

Heart Transplantation Using Donors after Circulatory Death: From Research to Clinical Practice

Trasplante cardíaco utilizando donantes cadavéricos. De la investigación a la práctica clínica

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ABSTRACT

Donation after circulatory death for heart transplantation was abandoned in the 1970s with the advent of the brain death law (donation after brain death), where the donor heart is beating and perfused up to the moment prior to organ retrieval. Shortage of donors has renewed the interest in animal and clinical research of donors after circulatory death for heart transplantation, aiming at optimizing heart function after the period of oxygen deprivation caused by severe hypotension and subsequent circulatory arrest. This study presents the initial experience with donation after circulatory death for heart transplantation at our institution. Papworth Hospital has performed a successful clinical investigation in which ten cardiac transplants were performed with hearts from donation after circulatory death, without mortality. Low risk recipients who had previously signed their consent were chosen. Most hearts from donation after circulatory death were reperfused with an extracorporeal circulation device, and following weaning from the circulatory support the heart was harvested and connected to the perfusion machine for transportation and simultaneous assessment of function before implantation. In conclusion, this technique could be used for cardiac transplantation with satisfactory outcomes.

Key words: Heart transplantation/methods - Organ preservation/methods - Tissue donor/classification - Tissue and Organ Procurement/methods - Cardiac arrest, induced

RESUMEN

Los donantes cadavéricos para trasplante cardíaco se abandonaron en la década de los setenta con el advenimiento de la ley de muerte cerebral (cadáveres con corazón latiendo), en los cuales el corazón se halla latiendo y perfundido hasta último momento previo al explante. La escasez de donantes ha reavivado el interés en la investigación en animales y clínica con el fin de utilizar donantes cadavéricos para trasplante cardíaco, intentando optimizar la función cardíaca luego del período de privación de oxígeno producido por la hipotensión muy pronunciada y la detención circulatoria posterior. Se presenta la experiencia inicial de trasplante cardíaco con donantes cadavéricos en nuestra institución. El Papworth Hospital ha realizado una investigación clínica exitosa, efectuando diez trasplantes cardíacos con donantes cadavéricos, sin mortalidad. Se eligieron recipientes de riesgo bajo con consentimiento previo. Los donantes cadavéricos fueron, en su mayoría, reperfundidos con el uso de dispositivo de circulación extracorpórea y, luego de ser destetados del apoyo circulatorio, en todos los casos el corazón fue explantado y conectado a la máquina de perfusión para ser trasladado y a la vez evaluado en su función para proceder al implante. En conclusión, esta técnica se podría utilizar para trasplante cardíaco con buenos resultados.

Palabras clave: Trasplante de corazón/métodos - Preservación de órganos - Donantes de tejidos - Obtención de tejidos y órganos - Paro cardíaco inducido

INTRODUCTION

Until recently, only heart-beating donors after brain death (DBD) were considered candidates for heart transplantation (HTx), as the heart remains perfused until the moment of organ retrieval. This strategy allowed better results than those obtained in the initial period of HTx with donation after circulatory death (DCD), in which both the donor and the recipient

were operated on in contiguous operating rooms to minimize the warm ischemic period.

The introduction of the brain death law in the middle 1970s ("beating heart cadavers") implied abandoning the retrieval of DCD hearts for HTx. However, the growing number of patients in waiting list worldwide compared with donor shortage has renewed the medical community interest in animal and clinical DCD re-

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search to achieve the excellent results obtained with DBD, as it would allow an increase of 10% to 17% in the number of HTx per year. Papworth hospital is currently the world leader in the number of HTx using DCD. After an initial clinical research program showing the effectiveness of the procedure, this technique, which has been performed in two hospitals of the country, has already been accepted in the United Kingdom and will probably extend shortly to other European countries. The aim of this study is to present the initial experience with DCD at our institution.

Donation after circulatory death describes donors with irreversible brain damage or in whom death is unavoidable based on the futility of any type of treatment, but who do not meet the formal parameters of DBD according to current tests. If the family decides to abandon the therapeutic treatment that keeps them "alive", the technical process is carried out taking the donor to the anesthesia room beside the operating room and interrupting respiratory and circulatory support. This starts the "agonic period", before which legal and ethical reasons do not allow heparinization, or cannulation, or the introduction of any type of catheter, or echography studies, which would be very useful to provide greater safety and speed to shorten the warm ischemic period. Once death is confirmed, and after 5 minutes, the donor is transferred to the operating room for organ retrieval with two surgical teams acting simultaneously in the thorax and abdomen.

In the DCD clinical program for HTx, the warm ischemic period must be under 30 minutes, (1) based on experimental studies at the University of Wisconsin showing that after 40 minutes, contractility and relaxation indicators are significantly impaired. The warm ischemic period is the time extending between systolic pressure drop to less than 50 mmHg during the agonic period until, after death, the heart is reperfused with blood using extracorporeal circulation or is subjected to cold ischemia by aortic clamping and administration of a cardioplegic solution with nutrients, depending on the technique used.

In all cases, recipients must sign an informed consent approving the reception of a DCD organ, accepting that mid-term and long-term prognosis are unknown using this alternative. Low-risk recipients, in terms of pulmonary vascular resistance and low transpulmonary pressure gradient, were chosen for this initial clinical research, excluding those with circulatory mechanical support. Due to the favorable results of this experience, patients in the intensive care unit with urgent transplantation status and biventricular Centrimag pump support, who could not be weaned from mechanical assistance while awaiting transplantation, were incorporated in the program.

The inclusion and exclusion criteria are similar to DBD, except for donor age; although the committee established a range between 18 and 60 years, the preference is donors under 40 years, as high risk for DCD is considered above this age.

The procedure is based on the following stages: reestablishment of cardiac function, organ transport preserved with continuous blood perfusion, organ evaluation during transportation and finally organ implant.

Reestablishment of cardiac function or heart "resuscitation" can be performed in two ways.

Direct retrieval and connection to the OCS (Organ Care System) perfusion device.

This was the procedure used at St Vincent Hospital, in Sydney, Australia, in the first 4 successful adult transplants. Moreover, it is the standard procedure selected by the Cardiothoracic Advisory Group Committee of the United Kingdom, for being logistically more feasible.

Once in the operating room, the DCD donor is reintubated, and immediately after, a bronchoscopy is performed. Simultaneously (or eliminating bronchoscopy if the lungs are not evaluated), median sternotomy and pericardial opening is performed. The right atrium is minimally opened and blood cell saver aspiration is started with the operating table in Trendelenburg position. Donor blood (1.2 to 1.5 liters) is withdrawn by gravity during one minute and mixed with heparinized solution for priming the OCS device to reperfuse the organ (Figure 1). The aorta is clamped, the inferior vena cava is sectioned, the left atrium is vented through the left inferior pulmonary vein or the left atrial appendage according to whether only the heart or the heart-lung are removed, and 800 to 1,000 ml of cold cardioplegic solution with nutrients are injected in the ascending aorta. The heart is removed using a different technique depending on whether the lungs are simultaneously harvested, and then it is rapidly connected to the OCS device to initiate continuous perfusion and proceed with heart resuscitation of the "ex vivo" donor (Figure 1).

Organ retrieval with regional normothermic perfusion (RNP). "Cadaveric reperfusion"

This type of procedure has been used in 9 out of 10 cases in Papworth Hospital, as in 3 hospitals around Papworth it was agreed that it is logistically feasible. Its use is still debated for ethical considerations, as it could be inferred that it implies "cadaver resuscitation". If necessary, initial intubation, and bronchoscopy maneuvers similar to direct harvesting are performed, with simultaneous sternotomy, pericardial opening and aortic arch branch clamping to optimize regional perfusion and ensure absolute impossibility of brain cortex and stem oxygenation. Heparin injection in the right atrium (RA), arterial cannulation of the distal ascending aorta and venous cannulation of the right atrium are performed. Regional normothermic perfusion is started using an extracorporeal membrane oxygenator (ECMO) circulation circuit. The time between donor transfer to the operating room and onset of perfusion should be shortened to a minimum.

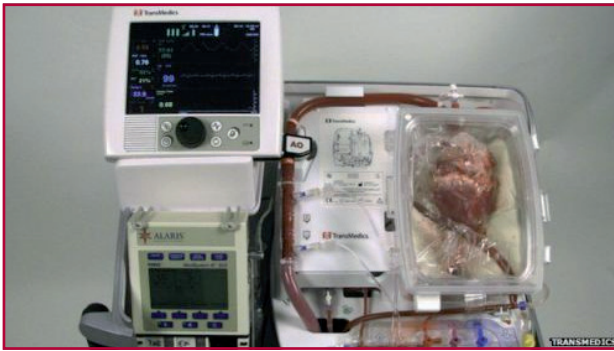


Fig. 1. Transmedics OCS (Organ Care System)

Simultaneously with sternotomy, arterial, central venous and Swan-Ganz catheters, as well as a transesophageal echo probe are inserted and continuous dopamine (5 micg/kg/min) and vasopressin (4U/h) administration is started. Once RNP is installed, the surgeons who remove the abdominal organs start dissection. After a variable RNP period, which initially lasted 50 minutes, but which has recently been successfully shortened (depending on the heart's response to decreasing flow and increased preload, as after routine cardiopulmonary bypass), progressive ECMO weaning is started and heart function is evaluated using hemodynamic parameters (cardiac index, pulmonary and wedge pressures, right atrial pressure, mixed venous oxygen saturation) and transesophageal echocardiography imaging. If function is adequate, blood is withdrawn by gravity for OCS priming, as previously explained. Then, aortic clamping is performed and cold crystalloid cardioplegic solution is injected to preserve the organ during the short period until connection to the OCS; finally, the heart is removed.

Transport, preservation, and metabolic and functional assessment of the heart

In an accessory, contiguous table, the aorta and PA are cannulated. The organ is immediately connected to the OCS and is reperfused with donor blood obtained before organ retrieval and other priming nutrients. An oxygenator is part of the circuit and perfusion temperature is 34° C. A perfusion pressure between 65 and 85 mmHg, 1,000 mL/min aortic flow and coronary flow between 650 and 8500 mL/min are established. Blood circulates in the OCS as in an extracorporeal circulation circuit. Arterial and venous blood samples are mainly obtained for lactic acid dosage every 15 minutes, and arteriovenous difference is determined. Also, myocardial contractility improvement is visually monitored, though this is a parameter of relative value, as the heart is beating "empty" in unloaded conditions and with the left atrial outlet draining into the machine reservoir. A descending trend in the lactate curve and good myocardial contractility are indirect signs of adequate coronary perfusion, recovery and preserved myocardial function.

An interesting advantage of the OCS is its ability of maintaining the heart ex-vivo for a longer period of time and more safely than cold preservation, as it is constantly reperfused with functional assessment. This allows acting more calmly in the calculation of times between harvesting and implantation, which is of great value in receptors with mechanical circulatory assistance or previous cardiac surgery in whom organ dissection is often complex, as the donated organ can be in the operating room connected to the OCS and "beating" while awaiting implantation. It also offers clear advantages in case of longer transfer in which "cold" ischemia would be more prolonged, considering that this is an independent primary organ failure factor.

Papworth Hospital clinical experience

Ten heart transplants with DCD donors were performed from March 2015 to August 2015, without mortality. Donor age ranged between 28 and 43 years. Only one case had primary organ dysfunction, mainly due to right ventricular failure, requiring balloon counterpulsation and ECMO support for 5 days, with functional recovery. All patients were discharged from hospital. To date, this is the world's largest experience in this type of transplantation. Reoperation for bleeding was performed only in the patient requiring ECMO, and receiving a total of 42 blood units during hospitalization. The heart transplantation research project with DCD donors was evaluated and approved by the hospital Ethics Committee. Moreover, this procedure is analyzed by an independent organ donation and transplant ethics committee of the United Kingdom.

Heart transplantation is still the treatment of choice for end-stage heart failure in terms of survival and significant improvement in quality of life. Organ shortage has been a decisive factor in HTx reduction worldwide, turning DCD as an attractive option to increase HTx in the future and reduce waiting list mortality. Previous research in animals has allowed the safe use of this technique. (1-5) A drawback for this option is the significant increase in costs due to the use of the OCS, but this is a fact that should be analyzed in detail comparing it with the cost of maintaining a growing number of patients with mechanical circulatory support or rehospitalizations for decompensated heart failure.

Between the two strategies, Papworth Hospital used perfusion with ECMO in nine out of ten cases, and removed the heart directly with connection to the OCS on two occasions, one organ of which was discarded for malfunctioning and the other was implanted with good outcome and without primary dysfunction. The experience of Australia, pioneer in the world in 2014, was direct retrieval and connection to the OCS. Professor Kumus Dithal of St Vincent Hospital in Sidney, the surgeon who performed these interventions, worked at Papworth Hospital in the past

decade, participating in research projects in these 10 years before moving to Australia. The United Kingdom Committee asked him to be advisor and external auditor of the program, and review it after a predetermined number of cases were transplanted with this technique. (6)

ECMO “resuscitation” and its subsequent weaning prior to removal has the important advantage of assessing the heart in physiological conditions (preload and pulmonary and peripheral vascular resistances). The disadvantage is extracorporeal circulation, with inflammatory response and elevated catecholamine level that could potentially impact on the donor heart, in addition to the already mentioned ethical considerations. Heart “resuscitation” and preservation after harvesting is vital. Continuous perfusion with the OCS is superior to cold preservation, as in the latter case, low anaerobic metabolic levels persist, with decreasing cell energy reserve and metabolic acidosis. Moreover, the OCS affords significant prolongation of the “ischemic” time, which is the weakest point of cold storage, as well as cardiac function monitoring during transportation, facilitating the final decision to determine whether the heart is suitable to be implanted.

The United Kingdom Committee will perform periodical audits to determine:

- The retrieval rate: relationship between the number of DCD offers and the number of hearts placed in the OCS
- The conversion rate: relationship between the number of organs placed in the OCS and the number of hearts effectively implanted
- Clinical effectiveness: Morbidity, Mortality, Logistics, and Costs.

In conclusion, technological advances and extensive animal and clinical research have allowed good DCD outcomes, adding to the successful use of lungs and abdominal organs in this type of donors. The removal and technique strategy, and the potential advantage of regional normothermic perfusion remain to be elucidated.

Invited comment:

Heart transplantation is the gold standard therapy for patients suffering from end stage heart failure. However, the demand of donor hearts far outweighs the supply, leading to increased number of deaths in the waiting list (10 to 20%). Several initiatives have been adopted to enhance the consent rate and early donor management to increase the number of heart transplantations, but this has remained under 150/year in the United Kingdom.

Until recently, hearts were retrieved only from Donation after Brain Death (DBD) donors who are older, have multiple co-morbidities and are often marginal hearts.

In his paper, Dr Knop illustrates that heart transplantation from DCD donors is feasible.

A hospital in Sydney has been the first to demonstrate successful adult heart transplantation from DCD donors. Thereafter, Papworth Hospital and Harefield Hospital, both in the United Kingdom, have successfully performed a series of heart transplants from DCD donors. In these cases, after the heart has been removed, it is placed in the Organ Care System (OCS) restoring its function. Once the heart is beating again the surgeon will determine whether it is suitable for transplantation. The current worldwide experience in adult DCD heart transplantation is 19 heart implants, with only 1 death. Introduction of this technique is the next big revolution in heart transplantation and puts the heart at par with other organs as lungs and kidneys that can be procured from both DBD and DCD donors. Dr Knop describes the state of the art of this technique and provides a detailed insight into this exciting development.

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