013

Citation: Ali AA, White C, Freed D, Ali Z, Large S (2013) Ethicality of Heart Transplantation from Donation after Circulatory Death Donors. J Clin Exp Cardiolog S9: 006. doi:10.4172/2155-9880.S9-006

Again their argument was that beyond this time auto resuscitation of the heart and circulation has never been described. Opponents of such short waiting times argue that through external stimulation, the heart can easily be resuscitated well beyond this duration [12]. The counter argument is that in the DCD donor, a deliberate decision has been made not to undertake any form of resuscitation with the aim of potentially restoring life in that individual. Therefore beyond a period where auto resuscitation is not possible, a definitive certification of death can be made. Protocols for preservation and procurement utilized by Boucek and colleagues and those at the University of Pittsburgh were designed to favour the recipient. They emphasize that once an individual is identified as a donor, efforts should be directed towards ensuring that the organ of interest is procured in an optimal state providing the intended recipient with the best opportunity for recovery of their health.

In the DCD donor, organs are susceptible to injury during several phases of the procurement process. Withdrawal of support involves discontinuation of supportive medications such as vasopressors for maintenance of blood pressure and inotropes for augmentation of hemodynamic function. The termination of ventilatory support is also a critical step which is often followed by rapid deterioration of the donor's condition. Extubation of the donor is commonly undertaken and inability of the donor to support their airway results in severe hypoxia precipitating hypoxic cardiac arrest. Cumulatively these interventions result in hypotension, hypoxia and metabolic derangement within the DCD donor. The duration between withdrawal of support and definitive loss of circulation is referred to as the agonal phase. Its duration varies widely and when it becomes protracted concerns over accumulating organ injury begin to arise. The "no-touch" period which follows circulatory arrest, corresponds to the onset of warm ischemia within the DCD donor. Once this has elapsed measures are undertaken to prepare the donor for organ procurement. This involves transportation of the donor to the operating room, followed by sterile preparation and commencement of the retrieval operation. Organs remain vulnerable to warm ischemic injury until some method of perfusion is established. Every effort is made to minimize the duration of the warm ischemic period. Exact protocols for the retrieval of organs from DCD donors vary widely from one institution to another.

In our local center for DCD organ transplantation, withdrawal of support is currently undertaken in a neuro-intensive care unit which specializes in the treatment of patients with severe neurological injuries. Both BSD and potential DCD organ donors are identified at this site. Termination of supportive therapy is undertaken within the ICU itself after family members have been given adequate time to spend with their deceased relative. Following circulatory arrest, the donor is promptly transferred to the operating theatre so that surgical retrieval of organs can commence. The transfer process takes approximately 10 minutes, during which time all organs are potentially exposed to warm ischemic injury. For this reason many institutions withdraw supportive therapy either within an anaesthetic area adjacent to the operating theatre or within the operating theatre itself, thereby minimizing the period of warm ischemia. The final phase of warm ischemia is associated with the time required for sterile preparation of the donor. Subsequently an incision is made to gain access to the relevant body cavity to allow cannulation of appropriate vessels for institution of some form of perfusion. This is achieved either using cold crystalloid solutions or following establishment of ECMO reperfusion of the DCD donor. The duration between surgical preparation and cannulation for central ECMO in our human DCD donor was under 5 minutes [3]. Therefore, withdrawal of support and circulatory arrest within the operating room can markedly reduce the duration of ischemia to which organs are exposed prior to procurement. It is at this stage where resuscitation of the heart raises ethical concerns. In a donor whose eligibility for donation has been defined by the absence of any effective cardiac function, is it appropriate to restore circulation by artificial means with a view to restoring heart beat? Proponents of heart transplantation from DCD donors argue that the purpose for withdrawing therapy and precipitating circulatory arrest in this setting is to establish irreversible injury to the brain. The of prospective DCD donors already have a degree of neurological injury. However, this falls short of criteria required for diagnosis of BSD. Consequently, conventional heart-beating donation cannot be undertaken.

In our case of cardiac resuscitation within a human DCD donor, a warm ischemic time of 23 minutes was observed prior to reperfusion of the heart and other organs [3]. Notably there was no perfusion of the brain as a large clamp was placed across the aortic arch and great vessels prior to reperfusion. The pre-morbid neurological status of this donor was already very grave with a GCS of 3. Exposure of the brain to another 23 minutes of normothermic ischemia surely would have led to irreversible ischemic injury of both the cerebral cortex as well as the brain-stem. Essentially, it can be argued that this process converts the DCD donor into a BSD heart-beating donor through institution of an artificial circulation. Such measures may seem extreme, but it can be suggested that a carefully planned decision has already been made in the DCD donor to withdraw support on the basis of futility of further treatment measures. Accordingly, once a decision to donate has been made it may be best for the donor, the donor's family, the recipient and transplantation as a whole that maximal benefit is obtained from the brave and selfless act of organ donation. In our protocol of in-vivo ECMO resuscitation of the heart it must be emphasized that after the certification of death cerebral reperfusion is never undertaken. Therefore it can be comprehensively stated that the brain including the brain-stem have ceased to function. The corpse of the DCD donor is utilized for the initial resuscitation and preservation of organs, whether achieved through cold perfusion or warm blood reperfusion. The ethicality of this can be questioned and this leads to the discussion as to whether extracorporeal resuscitation of organs procured from DCD donors may be more appropriate. Machine perfusion of donor organs has been extensively investigated over the past three decades and considerable advances have been made in the technology of such strategies [3].

Intervention in the DCD Donor Prior to Circulatory Arrest

The level of intervention in the DCD donor prior to withdrawal of support is also an ethically controversial area. Some advocate that absolutely no treatment of the donor prior to circulatory arrest is justified. Undoubtedly, certain measures such as the administration of heparin prior to removal of support would greatly facilitate the conduct and safety of the procurement process. Currently in the U.K. no procedures or treatment of the DCD donor is considered appropriate until after the certification of death. In the United States and some European countries treatment and interventions in the DCD donor prior to circulatory arrest are routinely undertaken [3-5]. One of the earliest experiences of ECMO resuscitation of DCD organs was described at the University of Michigan who utilized this for renal perfusion and preservation prior to renal transplantation [4,5]. Their protocol included the administration of heparin and insertion of percutaneous femoral and venous arterial cannulae for establishment of ECMO prior to termination of support. After circulatory arrest the

donor was promptly connected to an extracorporeal perfusion circuit for institution of ECMO. This minimized the warm ischemic time and eliminated the need for expeditious and hurried surgical manoeuvres to establish perfusion. From a logistical viewpoint such a protocol would be ideal and allow for the establishment of perfusion under completely controlled circumstances. Although the results of DCD liver and renal transplantation from controlled donors are largely similar to those of transplantation of organs from BSD donors, there is an increased incidence of primary donor organ dysfunction and graft failure [13,14]. Although this is uncommon, its incidence could potentially be reduced by further minimizing warm ischemic time through earlier intervention in the donor after the decision to withdraw support. It can be argued that at this time the prospective donor has already been consented for organ donation and that any procedures which are not excessively intrusive or harmful should be considered entirely appropriate.

Method and Site for Reperfusion of non-heart Beating Organs

Our protocol for cardiac resuscitation in the DCD donor incorporated the use of ECMO to establish in-vivo reperfusion of the donor. This is followed by the delivery of oxygenated blood to the coronary circulation which resulted in recovery of cardiac function. As discussed above the institution of an artificial circulation with cardiac reanimation and recovery of heart beat has raised many concerns. Such concerns could be completely abolished by explanting the organ from the donor and commencing ex-vivo reperfusion using an extracorporeal perfusion device. This would avoid the re-establishment of circulation by artificial means in an organ donor who has been certified dead on the basis of absence of heart beat and circulation.

Both ex-vivo and in-vivo methods for reperfusion have their own advantages and drawbacks. In-vivo reperfusion can be established more rapidly, which is of considerable value when considering that minimization of warm ischemic time is a primary aim of DCD organ retrieval. Vascular cannulae can be promptly inserted into large peripheral vessels, often via the percutaneous route, allowing rapid institution of perfusion. Percutaneous insertion of catheters avoids the need for large surgical incisions and the expenditure of time required for the dissection and isolation of vessels prior to cannulation and perfusion. In regions where donor intervention prior to circulatory arrest is permitted, this allows for immediate reperfusion of the donor after the stand-off period has elapsed. In-vivo perfusion may allow for more homeostatic perfusion of organs. Recovery of renal and liver function upon perfusion could allow for detoxification of the donor circulation, with removal of acid and metabolites produced during the warm ischemic period. Such metabolic washout may be problematic if isolated organs are perfused ex-vivo. Conversely, we have identified the potential for in-vivo reperfusion to produce an adverse internal milieu within the DCD donor. Reperfusion of the porcine DCD donor was associated with massively elevated plasma catecholamine levels, considerably greater than those seen in BSD [15]. The deleterious effects of excessive catecholamine exposure on cardiac function at both the molecular and macroscopic levels, along with purported contributions towards an exaggerated inflammatory response and adverse immunomodulatory effects, are amongst the many reasons why it would be preferential to avoid such a response [16-18]. Specific interventions must be taken to avoid cerebral reperfusion in association with in-vivo reperfusion. The impact of restoring cerebral circulation in donors who already have critical brain injury is uncertain. Although it is unlikely that this would result in restoration of consciousness, theoretical concerns and uncertainty over the effects of cerebral reperfusion after certification of death have the potential to provoke considerable anxiety.

Ex-vivo organ perfusion would address many of the ethical concerns associated with restoration of circulation in the DCD donor. Isolated organ perfusion could allow for the use of purposefully engineered perfusion solutions designed with an aim to minimize organ injury on reperfusion. Conversely, in-vivo reperfusion is predominantly undertaken using the donors own blood which as mentioned above contains organic acids, metabolites and unfavourable circulating mediators produced during warm ischemia. However, we have demonstrated in all subjects, human and animal, that the metabolic environment can be treated at the time of initial in-vivo reperfusion with subsequent restoration and maintenance of near normal blood biochemistry [4,15]. *Ex-vivo* machine perfusion can also potentially serve as a transport apparatus allowing for continuous perfusion and resuscitation of the organ up until the time of transplantation. However, despite considerable experimental experience with machine perfusion of donor organs and despite its feasibility, this technique has never gained widespread acceptance in the clinical setting. The complexities of establishing machine perfusion and the need for careful monitoring of the perfused organ are amongst some of the associated logistical considerations. Technological advances and simplification of devices and protocols for ex-vivo reperfusion are necessary if this is to become an established method for resuscitating DCD organs. Due to considerable ethical concerns associated with in-vivo cardiac resuscitation, the introduction of a reliable means for recovering the organ outside of the donor's body may be of critical importance in establishing the DCD donor as a routine source of organs for heart transplantation.

Comment

At the dawn of transplantation, the dead donor rule was introduced to guide the transplantation of organs from one individual to another. This rule stated that the removal of any vital organs for transplantation could only occur after death of the donor had been certified. In order to facilitate organ donation and stimulate transplantation surgery, efforts were made to equate devastating neurological injury with irreversible loss of circulation and respiration. This led to development of the concept of brain death and its inception had a dramatic impact on organ transplantation [19,20]. Organs could be safely removed from the donor in a relatively stable setting, reducing the logistical difficulties associated with the procurement of organs after cardiac arrest. Despite large scale acceptance of brain death there remain persistent questions as to whether patients with severe brain injury, and loss of brain-stem reflexes and apnoea can be regarded as dead. Some maintain arguments that these patients continue to retain essential neurological function and that if maintained through their acute illness they can survive for many years. Certainly, this places these definitions in conflict with the dead donor rule. Essentially, society and its laws have identified that this group of individuals with critical brain injury have no prospect for any meaningful recovery. Consequently, with appropriate consent the removal of organs for transplantation is considered ethically and legally appropriate. However, if the concept of brain death and the criteria developed for its diagnosis were to be intensely scrutinized, sufficient doubt could be raised as to whether brain dead donors could actually be regarded as being dead.

The re-emergence of organ donation from DCD donors has triggered further debate. The great majority of patients considered for DCD donation have also suffered severe neurological injury. However,

this falls short of fulfilling criteria for BSD. Therefore despite having suffered a profound and irreversible neurological insult they cannot be legally considered to be brain dead. Consequently, alternative strategies must be enlisted to render these donors eligible for organ donation. In fact, many donors who previously would have progressed towards brain death receive neurosurgical treatment aimed at preventing increases in intracranial pressure which culminate in BSD. In the majority of patients with such extensive neurological dysfunction the prognosis remains extremely poor and this is recognized by physicians and family alike. A decision to withdraw all supportive measures is undertaken and cardiac arrest is awaited. Once this is established a period of observation is necessary before the certification of death. A period of 2 minutes is considered to be the minimum duration which needs to elapse before confirming death. The cardiac definition of death is based on irreversible loss of cardiac function. In the setting of DCD donation, even after the certification of death the heart can be resuscitated either through institution of conventional CPR or using more invasive measures such as establishment of an artificial circulation. The fact that the heart can recover function challenges the diagnosis of death and the requirement for irreversible loss of function. As a consequence, whether the dead donor rule can be considered to be fulfilled in such circumstances is highly questionable.

It is imperative that the donor is safeguarded and that legal and ethical boundaries are carefully respected during the process of organ donation. Accordingly, the recipient must also be protected and every assurance is necessary that any organ procured for transplantation should offer the patient the best possible chance for regaining their health. The acquisition of informed consent from the donor and their next of kin represents the most important component of the donation process. Once a firm approval for the donation of organs has been obtained it can be argued that from this point onwards efforts should be concentrated towards optimizing the quality and quantity of organs due to be removed from the donor. As DCD organ donation continues to contribute towards an increasing proportion of organs for transplantation, our current perceptions related to the requirements for death may need to evolve for the optimal utilization of this donor population. Further emphasis needs to be placed on the role of informed consent for organ donation. Once this has been obtained it should be recognized that an agreement has been reached by all involved in the care of the patient in question, including next of kin, that their condition is terminal and will not benefit from any further treatment. Therefore, any attempts to resuscitate that individual for restoring life are unjustified as it will not alter their premorbid condition. Accordingly, an agreement to organ donation recognizes that individual organs within any such patient continue to possess sufficient function such that they may benefit other individuals through their removal and subsequent transplantation. In the context of cardiac donation from DCD donors, it must be appreciated that the heart can and will recover function if specific resuscitative measures are undertaken. In order for cardiac donation from this donor group to be considered feasible, the procurement of these organs must be achieved in a manner considered to be ethically appropriate. Currently there has been minimal debate related to this topic as it has largely been considered that cardiac donation from DCD donors is unfeasible on the basis that these organs would not remain viable after circulatory arrest. Our work has demonstrated the opposite and confirms that the heart does in fact remain viable and can regain sufficient function to be considered for transplantation [3,15]. Consequently, focused debate is necessary within the transplant community to establish ethically and scientifically appropriate protocols for procuring these organs.

References

1. http://www.organdonation.nhs.uk/ukt/statistics/latest_statistics/latest_statistics.jsp
2. Barnard CN (1967) The operation. A human cardiac transplant: an interim report of a successful operation performed at Groote Schuur Hospital, Cape Town. S Afr Med J 41: 1271-1274.
3. Starzl TE, Marchioro TL, Vonkaulla KN, Hermann G, Brittain RS, et al. (1963) Homotransplantation Of The Liver In Humans. Surg Gynecol Obstet 117: 659-676.
4. Ali A, White P, Dhital K, Ryan M, Tsui S, et al. (2009) Cardiac recovery in a human non-heart-beating donor after extracorporeal perfusion: source for human heart donation? J Heart Lung Transplant 28: 290-293.
5. Wang CC, Wang SH, Lin CC, Liu YW, Yong CC, et al. (2005) Liver transplantation from an uncontrolled non-heart-beating donor maintained on extracorporeal membrane oxygenation. Transplant Proc 37: 4331-4333.
6. Jimenez-Galanes S, Meneu-Diaz MJ, Elola-Olaso AM, Perez-Saborido B, Yilliam FS, et al. (2009) Liver transplantation using uncontrolled non-heart beating donors under normothermic extracorporeal membrane oxygenation. Liver Transpl 15:1110-1118.
7. Gravel MT, Arenas JD, Chenault R 2nd, Magee JC, Rudich S, et al. (2004) Kidney transplantation from organ donors following cardiopulmonary death using extracorporeal membrane oxygenation support. Ann Transplant 9: 57-58.
8. Rudich SM, Kaplan B, Magee JC, Arenas JD, Punch JD, et al. (2002) Renal transplantations performed using non-heart-beating organ donors: going back to the future? Transplantation 74: 1715-1720.
9. Herdman R, Beauchamp TL, Potts JT (1998) The Institute of Medicine's report on non-heart-beating organ transplantation. Kennedy Inst Ethics J 8: 83-90.
10. de Begona JA, Gundry SR, Razzouk AJ, Boucek MM, Kawauchi M, et al. (1993) Transplantation of hearts after arrest and resuscitation. Early and long-term results. J Thorac Cardiovasc Surg 106: 1196-1201.
11. DeVita MA, Snyder JV (1993) Development of the University of Pittsburgh Medical Center policy for the care of terminally ill patients who may become organ donors after death following the removal of life support. Kennedy Inst Ethics J 3: 131-143.
12. Lynn J (1993) Are the patients who become organ donors under the Pittsburgh protocol for "non-heart-beating donors" really dead? Kennedy Inst Ethics J 3: 167-178.
13. Abt PL, Desai NM, Crawford MD, Forman LM, Markmann JW, et al. (2004) Survival following liver transplantation from non-heart-beating donors. Ann Surg 239: 87-92.
14. Kaczmarek B, Manas MD, Jaques BC, Talbot D (2007) Ischemic cholangiopathy after liver transplantation from controlled non-heart-beating donors-a single-center experience. Transplant Proc 39: 2793-2795.
15. Ali AA, White P, Xiang B, Lin HY, Tsui SS, et al. (2011) Hearts from DCD donors display acceptable biventricular function after heart transplantation in pigs. Am J Transplant 11: 1621-1632.
16. Novitzky D, Wiscomb WN, Cooper DKC, Rose AG, Fraser RC, et al. (1984) Electrocardiographic, haemodynamic, and endocrine changes occurring during experimental brain death in the chacma baboon. Heart Transplant 4: 63-69.
17. White M, Wiechmann RJ, Roden RL, Hagan MB, Wollmering MM, et al. (1995) Cardiac beta-adrenergic neuroeffector systems in acute myocardial dysfunction related to brain injury. Evidence for catecholamine-mediated myocardial damage. Circulation 92: 2183-2189.
18. Osaki S, Ishino K, Kotani Y, Honjo O, Suezawa T, et al. (2009) Circulatory load during hypoxia impairs post-transplant myocardial functional recovery in donation after cardiac death. J Heart Lung Transplant 28: 266-272.
19. Beecher HK, Adas RD, Barger AC, the Ad Hoc Committee of the Harvard Medical School: Report of the ad hoc committee of the Harvard Medical School to examine the definition of brain death. A definition of irreversible coma. JAMA 205: 85-88.
20. A definition of irreversible coma. Report of the ad hoc committee of the Harvard Medical School to examine the definition of brain death. JAMA 205: 337-340.