

REVIEW

Normothermic donor heart perfusion: current clinical experience and the future

Simon Messer,¹ Abbas Ardehali² and Steven Tsui¹¹ Transplant Unit, Papworth Hospital, Cambridgeshire, UK² Division of Cardiothoracic Surgery, Department of Surgery, David Geffen School of Medicine at UCLA, Los Angeles, CA, USA**Keywords***ex vivo*, heart, normothermic, perfusion, transplant.**Correspondence**Steven Tsui, Director of Transplantation, Papworth Hospital, Papworth Everard, Cambridgeshire CB23 3RE, UK.
Tel.: +44 1480 364 297;
fax: +44 1480 364 332;
e-mail: steven.tsui@papworth.nhs.uk**Conflicts of interest**

The authors have declared no conflicts of interest.

Received: 18 November 2013

Revision requested: 5 March 2014

Accepted: 19 May 2014

Published online: 7 July 2014

doi:10.1111/tri.12361

Introduction

Despite 40 years of research into the management of end stage heart failure spanning total artificial hearts, ventricular assist devices and more recently, stem cell therapy, there remains no comparable alternative to human heart transplantation. This gold standard therapy remains unparalleled in improving survival and quality of life. Unfortunately the Achilles heel of this excellent treatment is the severe shortage of donor organs. The number of heart transplants performed in the United Kingdom (UK) and many Western countries has dropped dramatically over the last decade [1]. Despite this decline, the number of patients added to the waiting list continues to grow [2].

Of the estimated 750 000 patients diagnosed with heart failure in the UK [3], only around 0.02% undergo transplantation. Consequent to this mismatch between supply and demand, almost 10% of patients on the heart trans-

Abstract

Following the first successful heart transplant in 1967, more than 100 000 heart transplants have been carried out worldwide. These procedures have mostly relied on cold ischaemic preservation of the donor heart because this simple technique is inexpensive and relatively reliable. However, the well-known limitations of cold ischaemic preservation imposes significant logistical challenges to heart transplantation which put a ceiling on the immediate success on this life-saving therapy, and limits the number of donor hearts that can be safely transplanted annually. Although the theoretical advantages of normothermic donor heart perfusion have been recognised for over a century, the technology to transport donor hearts in this state has only been developed within the last decade. The Organ Care System (OCS) which is designed and manufactured by TransMedics Inc. is currently the only commercially available device with this capability. This article reviews the history of normothermic heart perfusion and the clinical experience with the TransMedics OCS to date. We have also attempted to speculate on the future possibilities of this innovative and exciting technology.

plant waiting list will die every year, whilst a further 10% will be permanently removed, presumed to die.

As the demand continues to outstrip the supply of suitable organs, surgeons have been forced to expand donor acceptance criteria. Organs that would have previously been declined on donor age, inotropic requirement, smoking history, prolonged cardiac arrest or intravenous drug abuse are now routinely being considered.

As the acceptance criteria for donor hearts continue to widen, the traditional predictors of primary graft failure (PGF) remain constant. According to the International Society of Heart and Lung Transplantation (ISHLT) registry, the 30-day mortality after heart transplantation is 8% with the leading cause of death attributable to PGF. Donor age and length of ischaemic time are strong predictors of PGF. The ISHLT registry reveals that the risk of PGF begins to increase once ischaemic time exceeds 3 h [4].

Currently in the UK, only 25% of all hearts offered are transplanted. Although various strategies have been

introduced to address this low conversion rate, a significant proportion of these hearts are being declined on age or prolonged ischaemic time. Despite the strong evidence showing that increasing donor age and ischaemic time potentiates the risk of PGF [5–7], there remains tremendous pressure to utilise these extended criteria donor (ECD) hearts.

At the dawn of heart transplantation, strategies for donor organ preservation had been limited. Cold storage was found to be simple, inexpensive and relatively reproducible to undertake. Over 100 000 heart transplants have been undertaken safely worldwide with cold ischaemic preservation provided that the predictors of PGF were respected.

Although universally adopted, cold ischaemic storage is known to be imperfect as low levels of anaerobic metabolism continue in the background with the subsequent depletion of adenosine triphosphate (ATP) stores and increase in acidosis [8]. Attempts at continuous machine perfusion using hypothermic preservation solutions have been made and found to provide superior systolic function with preserved ATP levels compared with cold storage [9–12]. There is, however, concern that diastolic function may be impaired as significant myocardial oedema develops. The main reluctance of adopting this technique for poorly contracting donor hearts is that there is no means of functional assessment during preservation. Without the reassurance of *ex situ* assessment following organ retrieval, reluctance will remain in expanding the donor pool any further.

History of normothermic *ex vivo* heart perfusion

Normothermic *ex vivo* heart perfusion allows continuous metabolic and functional assessment. The notion of explanting and perfusing the heart was first established in frogs almost 150 years ago by the scientist Elias Cyon [13].

The first isolated perfused mammalian heart is credited to one of the forefathers of cardiovascular research, Oscar Langendorff [14]. In 1895, he proposed the principle of cannulating the ascending aorta and delivering perfusate retrogradely down the aorta. The aortic valve under a hydrostatic pressure head would be closed, and perfusate would be channelled antegradely through the coronary arteries. Katz modified this technique in 1939 by incorporating a pump to set the perfusion pressure allowing vasoactive properties of various drugs to be assessed [15].

In 1967, Neely first described the working heart model, allowing the ventricles to both fill and eject [16]. With the left atrium cannulated, blood can be pumped through the left heart chambers and eject through the aortic valve into the ascending aorta. Perfusate then flows through the coronary vasculature under the root pressure generated by the

left ventricle or forward into a compliance chamber. The compliance chamber allows some elastic recoil imitating the elastic recoil of the native aorta. This serves two purposes: (i) it increases the compliance of the circuit thereby reducing the afterload that the heart has to overcome and (ii) it reduces the closing pressure of the aortic valve thus avoiding its exposure to excess mechanical stress. Beyond the compliance chamber, perfusate is pumped to a pressure head reservoir which sets the afterload and perfusion pressure [16].

The working heart system is the perfect method of assessing both left and right ventricular function in real time over varying workloads. The Papworth group is currently using pressure–volume relationship in the biventricular working rig to assess whether hearts following donation after circulatory determined death (DCD) could be reconditioned for safe transplantation.

Autoperfusing heart lung block

The concept of transporting a perfused heart was first made possible by the heart lung preparation introduced by Martin. In 1914, Ernest Starling used this technique to investigate ventricular volumes, formulating the Frank Starling laws of the heart [17].

In 1959, Robicsek modified Starling's heart lung preparation to investigate methods of perfusing the donor heart prior to transplantation. Hearts survived for an average of 11 h using this *ex vivo* perfusion technique as shown in Figure 1, [18] with transplanted hearts surviving beyond

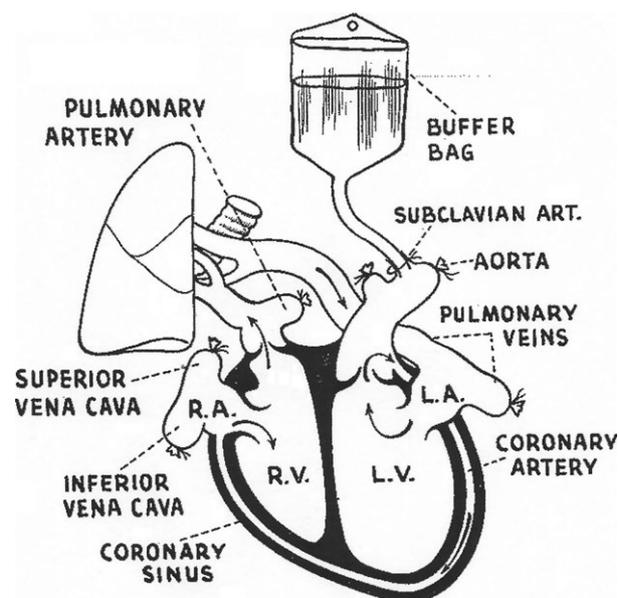


Figure 1 The Robicsek autoperfusing heart lung block. Copyright Elsevier (1963) [18].

6 h [19]. Further attempts were made using the technique of autoperfusion, but the practice was abandoned due to significant bleeding and pulmonary oedema [20].

The TransMedics Organ Care System

The foundation of the TransMedics (Andover, Massachusetts) Organ Care System (OCS) follows the development of a portable perfusion apparatus used as a research tool investigating donor heart preservation (Fig. 2) [21]. This is the first commercially available device to transport donor hearts in a normothermic perfused state. The perfusate is a proprietary priming solution with the addition of insulin, antibiotics, methylprednisolone, sodium bicarbonate, multivitamins and fresh donor blood. Pulsatile flow is generated by a diaphragmatic pump, and an integrated plate heater maintains normothermia.

After the donor has been systemically heparinised, between 1.2 to 1.5 l of donor blood is collected just prior to aortic cross-clamping, a process that usually takes 75–90 s. The collected donor blood is passed through a leucocyte filter and added to the priming solution in the OCS organ perfusion module. The donor heart is retrieved in the standard fashion, the only difference is that a lower volume of a short-acting cardioplegic solution is used (e.g. 500 ml of St. Thomas' solution) as the initial cold ischaemic period for instrumentation is usually no more than 20–30 min. The transected donor aorta is attached to a specially designed aortic tip connector, and the pulmonary trunk is cannulated with a malleable cannula. The aortic tip connector is attached to the perfusion port of the OCS organ chamber which supports the heart on a sloping cradle. As the donor heart is reperfused, sinus rhythm is either restored spontaneously or with the aid of a direct cur-

rent shock delivered through integrated ECG/defibrillator pads inside the organ chamber. During this time, any shed blood drains directly into the reservoir. Once the heart begins to beat, the inferior and superior cavae are sutured closed. Coronary sinus blood returning to the right atrium flows into the right ventricle which pumps it through a low resistance membrane oxygenator before it enters a blood reservoir (Fig. 3). The oxygenated blood is then delivered into the donor aortic root by a pulsatile pump.

A wireless monitor controls the perfusion rate of the OCS and displays a comprehensive panel of information including aortic pressure, coronary flow rate, haematocrit, temperature and oxygen saturation. A maintenance solution containing adenosine is used to counter any tendency for coronary vasoconstriction in the donor heart, and an epinephrine infusion at 5 µg/h is used to maintain physiological levels of circulating catecholamines. During transportation, the objective is to maintain the aortic pressure between 65 and 90 mmHg with a coronary flow of 650 to 850 ml/min. If coronary flow is inadequate, the operator can increase the rate of the vasodilatory maintenance solution or increase pump flow.

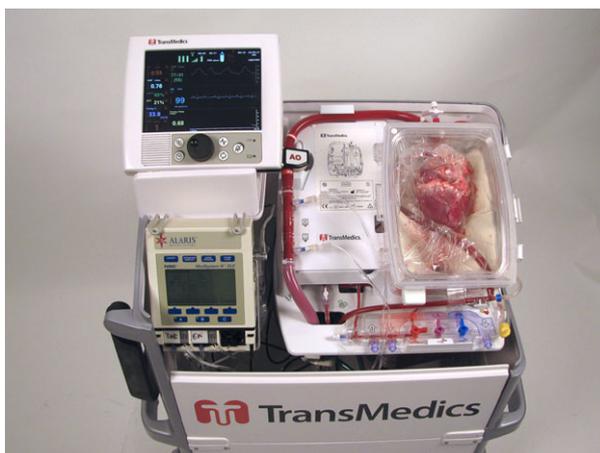


Figure 2 TransMedics Organ Care System.

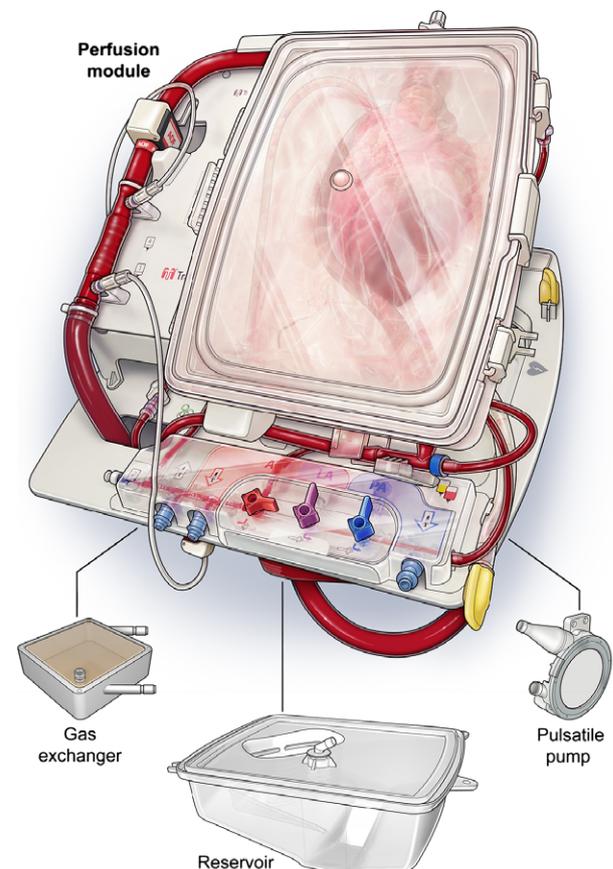


Figure 3 TransMedics OCS single-use organ perfusion module.

Organ assessment

The current OCS perfusion module is designed to maintain hearts that have been previously assessed within the donor and considered suitable for transplantation. Once reanimated in the OCS, these hearts are continuously assessed by the aortic pressure, coronary flow and differential lactate profile. Arterial and venous lactates are sampled at least every hour after stabilization and following every manipulation to aortic pressure. After reviewing the first 49 OCS clinical heart transplants, the final lactate level at the end of OCS preservation was found to be the most powerful predictor of outcome [22]. Used as a univariate, an ending lactate level of >4.96 mmol/l had 0.625 sensitivity and 0.976 specificity of poor outcome. Rising lactate levels over 5 mmol/l has also been shown to be a sensitive tool in revealing hidden pathologies. Of the initial 14 human donor hearts instrumented on the OCS at Papworth Hospital and UCLA, 12 were transplanted and 2 were turned down based on end lactate profile despite adequate coronary flow. The first donor had an ending lactate of 5.15 mmol/l. The heart was declined for transplantation and pathological examination revealed widespread triple vessel coronary artery disease with $>95\%$ stenosis. The second donor was a trauma victim with an ending lactate of 10 mmol/l, histopathology revealed significant myocardial contusion [23].

In the OCS PROCEED II trial, of the first 79 patients that were enrolled, three hearts were discarded due to lactate profile. The mean arterial lactate of this turn down group was 5.3 ± 0.4 mmol/l vs. 2.3 ± 0.9 mmol/l in the transplanted group. All donor hearts in the transplant group were weaned off cardiopulmonary bypass. In the turned down group, histology revealed evidence of myocardial contusion/infarction in two of the discarded hearts whilst unrecognised left ventricular hypertrophy existed in the other. Following these experiences and further animal experimental work, it is now accepted that an arterial lactate exceeding 5 mmol/l is associated with poor outcome post-transplantation. Although lactate is the cornerstone of organ assessment on the OCS device, haemodynamic parameters provide an additional means of evaluating the organ. There would be significant concern about transplanting a donor heart with persistently high perfusion pressures despite an acceptable lactate profile.

Benefits

Clearly the most apparent benefit of normothermic donor heart perfusion during transportation is the reduction of cold ischaemic time. The donor pool can be widened as retrieval zone boundaries can be extended. In Australia, a donor heart was successfully transplanted after 10.5 h on

the OCS. Theoretically in the UK, this would enable international organ sharing with Europe and the eastern United States. This expansion of the donor pool is one of the main potential benefits of the OCS device. For the retrieval team, removing the urgency related to ischaemic time avoids perilous high speed return journeys previously associated with serious injuries and fatalities amongst retrieval team members in the past.

Normothermic donor heart perfusion offers more flexibility to the implanting surgeon as well. Traditionally using cold storage, perfect coordination with the retrieval team is paramount to avoid prolonging the ischaemic time. With the reassurance that the donor heart is being continuously perfused, the pressures to perform difficult explants are reduced which should result in fewer bleeding complications.

Another clear advantage of the OCS device is that the implanting surgeon can assess the quality of the donor heart. Lactate profiles can be reviewed as well as physical inspection before any irreversible steps are undertaken on the recipient. A further clinical benefit is that the OCS device adds a time safety buffer in unanticipated circumstances. This became apparent when an intra-abdominal malignancy in the donor was suspected after the donor heart had arrived back at the recipient hospital. The OCS device allowed time for a reassuring frozen section examination of the abdominal lesion before transplanting the heart.

However, the full potential benefits of *ex vivo* heart perfusion have yet to be realised. An ultimate aim of the technology would be to thoroughly characterise the metabolic, biochemical, anatomical and mechanical function of the donor heart before implantation. Assessment needs to be simple, reproducible, reliable and sensitive. For example, coronary angiography can be performed on the OCS device allowing detection of occult coronary artery disease [24]. Contrast echocardiography has also been utilised to ensure myocardial perfusion [25]. Intravascular ultrasound has yet to be assessed on the system. Pressure volume relationships have previously been described in the working heart mode, but these are complicated, need specialist interpretation and are difficult to reproduce. The 'working mode' which was available on the earlier OCS perfusion modules has been removed from the current version to reduce complexity. However, in our opinion, such a modality for functional assessment must be available if donor hearts with questionable contractility are to be assessed on the OCS prior to decision to proceed with transplantation. This would also open up the possibility of reconditioning donor hearts with unacceptable function prior to implantation.

There are currently two other exciting avenues to explore; pharmacological interventions to reduce ischaemic

reperfusion injury and mesenchymal stem cell therapy. Over the last 40 years, there have been many compounds targeted at ischaemic reperfusion injury with seldom few making it to the clinical environment as many drugs are ineffective after the ischaemic insult has been inflicted. The OCS is a perfect platform to deliver these drugs before the anticipated 60 min of impending warm ischaemia during implantation. Mesenchymal stem cell therapy has been explored in other organs to attenuate innate immunity, downregulate adaptive immunity and promote engraftment after transplantation [26]. *Ex vivo* perfusion allows the delivery of these cells at very high concentrations.

Limitations

Deploying the OCS for donor heart maintenance requires a number of resources including additional surgical and technical support personnel, proprietary equipment, appropriate transport and the collection of donor blood to prime the perfusion module. Compared with cold static preservation techniques, this is inevitably more costly. However, this has to be balanced against the value of potentially making more donor hearts available for transplantation and the cost savings from a potential reduction in the incidence of primary graft failure (PGF). In the UK using proportional hazards regression and extrapolation of survival rates beyond 20 years, the impact of decreasing ischaemic time on survival was estimated [27]. It was found that for each additional hour of ischaemic time in excess of 1 h, patients had a 25% increased risk of death in the first year. This study supported similar analysis from the USA which showed that reducing ischaemic time by to 1 h increased survival by 2.2 years [28].

The cost of heart transplantation soon begins to spiral when a recipient develops PGF requiring mechanical circulatory support thus prolonging intensive care stay. If PGF could be minimised by using the OCS to reduce donor heart ischaemic time, the device could be financially justified.

During the early experience with the OCS, a number of donor hearts instrumented on the OCS became untransplantable, either because of high levels of vasoconstrictors in the perfusate which were traced to the collected donor blood or the donor heart became accidentally detached from the connector during transportation. These have since been addressed, respectively, with clearer instructions to avoid administering vasoconstrictors to the donor prior to blood collection and placing anchoring pledgets to the distal donor aorta beyond the securing cable tie.

Another potential concern of continuous cardiac perfusion is myocardial oedema. As observed with the Langendorff model, it has been associated with myocardial oedema. When crystalloid solution is used to perfuse

Langendorff hearts in the laboratory, it is recognised that a 10% decline in function is associated with myocardial oedema [29]. When blood is used as the perfusate to increase its oncotic pressure, oedema is significantly reduced and there seems to be no deleterious effect on function. To reduce the tendency for myocardial oedema, TransMedics have developed a synchronisation mode, replicating that of a balloon pump timed against the electrocardiogram to perfuse the donor heart during diastole. This allows a lower aortic root pressure to be tolerated with a subsequent reduction in oedema.

Clinical trials

A summary of the global clinical experience using the TransMedics OCS is shown in Table 1. The device has been used in seven countries and is currently utilised in 16 centres encompassing 205 human heart transplants to date.

PROTECT I

Prospective multicentre European trial to evaluate the safety and performance of the Organ Care System for heart transplants

PROTECT I was the first-in-man trial to evaluate the safety of the OCS device. This European study was a prospective single arm nonrandomised safety and performance study conducted both in the United Kingdom (Papworth & Harefield) and Germany (Bad Oeynhausen and Berlin) between January 2006 and February 2007. The primary endpoint was 7-day survival, and the secondary endpoints were 30-day patient and graft survival. The inclusion and exclusion criteria are listed in Appendix 1.

Results

Twenty-five donor hearts were instrumented on the OCS. Three hearts were turned down following assessment either due to a high aortic root pressure unresponsive to adenosine infusion or a high lactate profile. Two were

Table 1. Global organ care system (heart) clinical experience until October 2013.

	Year	N	Donor criteria
PROTECT I (EU)	2006–7	22	Standard
PROTECT II (EU)	2007–8	20+	Standard
PROCEED I (US)	2007–8	15	Standard
PROCEED II	2011–13	62	Standard
Berlin experience	2009–13	20	Extended
Other German experience	2012–	13+	Extended
Harefield EXPAND	2013–	17	Extended
Australian experience	2013–	4	Extended
Total	Approx. 205		

excluded from the trial as they were outside of the inclusion criteria. Of the 20 eligible hearts transplanted, the mean donor age was 34.2 ± 10.1 years (mean \pm SD). The total mean ischaemic time was 76 ± 19.7 min (mean \pm SD), with 222 ± 54 min (mean \pm SD) on the OCS device.

Nineteen of 20 recipients were weaned off bypass on the first attempt, whilst one was weaned on the second attempt. Five patients' experienced SAE: two required intra-aortic balloon pump (IABP) insertion for biopsy proven acute rejection; two had temporary left ventricular dysfunction, with one requiring IABP and one patient suffered a haemorrhagic stroke which resolved. All 20 patients met the primary endpoint of 30-day survival and the study was deemed a success. Of the six patients transplanted at Papworth Hospital, all remain alive >5 years post-transplant.

PROTECT II

Following the success of PROTECT I, the PROTECT II registry was launched. This registry soon merged into commercial use and data collection subsequently lapsed. Unfortunately, there are no available records for those transplants performed.

PROCEED I

Prospective multicentre safety and effectiveness evaluation of the Organ Care System device for cardiac use

PROCEED I was the first US clinical trial of the OCS device. It was planned as a 20 patient single arm, nonrandomised Food and Drug Administration (FDA) approved safety and performance study. It was undertaken at four sites including University of Pittsburgh Medical Centre, University of Chicago Hospital, Cleveland Clinic Ohio, and University of California, Los Angeles. The endpoints were the same as the PROTECT I trial. The inclusion and exclusion criteria are shown in Appendix 2.

The trial was conducted between April 2007 and February 2008. Of the 14 hearts instrumented on the OCS, one was declined after assessment and the other 13 were transplanted. Eleven of the 13 recipients reached the 7- and 30-day survival endpoints. Two recipients suffered PGF: one was successfully retransplanted but the other died on post-operative day 2. Of the 11 recipients that had completed the 30-day follow-up, the intensive care stay was 8.5 ± 8 days (mean \pm SD); the intubation duration was 4.7 ± 7 days (mean \pm SD), and total hospital stay was 11.2 ± 11.9 days (mean \pm SD). There were five serious adverse events (SAE) with two patients suffering from acute rejection on post-operative day 5 and 15, respectively, which subsequently resolved.

Following the completion of this pilot study, it was clear that the study was limited by the small sample size. However, in combination with results from the European PROTECT I experience, the FDA granted approval for a pivotal randomised trial in the US (PROCEED II).

PROCEED II

PROCEED II was a prospective, randomised, international multicentre, noninferiority trial comparing the safety and efficacy of OCS to standard of care, that is, cold storage. The primary endpoint was 30-day patient and graft survival. Secondary endpoints were incidence of cardiac related SAE, incidence of rejection and intensive care duration. The inclusion and exclusion criteria were the same as PROCEED I. The trial completed recruitment in September 2013 with 128 recipients transplanted. Although follow-up continues, an interim report was conducted in April 2013 on 92 patients who met the 30-day endpoint. The donor demographics and cause of death are listed in Table 2, and the recipient demographics and primary diagnosis are listed in Table 3.

Results

From Table 4, it can be seen that the total cross-clamp time is significantly longer by 120 mins for the OCS group whilst the total ischaemic time is considerably shorter by 96 min in comparison with cold storage. The primary outcome of 30-day patient survival was achieved in 93% of patients randomised to the OCS device compared with 96% in the standard of care arm. In the OCS group, two deaths were related to post-operative bleeding and the other related to multi-organ failure and disseminated intravascular coagulation. In the standard of care group, two deaths were related to intracerebral bleeds. The full results of the completed study are expected to be published in 2014.

Table 2. Interim report on PROCEED II: donor demographics and cause of death.

Donor	OCS (n = 43)	SOC (n = 49)	P-value
Age (year) mean \pm SD	34 \pm 13	35 \pm 12	0.70
Height (cm) mean \pm SD	174 \pm 9	173 \pm 9	0.60
Weight (kg) mean \pm SD	84 \pm 19	76 \pm 14	0.02
Cause of death			
Head trauma	47%	39%	0.53
Stroke	23%	33%	0.36
Anoxia	26%	20%	0.62
Other	5%	6%	1.00
CNS tumour	0%	2%	1.00

OCS, Organ Care System; SOC, standard of care.

Table 3. Interim report on PROCEED II: recipient demographics and primary diagnosis.

Recipient	OCS (n = 43)	SOC (n = 49)	P-value
Age (year) mean ± SD	52 ± 12	56 ± 13	0.13
Height (cm) mean ± SD	173 ± 11	171 ± 8	0.32
Weight (kg) mean ± SD	77 ± 18	71 ± 15	0.08
Primary diagnosis			
Dilated cardiomyopathy	81%	84%	0.79
Restrictive cardiomyopathy	2%	6%	0.62
Valvular heart disease	9%	10%	1.00
Congenital heart disease	2%	0%	0.47
Other	12%	12%	1.00
Risk factors			
Diabetes	26%	31%	0.65
Renal dysfunction	26%	33%	0.50
VAD at time of transplant	30%	20%	0.34

OCS, Organ Care System; SOC, standard of care.

Table 4. Interim analysis on PROCEED II: ischaemic time and clinical results.

	OCS (n = 43)	SOC (n = 49)	P-value
Total cross-clamp time (mins)			
Mean ± SD	324 ± 84	204 ± 66	<0.0001
Range	156–546	72–462	
Total ischaemic time (mins)			
Mean ± SD	108 ± 24	204 ± 66	<0.0001
Range	60–168	72–462	
30-day recipient survival	93%	96%	0.66
30-day graft survival	93%	96%	0.66
Cardiac SAE	5	9	–
Early graft dysfunction	5	7	–
Grade 2 rejection	5	4	–

OCS, Organ Care System; SOC, standard of care.

The future

Whilst the OCS may provide additional safety margins for transporting donor hearts that meet standard acceptance criteria, greater potential gains probably lie with ECD hearts, where cold storage would traditionally be associated with poorer outcomes, and donor hearts that are currently not even considered for transplantation. These might include

1. Older donors
2. Expected total cross-clamp time of ≥ 4 h
3. Donor cardiopulmonary resuscitation <24 h of organ procurement
4. Left ventricular hypertrophy
5. Moderately impaired left ventricular function

Although there is a small experience with ECD hearts on the OCS, its efficacy in these settings is yet to be formally assessed. The EXPAND registry which is due to start

recruitment in 2014 is a multicenter international single arm pivotal study designed to address this question.

Donation after circulatory determined death

During the last decade, a dramatic increase in the number of DCD donors has seen abdominal organ transplants flourish despite the declining number of brain stem dead (BSD) donors. There remain deep concerns that even brief periods of ischaemia of the heart following circulatory arrest would result in PGF despite evidence of successful heart transplants from donors with a history of prior cardiac arrests [30,31].

DCD heart transplantation has been shown to be possible in animal models [32–34] and in humans [35,36] provided that the warm ischaemic time could be kept below 30 min. However, we suspect that the only safe way to adopt DCD heart transplantation into routine clinical practice is by *ex vivo* functional and metabolic assessment following appropriate reconditioning. Normothermic blood perfusion has been shown to be superior to cold storage in preserving DCD hearts in dogs [37]. In the pig, reconditioned DCD hearts were shown to have comparable function to BSD donor hearts [38]. In an asphyxiation pig model, DCD hearts exposed to 30 min of warm ischaemia were evaluated on the OCS using lactate assessment. Four of seven transplanted DCD hearts were subsequently weaned off cardiopulmonary bypass on low dose inotrope [39].

It is estimated that use of DCD hearts may increase the number of heart transplants by 11–15% [40]. We believe that functional assessment during *ex situ* normothermic donor heart perfusion must be made prior to transplantation in this setting. In Papworth Hospital, we are currently investigating whether DCD human hearts can be assessed on the OCS using pressure volume loop measurements.

In conclusion, cold ischaemic preservation for the donor heart has been universally adopted into clinical practice over the last 45 years. However, the diminishing pool of ideal donors coupled with the drive to further improve heart transplant outcomes mandate a rethink in this area. Normothermic donor heart perfusion is the logical next step and from the clinical experience to date, appears to hold promise.

Funding sources

The authors have declared no funding.

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6. Transpulmonary gradient >12 mmHg
7. Pulmonary vascular resistance >4 woods units
8. Panel reactive antibodies >20% and positive T-cell cross-match
9. Chronic renal failure
10. Ventilator dependence
11. Ventricular assist device
12. Patient deemed to be high risk by investigator

Appendix 1: PROTECT 1 – Donor and recipient criteria

Donor inclusion and exclusion criteria

1. Age <50 years
2. Stable haemodynamics
3. No echo abnormalities
4. No coronary artery disease
5. Inotrope support at final assessment
 - a. Dopamine <10 mcg/kg/min
 - b. Dobutamine <15 mcg/kg/min
 - c. Epinephrine <0.2 mcg/kg/min
 - d. Norepinephrine <0.02 mcg/kg/min

Recipient exclusion criteria

1. Congenital heart disease
2. Prior organ transplant
3. Simultaneous transplant of non heart allograft
4. Total artificial heart
5. Three or more previous sternotomies

Appendix 2 PROCEED I – Donor and recipient criteria

Donor inclusion criteria

1. Age <60 years
2. Mean systolic blood pressure >80 mmHg
3. Satisfactory echo
4. Ejection fraction >40%
 - a. Absence of severe segmental wall abnormalities
 - b. Absence of left ventricular hypertrophy, septum <12 mm
 - c. Absence of valve abnormalities

Donor exclusion criteria

1. Abnormal coronary angiogram
2. <0.6 donor to recipient body weight ratio
3. Inotropic support at time of final heart assessment
 - a. Dopamine >10 mcg/kg/min
 - b. Dobutamine >10 mcg/kg/min
 - c. Epinephrine <0.05 mcg/kg/min
 - d. Norepinephrine >0.03 mcg/kg/min
 - e. Milrinone >0.3 mcg/kg/min
 - f. Isoproterenol >0.03 mcg/kg/min

Recipient exclusion criteria

1. Congenital heart disease
2. Prior organ transplant
3. Simultaneous transplant of non heart allograft
4. Total artificial heart
5. >2 sternotomies
6. Trans pulmonary gradient >15 mmHg
7. Panel reactive antibodies >20% and positive T-cell cross-match
8. Chronic renal failure
9. Ventricular assist device <30 days or >30 days in presence of sepsis, intra cranial bleed or heparin induced thrombocytopenia
10. Patient deemed high risk by the investigator