Adult heart transplantation with distant procurement and ex-vivo preservation of donor hearts after circulatory death: a case series

Kumud K Dhital, Arjun Iyer, Mark Connellan, Hong C Chew, Ling Gao, Aoife Doyle, Mark Hicks, Gayathri Kumarasinghe, Claude Soto, Andrew Dinale, Bruce Cartwright, Priya Nair, Emily Granger, Paul Jansz, Andrew Jabbour, Eugene Kotlyar, Anne Keogh, Christopher Hayward, Robert Graham, Phillip Spratt, Peter Macdonald

Summary

Background **Orthotopic heart transplantation is the gold-standard long-term treatment for medically refractive end-stage heart failure. However, suitable cardiac donors are scarce. Although donation after circulatory death has been used for kidney, liver, and lung transplantation, it is not used for heart transplantation. We report a case series of heart transplantations from donors after circulatory death.**

Methods **The recipients were patients at St Vincent's Hospital, Sydney, Australia. They received Maastricht category III controlled hearts donated after circulatory death from people younger than 40 years and with a maximum warm ischaemic time of 30 min. We retrieved four hearts through initial myocardial protection with supplemented cardioplegia and transferred to an Organ Care System (Transmedics) for preservation, resuscitation, and transportation to the recipient hospital.**

Findings **Three recipients (two men, one woman; mean age 52 years) with low transpulmonary gradients (<8 mm Hg) and without previous cardiac surgery received the transplants. Donor heart warm ischaemic times were 28 min, 25 min, and 22 min, with ex-vivo Organ Care System perfusion times of 257 min, 260 min, and 245 min. Arteriovenous lactate values at the start of perfusion were 8·3–8·1 mmol/L for patient 1, 6·79–6·48 mmol/L for patient 2, and 7·6–7·4 mmol/L for patient 3. End of perfusion lactate values were 3·6–3·6 mmol/L, 2·8–2·3 mmol/L, and 2·69–2·54 mmol/L, respectively, showing favourable lactate uptake. Two patients needed temporary mechanical support. All three recipients had normal cardiac function within a week of transplantation and are making a good recovery at 176, 91, and 77 days after transplantation.**

Interpretation **Strict limitations on donor eligibility, optimised myocardial protection, and use of a portable ex-vivo organ perfusion platform can enable successful, distantly procured orthotopic transplantation of hearts donated after circulatory death.**

Funding **NHMRC, John T Reid Charitable Trust, EVOS Trust Fund, Harry Windsor Trust Fund.**

Introduction

The first successful clinical heart transplantation was done with a heart donated after circulatory death in 1967 by Christiaan Barnard and the South African Groote Schuur Hospital team.[1] In that era, before the establishment of brain-stem death criteria, numerous heart transplantations were carried out around the world with the donor and recipient located in adjacent operating rooms.[2] The introduction of brain-death legislation and the adoption of cardioplegic arrest and static cold preservation, enabled distant procurement and avoided the necessity of transferring donors to the recipient hospital.

Unlike hearts from brain-dead donors who still have a beating heart, for which cardiac structure and function can be assessed after death, hearts donated after circulatory death have unknown functional status, risk of occult pathology, and substantial warm ischaemic insult. The difficulties of assessing the suitability of hearts donated after circulatory death and of co-locating multiorgan donors and recipients has meant that heart transplantation has had to rely solely on donation after brain death.

New policies related to donation after circulatory death have aimed to narrow the gap between the number of patients awaiting a new heart and the number of suitable organs available.[3] Use of organs donated after circulatory death has improved the number and outcomes of kidney and lung transplantation,[4,5] and to a lesser extent, liver transplantation.[6]

A series of three successful paediatric heart transplantations from colocated neonatal donors after circulatory death was described in 2008,[7] in whom in-situ cooling following pre-withdrawal heparinisation and insertion of femoral cannulae were done. In 2009, in-situ resuscitation of an adult human heart donated after circulatory death with subsequent weaning from cardiopulmonary support was reported.[8] The major hurdles to the transplantation of hearts from human donors after circulatory death are the ability to mitigate warm

Lancet 2015; 385: 2585–91

Published Online
April 15, 2015
http://dx.doi.org/10.1016/S0140-6736(15)60038-1

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Heart & Lung Transplant Unit (K K Dhital FRCS-CTh, A Iyer MBBS, M Connellan FC Cardio (SA), H C Chew MS, E Granger MBBS, P Jansz PhD, A Jabbour PhD, E Kotlyar MD, Prof A Keogh MBBS, Prof C Hayward MD, P Spratt FRACS, Prof P Macdonald MD), **Department of Cardiothoracic Surgery** (K K Dhital, A Iyer, M Connellan, H C Chew, C Soto MSc, A Dinale BAppSc, E Granger, P Jansz, P Spratt), **Department of Cardiology** (A Jabbour, E Kotlyar, Prof A Keogh, Prof C Hayward, Prof R Graham MD, Prof P Macdonald), **Department of Anaesthesia** (B Cartwright MBBS), **Department of Clinical Perfusion** (C Soto, A Dinale), **Department of Clinical Pharmacology** (M Hicks PhD), **and Department of Intensive Care** (P Nair FCICM), **St Vincent's Hospital, Sydney, NSW, Australia; The Victor Chang Cardiac Research Institute, Sydney, NSW, Australia** (K K Dhital, A Iyer, H C Chew, L Gao PhD, A Doyle MEngSc, M Hicks, G Kumarasinghe FRACP, A Jabbour, Prof R Graham, Prof P Macdonald); **and St Vincent's Clinical School, Faculty of Medicine** (K K Dhital, E Granger, P Jansz, A Jabbour, E Kotlyar, Prof A Keogh, Prof C Hayward, Prof R Graham, P Spratt, Prof P Macdonald), **Department of Physiology and Pharmacology** (M Hicks), **University of New South Wales, Randwick, NSW, Australia**

Correspondence to:
Kumud K Dhital, St Vincent's Hospital, 390 Victoria Street, Darlinghurst, NSW 2010, Australia
kumud.dhital@svha.org.au

ischaemia during withdrawal of life-support, the need to preserve the heart during transportation from the donor to the recipient hospital, and the need to assess the viability of the heart before transplantation. In preclinical studies, we have shown that the tolerance of a heart donated after circulatory death to warm ischaemia can be enhanced by modification of the initial flush solution[9] and that normothermic ex-vivo perfusion preserves the heart better than hypothermic storage and enables the heart's viability to be assessed.[10] These findings, combined with those of other investigators,[9–15] have led to a renewed effort to explore the potential for clinical heart transplantation from donors after circulatory death.[16]

The transportable Organ Care System (TransMedics; Andover, MA, USA) enables both standard and marginal-criteria ex-vivo donor hearts to be preserved,[17] and enables detection of occult pathology during normothermic ex-vivo perfusion. The heart Organ Care System has been used for 246 orthotopic heart transplantations worldwide. We report the first three successful human heart transplants after distant procurement of orthotopic hearts donated after circulatory death.

Methods

Recipients

The patients were included in the Marginal Heart Study at St Vincent's Hospital (Sydney, Australia), which involves a protocol for the use of extended-criteria donor hearts including those donated after circulatory death. This single-centre study defined extended-criteria for both hearts donated after brain death and hearts donated after circulatory death. We considered all Maastricht category III controlled hearts from donors after circulatory death aged younger than 40 years with less than 30 min from withdrawal of support to delivery of cardioplegia. We limited donor age to 40 years to minimise the risk of retrieving hearts with pre-existing pathology and because of concern about the tolerability to ischaemic injury of hearts from older donors.[18] The 30-min warm ischaemic time was chosen on the basis of preclinical studies.[9] The recipient and donor characteristics are shown in table 1.

Patient 1 was a 57-year-old woman with end-stage familial dilated cardiomyopathy admitted for orthotopic heart transplantation 6 weeks after placement on the waiting list for rapid deterioration of her symptoms and with less than 30 days out of hospital in the preceding 4 months.

Patient 2 was a 43-year-old man with cardiomyopathy presumed secondary to viral myocarditis 4 years previously. Over the past 12 months, he had substantial deterioration with recurrent hospital admissions for decompensated heart failure requiring treatment with levosimendan. He was admitted for cardiac transplantation 4 days after placement on the waiting list

Patient 3 was a 57-year-old man with arrhythmogenic right ventricular dysplasia who had been waiting 321 days on the transplantation list. He had had several storms of ventricular tachycardia and multiple shocks from an internal defibrillator.

The study was approved by the St Vincent's Hospital Research Ethics Committee, and endorsed by the New South Wales Ministry of Health and the New South Wales DonateLife Organ & Tissue Service. All recipients provided written informed consent.

Donors and donation procedures

Potential donors were referred by DonateLife agencies for consideration for heart and lung transplantation. Donors had medical history recorded and routine investigations done including venous and arterial blood tests, microbiological cultures, electrocardiography, haemodynamic assessment, and chest radiography. An echocardiogram, if done before referral, was also assessed, as well as the requirement for any vasopressor or inotropic drugs. The process of organ donation and subsequent withdrawal of life-support was done by the intensive care team, who were separate from the thoracic and abdominal organ retrieval teams. The observation period after cessation of circulation varies in Australia and is legally defined by each state. It is at least 2 min in New South Wales and 5 min in other jurisdictions.

At the end of the observation period the donors were declared deceased and quickly transferred to an operating room. The location of withdrawal of support varied from an adjacent operating room, an anaesthetic bay, or an intensive care unit. The thoracic and abdominal retrieval teams were ready before life-support was withdrawn. The donors were only intubated and prepared for surgery on arrival at the retrieval operating room. A median sternotomy and laparotomy were done simultaneously with a large venous cannula placed directly into the grossly distended right atrium to enable rapid collection of 1·5 L of blood to prime the ex-vivo perfusion apparatus.

	Recipient 1	Recipient 2	Recipient 3	Donor 1	Donor 2	Donor 3
Age (years)	57	43	57	26	26	27
Sex	Male	Female	Male	Male	Male	Male
Diagnosis	Familial DCM	Viral DCM	ARVD*	Hypoxia	Trauma	Trauma
Blood group	A	A	O	A	A	O
Height (cm)	163	176	170	183	173	182
Bodyweight (kg)	71	70	79	92	70	79
Ejection fraction (%)	20	18	19	75	50	NA
LVEDD (mm)	84	61	67	..	..	..
TPG (mm Hg)	7	5	8	..	..	..
Creatinine concentration (μmol/L)	99	135	149	..	..	..
eGFR (mL/min BSAc)	44	65	42	..	..	..
Total bilirubin concentration (μmol/L)	30	60	42	..	..	..

DCM=dilated cardiomyopathy. ARVD=arrhythmogenic right ventricular dysplasia. LVEDD=left ventricular end-diastolic dimension. eGFR=estimated glomerular filtration rate. NA=not available. TPG=transpulmonary gradient.

Table 1: **Recipient and donor characteristics**

Heparin was only added to the blood collection bag and not administered to the donor, as per New South Wales state regulations on donation after circulatory death. A clamp was placed on the ascending aorta and 1 L of cold crystalloid St Thomas' cardioplegia supplemented with erythropoietin (5000 units per L) and glyceryl trinitrate (100 mg/L) was delivered via the aortic root at a pressure of 150 mm Hg. The heart was vented by cutting across the left atrial appendage and the inferior vena cava at the pericardial reflection.

After delivery of both cardioplegia and pneumoplegia, the heart was immediately explanted with transection at the mid-aortic arch, across the pulmonary artery at its bifurcation, across the superior vena cava at its confluence with the innominate vein, and leaving behind sufficient left atrial tissue with the pulmonary veins as required for bilateral lung transplantation. In all three patients, the liver, both lungs, and kidneys were also retrieved for transplantation.

Ex-vivo preservation

The donor hearts were attached to the Organ Care System after cannulation of the aorta and pulmonary artery. The Organ Care System circuit prime was made up by mixing 1·5 L of donor blood that had been passed through a leucocyte filter (Pall LeukoGuard BC2; Pall Corporation, Port Washington, NY, USA) with 500 mL of TransmedicsR priming solution containing buffered electrolytes, mannitol, vitamins, and steroids. A TransmedicsR proprietary maintenance solution (1 L) containing isotonic electrolytes, aminoacids, dextrose-insulin, and low-dose adenosine was infused at a rate of 0–30 mL/h during ex-vivo perfusion to keep coronary flow within an acceptable range of 650–900 mL/min. Two of the three hearts needed 5 J direct current cardioversion for initial ventricular fibrillation on reperfusion. The rhythm subsequently converted to sinus bradycardia requiring pacing with biventricular epicardial pacing wires for two patients. The third heart started beating spontaneously in sinus rhythm and did not require pacing.

A vent was placed in all hearts via the left atrium to decompress the left ventricle, and then the superior vena cava and inferior vena cava were both closed. The heart was positioned so that oxygenated blood directly entered the ascending aorta in a retrograde manner and then necessarily down the coronary arteries. Blood then returns to the right side of the heart and is diverted up a cannula placed in the pulmonary artery before draining into the circuit reservoir. The apparatus principally uses aortic pressure, coronary flow, and arteriovenous lactate concentrations to assess cardiac function, with a lower venous concentration indicating lactate uptake and therefore satisfactory myocardial function. An infusion of low-dose adenosine, another infusion containing adrenaline, and adjustable circuit pump flow were used to control coronary vascular resistance and heart rate to keep parameters within the following ranges: aortic pressure 65–90 mm Hg; coronary flow 650–900 mL/min; heart rate 65–100 beats per min. Simultaneous sampling from the coronary inflow and coronary effluent ports on the perfusion circuit was done at regular intervals to measure myocardial lactate extraction. Lactate concentrations in the perfusate were measured with an automated iSTAT analyser (Abbott; Princeton, NJ, USA) according to the manufacturer's instructions. A total concentration of lactate of less than 5 mmol/L in the perfusate combined with myocardial lactate extraction (coronary inflow lactate>coronary effluent lactate) was considered evidence of myocardial viability.[19]

Role of the funding source

None of the funders had any role in data collection, analysis, or interpretation, writing of the report, or in the decision to submit for publication. KKD, AI, MC, HCC, CS, AD, EG, PJ, PS, and PM had access to all the data. KKD, AI, MC, HCC, EG, PJ, AJ, AK, CH, RG, PS, and PM were responsible for decision to submit for publication.

Results

Cessation of circulation occurred in less than 20 min in all three patients and the start of cardioplegia delivery took another 3–6 minutes (table 2). Attachment of the heart to the Organ Care System took an additional 23–28 min, as a result of the additional time needed to deliver pneumoplegia for procurement of lungs.

For patient 1, closure of both the inferior vena cava and the superior vena cava led to an immediate distension of the heart, particularly the right side. The

	Donor 1	Donor 2	Donor 3
Withdrawal parameters			
Location of withdrawal	Operating theatre	Intensive care unit	Anaesthetic bay
Withdrawal to systolic blood pressure <50 mm Hg (min)	7	5	11
Withdrawal to SaO_2 <50% (min)	8	2	1
Withdrawal to cessation of circulation (min)	16	10	11
Observation period (min)	2	2	5
Warm ischaemic time (min)*	28	25	22
OCS parameters			
Pacing	Yes	Yes	No
Adrenaline infusion (μg/h)	5	5	5–7
Adenosine infusion (mg/h)	0–21	0–21	0–21
Total OCS perfusion time (min)	257	260	245
Total ischaemic time (min)†	90	96	107
A-V lactate at start of perfusion (mmol/L)	8·30–8·10	6·79–6·48	7·60–7·40
A-V lactate at end of perfusion (mmol/L)	3·60–3·60	2·80–2·30	2·69–2·54

OCS=Organ Care System. A-V=arteriovenous. *Time from withdrawal of support to cardioplegia delivery. †Composite of the time from cessation of circulation to instrumentation on the OCS apparatus plus the time from cardioplegia delivery at the end of OCS perfusion to post-transplant reperfusion.

Table 2: **Donor heart management**

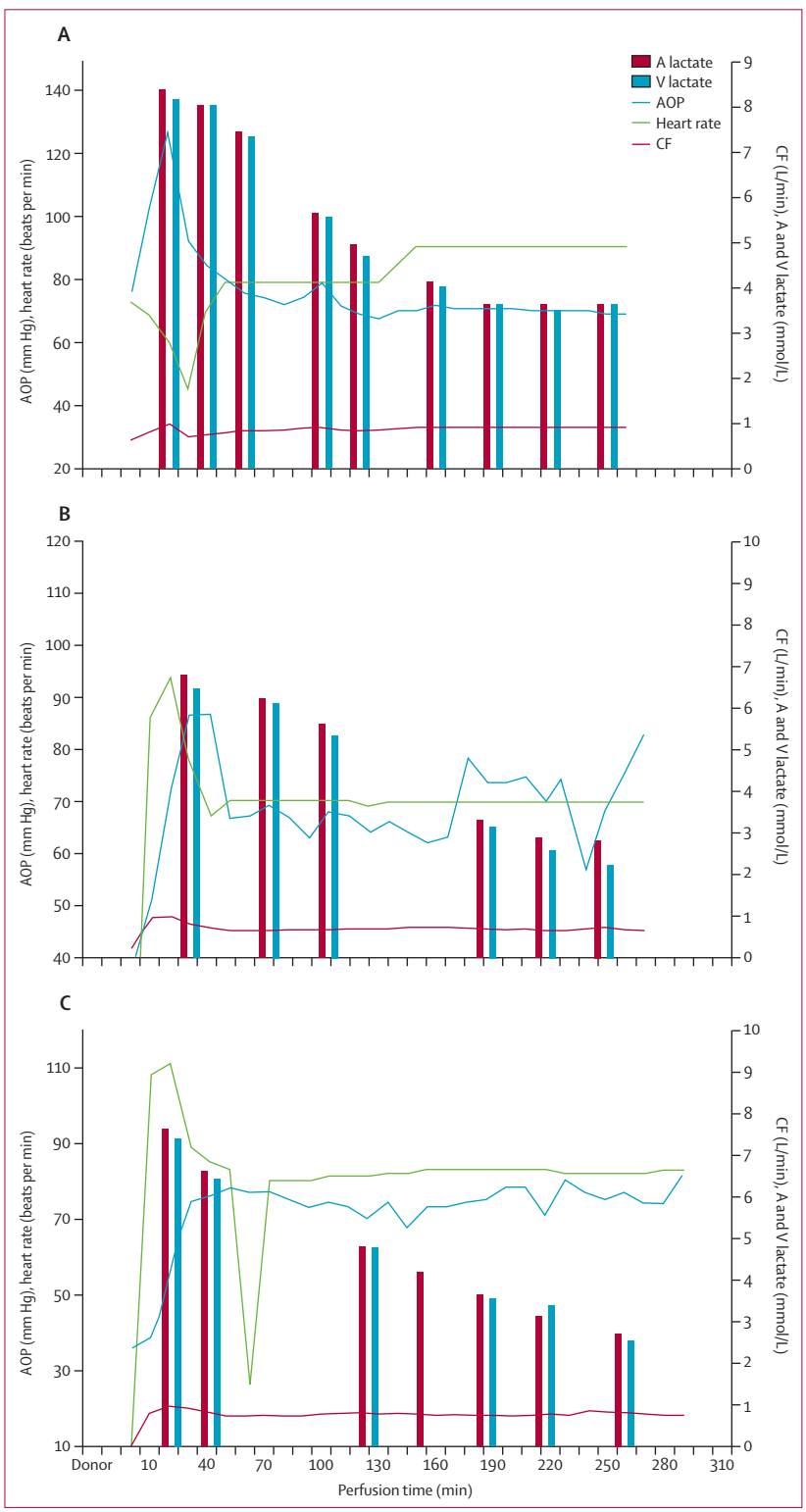

Figure 1: **Aortic pressue, heart rate, coronary flow, and lactate concentrations during ex-vivo perfusion**
(A) Donor 1, (B) donor 2, (C) donor 3. A lactate=arterial lactate. V lactate=venous lactate. AOP=aortic pressure. CF=coronary flow.

superior vena cava tie was immediately removed, allowing right ventricle decompression and the heart paced through direct epicardial pacing leads. Figure 1 shows aortic pressure, coronary blood flow, heart rate, and lactate values for both arterial and venous samples for the three patients. Despite the favourable downward trend in serum lactate concentrations, the right ventricle continued to show substantial dyskinesia for the first 2 h. During this time, the heart was transported by road to the recipient hospital. Thereafter, right ventricle function improved greatly and both coronary blood flow and mean aortic pressure remained constant and in the prescribed range. The difference in arteriovenous lactate improved further and remained stable at less than 5 mmol/L. An analysis of the data logged during machine perfusion of the first heart suggested that there was an acute and inadvertent rise in pump flow during the initial phase of machine perfusion that was likely to be iatrogenic. We were cautious during manipulation of pump flow in the subsequent two transplantations and we did not see similar right ventricle dysfunction after initial attachment to the Organ Care System.

The second and third hearts were retrieved at a greater distance by air and had excellent perfusion parameters and absorbing lactate values. The decision to proceed with transplantation was made only once the perfusion and lactate profiles met Organ Care System parameters. Only then were the recipients anaesthetised and placed on cardiopulmonary bypass. Ex-vivo perfusion was turned off, supplemented cold St Thomas' cardioplegia delivered to the donor heart with prompt electromechanical arrest, and the heart taken off the Organ Care System apparatus for implantation.

A fourth donor was a 35-year-old woman who had been in a motor vehicle accident. The time from withdrawal of ventilator to cessation of circulation was 35 min and the total warm ischaemic time was 49 min, which exceeded our limit. The heart was therefore excluded from the heart transplant pathway and implemented on the Organ Care System apparatus for a research protocol for which there was prior consent. The initial arteriovenous lactate concentrations were 9·6–9·8 mmol/L and eventually increased to 11·0–11·0 mmol/L with substantial dyskinesia and poor cardiac contractility.

After completion of left atrium anastomosis, cold blood cardioplegia was administered via the aortic root. The pulmonary artery and aortic anastomoses were then completed and followed by warm blood hyperkalaemic reperfusion before removal of the recipient cross-clamp and start of cardiac reperfusion on cardiopulmonary bypass. The inferior vena cava and superior vena cava anastomoses were done with the heart beating in two patients with bi-caval connections. The third case involved a bi-atrial anastomosis. In this case, the right atrial anastomosis was also done on the beating heart. The total ischaemic times for the three patients were

90 min, 96 min, and 107 min and consisted of the time from cessation of circulation in the donor to attachment to the Organ Care System, plus time from cardioplegic arrest of the donor heart on the Organ Care System to cardiac reperfusion in the recipient.

The hearts were then reperfused on cardiopulmonary bypass for 20 min for each hour of ischaemia. After weaning from cardiopulmonary bypass, both visually and on trans-oesophageal echocardiography, the right ventricle of the first recipient showed only mild impairment whereas the left ventricle was severely impaired. The recipient was then placed on venoarterial femoro-femoral extra-corporeal membrane oxygenation. An intra-aortic balloon was also placed percutaneously. Thereafter, biventricular function improved daily with removal of intra-aortic balloon 24 h later and decannulation of extra-corporeal membrane oxygenation on day 4. The third patient had a similar Takotsubo-type cardiomyopathy affecting the left ventricle and required an intra-aortic balloon for weaning off cardiopulmonary bypass, which was subsequently removed on day 2. Right ventricle function was good throughout. The second heart recipient was weaned off cardiopulmonary bypass with ease and needed only small doses of inotropic support. Peri-operative trans-oesophageal echocardiogram showed excellent biventricular function.

Patient 1 was discharged on day 26 and remained well with no evidence of ischaemic injury in any endomyocardial biopsy (figure 2). 105 days after surgery, she had mildly diminished left ventricle contractility coinciding with moderate cellular rejection. She was briefly admitted for steroid-pulse treatment and then returned home where she remains well, with normal left ventricular function at 176 days after transplantation.

The second recipient has had normal biventricular function on all echocardiograms. He also developed moderate cellular rejection on endomyocardial biopsy at day 20 but this was not associated with any reduction in left ventricle function. The biopsies showed no evidence of ischaemic injury on histological examination. He was discharged 28 days after surgery and remains well at 91 days after transplantation.

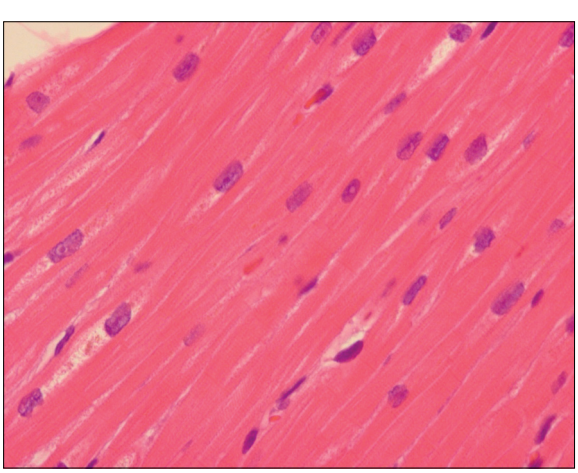

***Figure 2*: Endomyocardial biopsy sample from patient 1 on day 8**
Shows normal myocardial architecture and no evidence of ischaemia reperfusion injury or rejection. Haematoxylin and eosin stain. Magnification ×400.

The third recipient has had hyperdynamic biventricular function since 2 days after surgery, when the intra-aortic balloon was removed. His endomyocardial biopsies have also been negative for ischaemic injury and, to date, there has been no evidence of cellular rejection. His planned discharge on day 13 was postponed because of a moderate pericardial effusion, which was drained without complication. He was discharged on day 21 and remains well 77 days after transplantation.

Discussion

To our knowledge, this report describes the first successful clinical heart transplantations after circulatory death with donor organs procured at a distance necessitating reanimation, resuscitation, and transportation with use of an ex-vivo cardiac perfusion device (panel). Of the strategies to slow the growing discrepancy between the number of patients awaiting transplantation and the scarcity of suitable donors, the use of organs donated after circulatory death has been successful for lung and intra-abdominal organ transplants. Strong endorsements of protocols for such transplants by national and international regulatory bodies have led to wider adoption of this strategy, with organs donated after circulatory death contributing an increasing percentage of the total number of donors, especially in Australia, Belgium, Netherlands, Spain, UK, and USA.[3]

The results of kidney transplantation are much the same for kidneys donated after circulatory death and those from brain-dead donors, with similar long-term survival despite a higher incidence of delayed graft function in patients given kidneys from donors after circulatory death.[4] Outcomes of liver transplantation from donors after circulatory death have been poorer, with more frequent biliary strictures and primary graft failures ascribed to a greater sensitivity to warm ischaemia.[6] Nevertheless, other studies[20] report similar outcomes for livers donated after circulatory death and those donated after brain death.

Promising results have been reported for lung transplantation after circulatory death. The International Society of Heart & Lung Transplantation DCD Registry has shown similar outcomes at 1 year between lung transplants donated after brain death and those donated after circulatory death.[21] Data from a multicentre Australian study[5] showed survival of 97% at 1 year and 90% at 5 years for patients given lungs donated after circulatory death compared with 90% at 1 year and 61% at 5 years for patients given lungs donated after brain death.

Several large studies of animals[9–13] and a series of studies of ex-vivo human heart resuscitation,[8,14,16,22] have shown the feasibility of using hearts donated after

Panel: **Research in context**

Systematic review

We searched PubMed with the terms "donation after circulatory death", "donation after cardiac death", "non heart beating donation", "ex vivo perfusion", and "heart transplantation" to find relevant articles language in any language published up to Aug 14, 2014. We searched for both animal and human studies of donor hearts from a non-brain-dead but deceased donors. Several studies describe satisfactory ex-vivo reanimation of animal[9–13] and human[14,15] hearts donated after circulatory death. Heart transplantations done in the late 1960s[1] and a report[7] of three neonatal heart transplantations after circulatory death in 2008, both refer to colocated donors and recipients. There were no reports of clinical heart transplantation with distantly procured hearts from donors after circulatory death.

Interpretation

To our knowledge, this report describes the first successful clinical heart transplantations after circulatory death with donor organs procured at a distance necessitating reanimation, resuscitation, and transportation with use of an ex-vivo cardiac perfusion device. Our findings confirm that human hearts donated after circulatory death can be adequately preserved and their function assessed in a physiological ex-vivo platform before safe clinical transplantation with excellent outcome. A broader adoption of this strategy would lead to a significant increase in the number of heart transplantations and limit the loss of patients on transplantation waiting lists as well as potentially reducing the number of patients requiring urgent palliative bridging strategies.

circulatory death for clinical transplantation. In a study of donation after circulatory death in pigs,[9,23] we have shown that pharmacological post-transplantation conditioning, achieved by supplementing cardioplegia with erythropoietin, glyceryl trinitrate, and zoniporide, increased the tolerance of the heart to warm ischaemia. Moreover, the commercially available portable ex-vivo heart Organ Care System has made it possible to maintain physiological perfusion of a donor organ during distant organ procurement.[10,24] The device has been used for both resuscitation and assessment of marginal hearts donated after circulatory death for transplantation[17] as well as in research assessing functional recovery of unused human hearts donated after circulatory death.[15]

Although several groups are developing more robust means to assess ex-vivo myocardial function, in this study we had the ideal donor–recipient match, in which the donor hearts' metabolisms improved sufficiently with ex-vivo perfusion to warrant a clinical transplantation. The delayed graft function in our first patient might be analogous to that reported for kidneys transplanted from donors after circulatory death.[25] In this regard, a strategy of prophylactic extracorporeal membrane oxygenation support, which is safe and effective,[26] might enable hearts donated after circulatory death to recover. Roughly 17% more transplantations could be done by use of hearts donated after circulatory death.[27–29]

Our findings could fuel further ethics debates, particularly with respect to the definition of death; the conflict between death of a donor and death of individual organs; the acceptable length of observation from cessation of circulation to declaration of death; and the variable acceptance for a range of pre-mortem interventions aimed at safeguarding organ function at the cost of inconvenience to the donor. Donation of organs after circulatory death is a well-established practice. In this respect, we believe that the heart is no different to the lungs, liver, or kidneys. All these organs remain viable for a short time after permanent cessation of circulation. In developing a heart transplantation programme from donors after circulatory death, we adhered to established jurisdictional criteria and processes for determination of circulatory death and subsequent removal of organs for transplantation. In addition to the necessity of further refining strategies to counteract the effects of warm ischaemia, and improving the technical aspects of ex-vivo heart preservation and assessment, we believe it is time to move this debate towards development and implementation of broader international consensus guidelines.

Expansion of heart transplantation from donors after circulatory death would help to reverse the trend of fewer organs per donor after circulatory death compared with brain-dead donors. It would also enable doctors to better honour the wishes of donors and their relatives to maximise opportunities for organ transplantation, and clinicians' professional responsibility to reduce the time spent on transplantation waiting lists caused by the shortage of suitable donor hearts.

Acknowledgments

This study was funded by the National Health and Medical Research Council (Program Grant 573732), the John T Reid Charitable Trust, the EVOS Trust Fund, National Heart Foundation of Australia (grants G04S 1619 and G07S 3044), St Vincent's Clinic Foundation, and the Harry Windsor Trust Fund. We thank the Ministry of Health, NSW, Australia. Abdominal transplant surgeons: Michael Crawford, Henry Pleass, and Deborah Verran. Transplant coordinators: Peta Tunnicliff, Elyn Montgomery, Angela Smith, Natalie Hay, Vicky Morgan, Michelle Harkess, and Sara Shaw. Staff at New South Wales donor hospital intensive care units: P Saul, John Hunter Hospital; A Aneman, Liverpool Hospital; A Rajamani, Nepean Hospital; G Flynn, Prince of Wales Hospital; R Raper, Royal North Shore Hospital; R Herkes, Royal Prince Alfred Hospital; A Cheng, St George Hospital; S Al-Soufi, St Vincent's Hospital; D Goh, Westmead Hospital; M MacPartlin, Wollongong Hospital.

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