Ex-vivo perfusion of donor hearts for human heart transplantation (PROCEED II): a prospective, open-label, multicentre, randomised non-inferiority trial

*Abbas Ardehali, Fardad Esmailian, Mario Deng, Edward Soltesz, Eileen Hsich, Yoshifumi Naka, Donna Mancini, Margarita Camacho, Mark Zucker, Pascal Leprince, Robert Padera, Jon Kobashigawa, for the PROCEED II trial investigators**

Summary

Background **The Organ Care System is the only clinical platform for ex-vivo perfusion of human donor hearts. The system preserves the donor heart in a warm beating state during transport from the donor hospital to the recipient hospital. We aimed to assess the clinical outcomes of the Organ Care System compared with standard cold storage of human donor hearts for transplantation.**

Methods **We did this prospective, open-label, multicentre, randomised non-inferiority trial at ten heart-transplant centres in the USA and Europe. Eligible heart-transplant candidates (aged >18 years) were randomly assigned (1:1) to receive donor hearts preserved with either the Organ Care System or standard cold storage. Participants, investigators, and medical staff were not masked to group assignment. The primary endpoint was 30 day patient and graft survival, with a 10% non-inferiority margin. We did analyses in the intention-to-treat, as-treated, and per-protocol populations. This trial is registered with ClinicalTrials.gov, number NCT00855712.**

Findings **Between June 29, 2010, and Sept 16, 2013, we randomly assigned 130 patients to the Organ Care System group (n=67) or the standard cold storage group (n=63). 30 day patient and graft survival rates were 94% (n=63) in the Organ Care System group and 97% (n=61) in the standard cold storage group (difference 2·8%, one-sided 95% upper confidence bound 8·8; p=0·45). Eight (13%) patients in the Organ Care System group and nine (14%) patients in the standard cold storage group had cardiac-related serious adverse events.**

Interpretation **Heart transplantation using donor hearts adequately preserved with the Organ Care System or with standard cold storage yield similar short-term clinical outcomes. The metabolic assessment capability of the Organ Care System needs further study.**

Funding **TransMedics.**

Lancet 2015; 385: 2577–84

Published Online
April 15, 2015
http://dx.doi.org/10.1016/S0140-6736(15)60261-6

See Comment page 2552

*Investigators listed at end of paper

UCLA Medical Center, Los Angeles, CA, USA (Prof A Ardehali MD, Prof M Deng MD); **The Cedars-Sinai Heart Institute, Los Angeles, CA, USA** (Prof F Esmailian MD, Prof J Kobashigawa MD); **Cleveland Clinic Foundation, Cleveland, OH, USA** (Prof E Soltesz MD, Prof E Hsich MD); **Columbia University Medical Center, New York, NY, USA** (Prof Y Naka, Prof D Mancini MD); **St Barnabas Heart Center, Newark Beth Israel Medical Center, Newark, NJ, USA** (Prof M Camacho MD, Prof M Zucker MD); **Hôpital de la Pitié-Salpêtrière, Paris, France** (Prof P Leprince MD); **and Brigham and Women's Hospital, Boston, MA, USA** (Prof R Padera MD)

Correspondence to:
Prof Abbas Ardehali, Division of Cardiac Surgery, UCLA Medical Center, Los Angeles, CA 90049, USA
aardehali@mednet.ucla.edu

Introduction

Heart transplantation is the treatment of choice for many patients with end-stage heart disease.[1–3] Despite substantial progress in most aspects of heart transplantation (ie, donor management, operative technique, post-operative care, and immunosuppressive regimens), the technique for preservation of donor hearts is still cold ischaemic storage. Cold storage leads to time-dependent ischaemic and subsequent reperfusion injuries of the donor heart, which can impair heart function after transplantation.[4] Prolonged cold ischaemia time is an important risk factor for early dysfunction of the donor heart and death of the recipient.[5,6] Limitations of cold ischaemia time can also adversely affect use of donor hearts and possible organ sharing.[7–10] In the past several decades there has been scientific and clinical interest towards ex-vivo heart perfusion with oxygenated and nutrient enriched blood to reduce ischaemic injury to the donor heart and potentially enable ex-vivo assessment of metabolic and mechanical function. Several reports[11–13] have investigated use of continuous infusion drips of glucose, fatty acids, insulin, heparin, steroids, and antibiotics to maintain a steady state of metabolism of the donor heart ex vivo. The feasibility of ex-vivo heart perfusion for 12 h has been shown with recovery of cardiac function and preservation of endothelial cell function.[14] These studies have paved the way for development of systems for clinical ex-vivo heart perfusion.

The Organ Care System is the first and only clinical ex-vivo heart perfusion platform that can maintain the donor heart in a warm, beating, near-physiological state ex vivo for transplantation. Because the system maintains the donor heart in a perfused state during transportation from the donor hospital to the recipient hospital, cold ischaemia time is likely to be shortened for hearts preserved with this method. Consequently, use of this system might allow for distant procurement of donor hearts, which could balance sharing of donor hearts among regions and possibly enable resuscitation of marginal donor hearts, thus expanding the donor pool. In view of the potential benefits of the Organ Care System, and because standard cold storage has been the gold standard for heart preservation with excellent clinical outcomes, it was paramount to initially show that the Organ Care System is as safe and effective as cold storage for preservation of routine donor hearts.

We did the PROCEED II trial to assess the clinical outcomes of the Organ Care System compared with standard cold storage of donor hearts for transplantation. We postulated that the outcomes of patients undergoing heart transplantation with donor hearts preserved with the Organ Care System would be non-inferior to those of recipients whose donor hearts were preserved with standard cold storage. The study was not designed to test whether the Organ Care System can expand the donor heart pool.

Methods

Study design and participants

We did this prospective, open-label, multicentre, randomised non-inferiority trial at ten heart-transplant centres in the USA and Europe. The appendix provides a complete list of donor and recipient inclusion and exclusion criteria. Eligible recipients (aged ≥18 years) had to be active on the heart-transplant waiting list at each participating centre and meet the study inclusion criteria (appendix). Protocol compliance and outcome data were monitored regularly by an Independent Data Safety and Monitoring Board. An independent Clinical Events Committee adjudicated all causes of death and clinical events. The protocol was approved by the Institutional Review Board at each participating centre. All patients provided written informed consent.

See Online for appendix

For the **protocol** see https://www.uclahealth.org/documents/providers/Proceed-II-Rev-1.6.pdf

Randomisation and masking

When a donor heart that met the study inclusion criteria became available for the recipient, a second assessment of the recipient was done. Participants eligible at the second assessment were randomly assigned (1:1) to receive donor hearts preserved with either the Organ Care System or standard cold storage. An independent biostatistician prepared sealed and masked randomisation envelopes, which were assigned to each trial site. Participants, investigators, and medical staff were not masked to group allocation. We chose this open-label design because masking of medical staff to the method of preservation would have been unrealistic. All hearts preserved with the Organ Care System or by standard cold storage were to be transplanted unless the surgeon's clinical judgment deemed transplantation not in the best interest of the patient. Any organ that was accepted but not transplanted was sent to a pathology core laboratory (Brigham and Women's Hospital, Boston, MA, USA).

Procedures

The Organ Care System is a portable platform designed for ex-vivo heart perfusion with warm, oxygenated, nutrient-enriched donor blood. The heart is beating and metabolically active (figure 1, video). The system is composed of a portable console with a wireless monitor, a disposable perfusion module, and a heart solution set that is given via a standard intravenous infusion pump into the donor blood circulating in the system to replenish substrates and supplement perfusate with vasodilators and antimicrobials (figure 1). The appendix lists the components of the heart solution and additives.

See Online for video

With the Organ Care System, warm oxygenated blood is pumped into the aorta, perfusing the coronary arteries (figure 1). The coronary sinus flow then passes through the tricuspid valve (as both the superior and inferior vena cava are sutured closed) and is ejected by the right ventricle into a pulmonary artery catheter, and returned to the blood reservoir (figure 1). For patients in the Organ Care system group, at the donor hospital and just before arrest of the donor heart 1200–1500 mL of donor blood was collected and used to prime the perfusion module. The donor heart was arrested with 500–750 mL of the centre's standard heart-preservation solution. The aorta and pulmonary artery of the donor heart were cannulated and the heart connected to the Organ Care System device. Once the heart was reanimated to normal sinus rhythm, the pump flow and solution flow rates of the Organ Care System were adjusted to maintain the mean aortic pressure between 60 mm Hg and 90 mm Hg, and coronary blood flow between 650 mL/min and 850 mL/min. Throughout the perfusion process with the Organ Care System, arterial and venous lactate samples were taken regularly from the system perfusate to assess the adequacy of perfusion. The samples were analysed with a handheld lactate analyser (i-Stat, Abbott Diagnostics, East Windsor, NJ, USA). Adequate perfusion was verified if the concentration of venous lactate was lower than the arterial lactate concentration, with a goal of less than 5 mmol/L at the completion of the Organ Care System run, as pre-specified in the protocol.[15] Upon arrival at the recipient hospital, the donor heart was arrested with about 1 L of the centre's standard heart preservation solution and was disconnected from the Organ Care System for implantation into the recipient.

For the standard cold storage group, the donor heart was arrested with the participating centre's standard heart-preservation solution. The transplantation procedure and peri-operative care was completed according to the standard practices at each participating centre. Because each transplant centre had an almost equal number of patients assigned to the Organ Care System and standard cold storage groups, any centre-specific treatments were equally shared between the two groups.

Outcomes

The primary endpoint was 30 day patient and graft survival. Secondary endpoints were cardiac-related serious adverse events, severe rejection rates, and median length of stay in the intensive-care unit. We defined severe rejection as biopsy-proven grade 2R or 3R rejection, based on the International Society for Heart and Lung Transplantation classification system.[16] In view of the theoretical benefit of the Organ Care

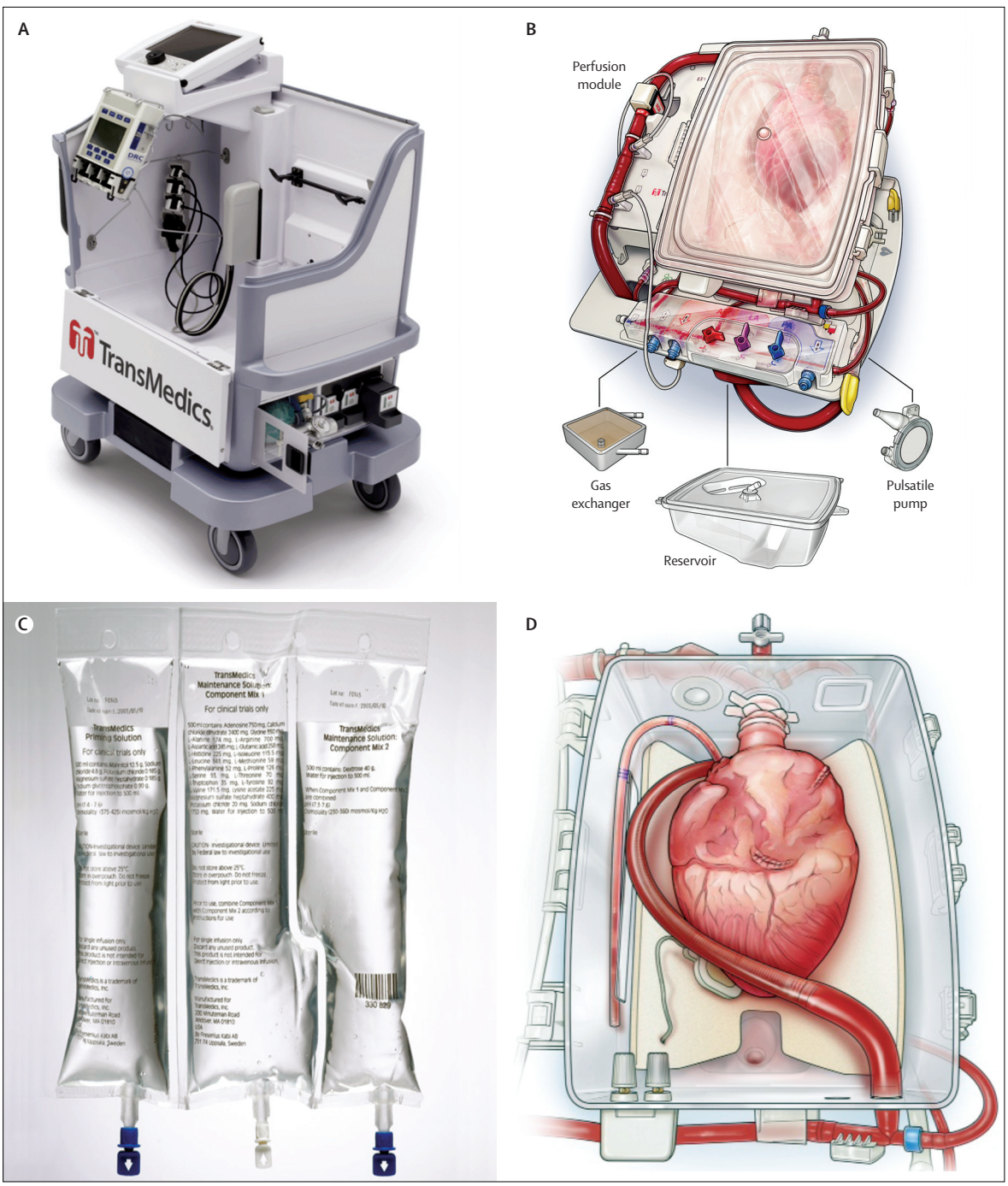

Figure 1: **The Organ Care System**
The Organ Care System is composed of a portable console with heart console (A), heart perfusion set (B), and heart solution set (C). The system is designed for ex-vivo heart perfusion with warm, oxygenated, nutrient-enriched donor blood (D). The heart is beating and metabolically active. This figure has been reproduced by permission of Transmedics (Andover, MA, USA).

System on reduction of cold ischaemia time, we also explored the differences in total preservation time and cold ischaemia time between the Organ Care System and standard cold storage groups. We defined total preservation time as the donor heart's out-of-body time—ie, the period from the time the donor heart was stopped in the donor chest to the time of reperfusion in the recipient chest. Cold ischaemia time refers to the length of time that the donor heart was kept on ice and without any blood supply.

Statistical analysis

The null and alternative hypotheses were:

$$H_0 : \prod_{OCS} \leq \prod_{SOC} - \delta \text{ and } H_1 : \prod_{OCS} > \prod_{SOC} - \delta$$

where $\prod_{OCS}$ is the true proportion of patients surviving at day 30 after transplantation with the originally transplanted heart and no mechanical circulatory support with the Organ Care system, and $\prod_{SOC}$ is the true proportion surviving with the standard cold storage treatment. δ is the non-inferiority margin, which was taken to be 0·10 (ie, 10%).

We calculated the one-sided 95% upper confidence bound based on the normal approximation for the difference between the two population proportions ($\prod_{SOC} - \prod_{OCS}$). An upper confidence bound less than the 10% non-inferioirty margin would result in rejection of the null hypothesis (H_0) in favour of the alternative hypothesis (H_1) and evidence of non-inferiority for the primary effectiveness endpoint. Non-inferiority comparisons of the primary endpoint were done for all study populations. The intention-to-treat population consisted of all randomised recipients for whom a matching and eligible heart were available, as determined at the donor site. The as-treated population consisted of all randomised recipients who received a donor heart transported by either the Organ Care System platform or standard cold storage technique, subsequent to randomisation. The per-protocol population consisted of all patients randomised to their original group who were transplanted and had no major protocol violations. Analysis of the primary efficacy endpoint was based on all study populations. Because the pre-specified analysis of the safety endpoint of cardiac-related serious adverse events was based on the as-treated population, we analysed other secondary endpoints, total preservation time, and cold ischaemia time in the as-treated populations. We used the χ^2 to compare the secondary endpoints, except length of stay in the intensive-care unit, for which we used the Wilcoxon rank-sum test.

For the purpose of sample-size calculation, we assumed that $\prod_{OCS}$=0·95 and $\prod_{SOC}$=0·94. On the basis of these assumptions, use of a normal approximation test, and a one-sided α level of 0·05, inclusion of 54 patients per treatment group would provide 80% power for a test of H_0 versus H_1. To enrol a sufficient sample size in the Organ Care System group to improve the probability of detection of frequently occurring types of adverse events, we increased the sample size to 64 patients per group, for a total of 128 subjects. This trial is registered with ClinicalTrials.gov, number NCT 00855712.

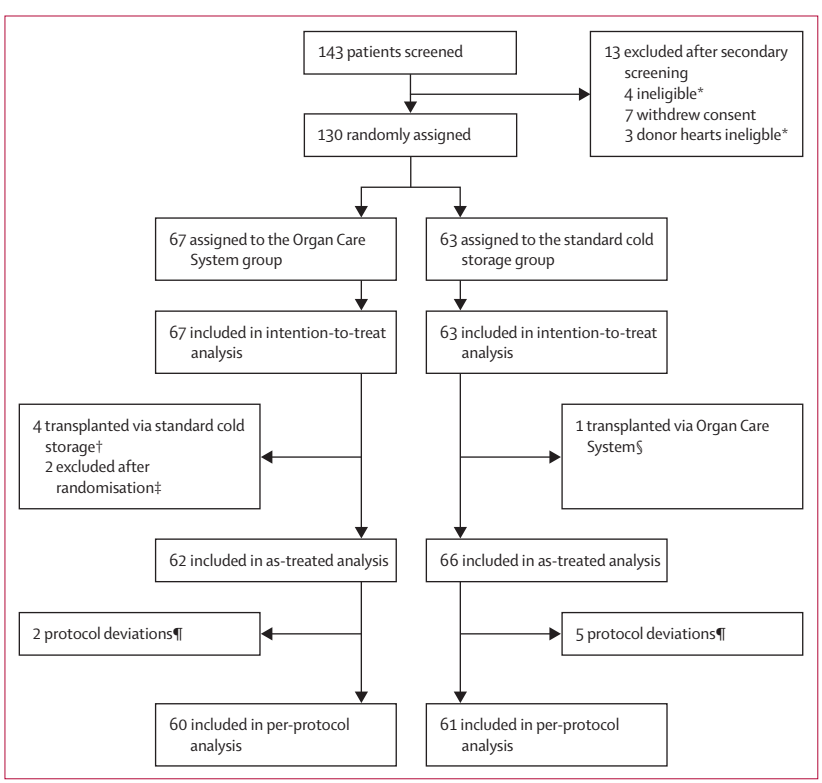

Figure 2: **Trial profile**

*One patient developed clinically significant ventricular assist device-related complications while waiting for a second donor offer, one patient needed a combined heart-kidney transplant while waiting for a second offer; one patient became ventilator dependent on day of transplant, and one patient deteriorated and was delisted; one donor heart had left-ventricular hypertrophy (>1·3 cm) and one donor was older than 60 years. †Two opened randomisation envelopes before confirming availability of the Organ Care System team, one organ procurement organisation refused to retrieve the Organ Care System because of absence of research consent, and one donor heart had a high concentration of serum lactate before retrieval. ‡After turning down initial donor heart offers, one recipient had more than two sternotomies while waiting for a third offer and one recipient withdrew before a second offer. §Because of misreading of the randomisation card. ¶Deviations in the Organ Care System group were due to user error in cannulation and one recipient receiving unassigned treatment; in the standard cold storage group one recipient was enrolled in another pharmaceutical trial and four received unassigned treatment.

Role of the funding source

The funder of the study had a role in study design and data collection. The authors were responsible for data interpretation, data analysis, and writing of the report. AA and JK had full access to all the data in the study. All authors had final responsibility for the decision to submit for publication.

Results

Figure 2 shows the trial profile. Between June 29, 2010, and Sept 16, 2013, we randomly assigned 130 patients to the Organ Care System Group (n=67) or the standard cold storage group (n=63; intention-to-treat population). The as-treated population comprised 128 (93%) patients and the per-protocol population comprised 121 (93%) patients. Donor and recipient characteristics and risk factors were roughly similar between groups (table 1). All the donor hearts that were maintained with the Organ Care System platform, and subsequently transplanted, had stable perfusion and metabolic characteristics; figure 3 provides a summary of the Organ Care System heart perfusion measures and perfusate lactate trends.

In the intention-to-treat population, the 30 day patient and graft survival rates were 94% in the Organ Care System group and 97% in the standard cold storage

group (table 2). Patient and graft survival rates were similar because no redo heart transplant surgeries were done. The 95% upper confidence bound for the difference between the two population proportions for the primary effectiveness endpoint was 0·088 (ie, <0·10), so the null hypothesis was rejected in favour of the alternative hypothesis, and non-inferiority was shown. Similar primary endpoint findings of non-inferiority were noted in the as-treated and per-protocol study populations (table 2). The proportion of patients who had cardiac-related serious adverse events did not differ significantly between the two groups (table 2). The list of cardiac-related serious adverse events was similar between the two groups (table 3). The other secondary endpoints of severe rejection and stay in the intensive-care unit likewise did not differ significantly between the groups (table 2).

Figure 4 describes the total preservation time of the donor hearts in the Organ Care System group. Mean total preservation (out-of-body) time was significantly longer in the Organ Care System group than in the standard cold storage group (324 min [SD 79] *vs* 195 min [65]; p<0·0001). However, mean total cold ischaemia time was significantly shorter in the Organ Care System group than in the standard cold storage group (113 min [27] *vs* 195 min [65]; p<0·0001; figure 5). The appendix summarises additional transplant details of both study groups.

Five donor hearts selected for four patients (one patient was offered two donor hearts) were deemed unacceptable for transplantation while on the Organ Care System and were discarded. The four patients were subsequently transplanted with another donor heart. The five discarded donor hearts are not shown in figure 2 because only eligible recipients (not donor hearts) were randomised in this trial. Four of the five donor hearts were discarded because of rising total perfusate lactate concentrations during the Organ Care System process, which indicated

	Organ Care System group (n=67)	Standard cold storage group (n=63)
Recipient characteristics*		
Age (years)	56 (20–75)	57 (20–76)
Sex		
Male	55 (82%)	45 (71%)
Female	12 (18%)	18 (29%)
Weight (kg)	80 (53–125)	69 (40–113)
Height (cm)	173 (145–195)	173 (152–191)
Body-mass index (kg/m^2)	25 (17–41)	23 (16–38)
Diagnosis of cardiomyopathy		
Ischaemic	25 (38%)	18 (29%)
Idiopathic	30 (45%)	30 (48%)
Other	8 (12%)	14 (22%)
On ventricular assist device	18 (27%)	15 (24%)
Clinical history of diabetes	19 (28%)	15 (24%)
United Network Organ Sharing status 1A†	45 (67%)	50 (79%)
Donor characteristics		
Age (years)	35 (18–58)	34 (13–60)
Sex		
Male	44 (66%)	45 (71%)
Female	23 (34%)	18 (29%)
Weight (kg)	80 (48–143)	77 (51–133)
Height (cm)	174 (150–198)	173 (152–198)
Body-mass index (kg/m^2)	27 (18–44)	26 (15–45)
Cause of death		
Anoxia	15 (22%)	13 (21%)
Stroke or cerebrovascular accident	18 (27%)	17 (27%)
Head trauma	26 (39%)	28 (45%)
Other	6 (9%)	5 (8%)
Female donor to male recipient	13 (19%)	11 (18%)

Data are median (range) or n (%). *One recipient in the Organ Care System group did not have information about medical history and was excluded from analyses of diagnosis of cardiomyopathy, ventricular assist device, clinical history of diabetes, and United Network Organ Sharing status. †Most urgent status for heart transplant candidates.

Table 1: **Donor and recipient characteristics (intention-to-treat population)**

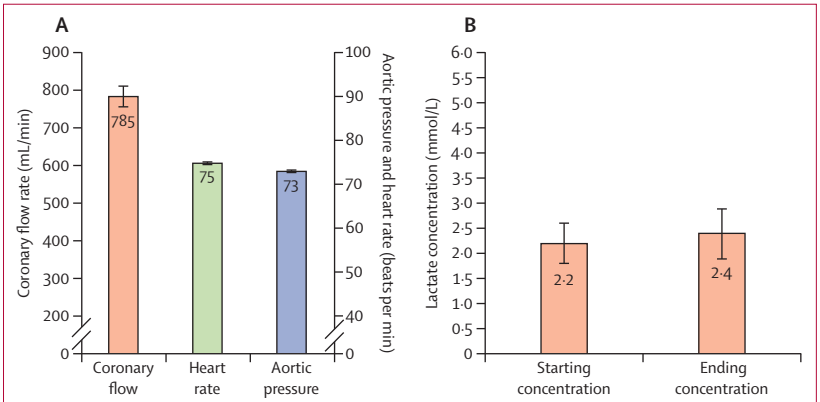

Figure 3: **Mean changes in Organ Care System perfusion measures (A) and lactate trends (B) for transplanted hearts**
Error bars show SDs.

	Organ Care System group	Standard cold storage group	Between-group difference (one-sided 95% UCB or 95% CI)	p value
Primary endpoint (30 day patient and graft survival)				
Intention-to-treat	63/67 (94%)	61/63 (97%)	2·8 (8·8)	0·45
As-treated	58/62 (94%)	64/66 (97%)	3·5 (9·6)	0·36
Per-protocol	56/60 (93%)	59/61 (97%)	3·4 (9·9)	0·39
Secondary endpoints (as-treated population)				
Patients with cardiac-related serious adverse events	8 (13%)	9 (14%)	1 (–12 to 11)	0·90
Incidence of severe rejection	11 (18%)	9 (14%)	4 (–8 to 17)	0·52
Median ICU length of stay (h)	147 (107–212)	137 (97–197)	10 (–10 to 42)	0·24

Data are n/N (%) or n (%), or median (IQR), unless otherwise indicated. UCB=upper confidence bound. ICU=intensive-care unit.

Table 2: **Outcomes of primary and secondary endpoints**

persistent myocardial ischaemia despite optimisation of myocardial perfusion. The appendix shows the Organ Care System heart perfusion measures and circulating lactate concentrations of the four discarded donor hearts and the pathological findings of these hearts. In the first declined heart, there was history of cardiac arrest with chest compressions. The pathological examination showed areas of myocardial haemorrhage and necrosis suggestive of clinically significant myocardial contusion. The second heart was from a young donor with history of drug abuse. Pathological examination showed myocardial scarring and necrosis consistent with cocaine use. The third heart had left ventricular hypertrophy (septal thickness >1·3 cm) that was overlooked by the procurement team members. In the fourth heart, there was congenital fusion of the left and right aortic valve cusps resulting in mild to moderate aortic regurgitation and inability to stabilise aortic perfusion pressure. The fifth donor heart could not be placed on the Organ Care System because of friability of the aorta due to connective tissue disorder. This heart might have been successfully implanted if procured with standard cold storage.

	Organ Care System group (n=62)	Standard cold storage group (n=66)	p value
Left ventricular dysfunction	5 (8%)	4 (6%)	0·657
Right ventricular dysfunction	2 (3%)	6 (9%)	0·170
Graft failure	1 (2%)	0	0·330

Data are n (%). We defined left ventricular dysfunction as a left atrial pressure greater than 18 mm Hg with a cardiac index less than 2·0 L/min per m², requiring implantation of a left ventricular assist device or inotropic treatment for more than 7 days. We defined right ventricular dysfunction as central venous pressure greater than 18 mm Hg with a cardiac index less than 2·0 L/min per m², in absence of left atrial pressure greater than 18 mm Hg, requiring implantation of a right ventricular assist device or inotropic treatment for more than 7 days. We defined graft failure as heart dysfunction requiring sustained (>30 days) assist devices or relisting for transplantation. Numbers in this table differ from those in table 2, because this table depicts the number of events.

Table 3: **List of cardiac-related serious adverse events (as-treated population)**

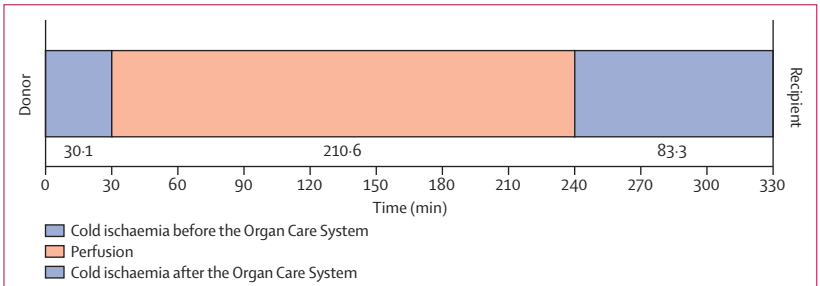

Figure 4: **Cold ischaemia time and perfusion time for donor hearts preserved with the Organ Care System**
Cold ischaemia time consists of the initial retrieval phase (time needed to harvest and implement the heart into the Organ Care System) and the final re-implantation phase (to place the donor heart into the recipient).

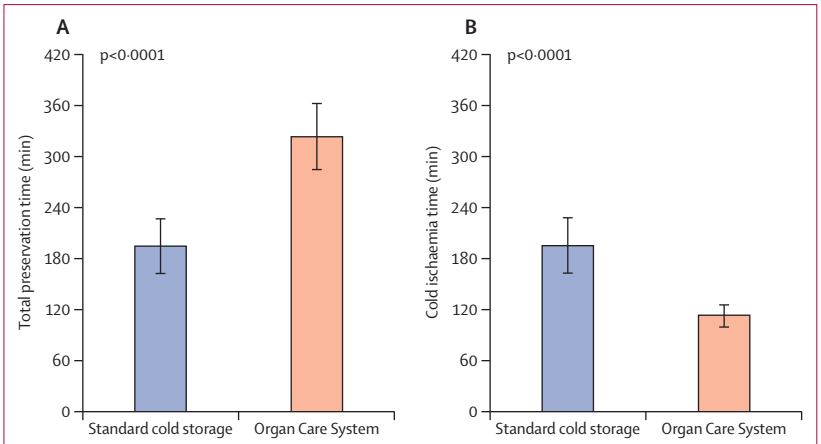

Figure 5: **Mean total preservation (out-of-body) time (A) and total cold ischaemia time (B) in the Organ Care System group versus the standard cold storage group**
Error bars show SDs.

Discussion

In the past few years, there has been a global scientific and clinical focus on ex-vivo donor organ perfusion for solid organ transplantation. Ex-vivo perfusion is viewed as a potential leap forward to overcome the limitations and effects of cold ischaemic preservation on donor organs. Several platforms have been developed for kidney, lung, and liver ex-vivo donor organ perfusion;[17–19] however, the Organ Care System we used is the only platform developed for ex-vivo heart perfusion for transplantation.

In our study, use of the Organ Care System did not seem to affect short-term patient outcomes of 30 day patient and graft survival compared with the standard cold storage method. Likewise, rates of cardiac-related serious adverse events, incidence of severe rejection, and length of stay in the intensive-care unit did not differ significantly between the two study groups. Donor hearts in the Organ Care System group had a significantly longer preservation (out-of-body) time, but a shorter cold ischaemia time, than did those in the standard cold storage group. The longest preservation time with the Organ Care System was 9 h and 7 min. The long preservation time is probably due to the extra time needed to instrument the donor heart into the Organ Care System circuit and optimise the perfusion characteristics. Because this study was not and could not be masked, the surgical team might have lacked a sense of urgency in the Organ Care System group, especially in recipents needing explantations of complex ventricular assisted devices. Despite the prolonged mean preservation time, the Organ Care System group had a shorter mean cold ischaemia time than the standard cold storage group. The cold ischaemia time in the Organ Care System group is limited to the obligatory initial retrieval (ie, the time needed to harvest and instrument the heart into the Organ Care System) and final re-implantation phases. Because of the present time limitation of donor heart cold ischaemia time of 6 h, maintenance of the cold ischaemia time within a

reasonable range (while prolonging the preservation time of donor hearts) holds promise for long-distance procurements. A prolonged preservation time could also lead to increased sharing of the donor hearts to balance the inequities in donor heart availability in different regions, and possible future HLA matching in heart transplantation.

In this study, five donor hearts preserved with the Organ Care System were discarded: four because of rising lactate concentrations despite optimisation of coronary flow and one because of technical issues (aortic cannulation). The ex-vivo metabolic assessment afforded by the Organ Care System is a new capability that enables some biomarker data to be assessed by the transplant team up to the point of transplantation. Such assessment is not afforded by cold storage. The decline of these five donor hearts is a reflection of this new capability. The clinical decision to decline these hearts might have been due to the surgical team's growing knowledge about how to react to the metabolic assessment data of the Organ Care System. Whether these donor hearts would have had problems or failed if transplanted is unclear. However, there is a possibility that the Organ Care System was the cause of the hearts becoming unacceptable, in view of these five hearts seeming appropriate for transplantation at harvest. It is also possible that the Organ Care System platform might have been able to uncover pathological findings in donor hearts that would have been otherwise acceptable by present standards. All the discarded hearts had anatomical or structural abnormalities that could have affected their function. Because no donor hearts were discarded for quality reasons in the standard cold storage group, it is possible that less than optimum, donor hearts could have been transplanted in this group. However, post-transplant outcomes were satisfactory in the standard cold storage group. Further studies to assess and understand the metabolic assessment capability of the Organ Care System are planned (ClinicalTrials.gov, number NCT02323321).

The Organ Care System is the first platform for ex-vivo preservation of human hearts (panel). Improvements in aortic cannulation techniques, standardisation of myocardial protection before and after the Organ Care System process, development of new biomarkers for adequacy of myocardial perfusion, and automation of adjustments in perfusion measures will undoubtedly improve this technology. In addition to reducing cold ischaemia time, Organ Care System technology can conceivably allow longer preservation time, which could improve organ sharing and matching, and possibly change heart transplantation to a less urgent operation. Other potential benefits might include resuscitation of unused or unacceptable hearts with expansion of the donor pool.[20] The ability of the Organ Care System to reanimate hearts from donors after cardiac death to a near physiological state and assess metabolic state before transplantation might present a new pool of donor hearts for transplantation (unpublished).[23] Finally, ex-vivo donor heart perfusion might provide a metabolically active donor heart for potential pharmacological or genetic modifications before transplantation.[24]

Our study has some limitations. The protocols for myocardial protection before and after the Organ Care System were not standardised among all participating centres and might have affected clinical outcomes in the Organ Care System group. Furthermore, the discarding of Organ Care System donor hearts before transplantation was not anticipated; however, we have included a detailed analysis of these discarded donor hearts. Through advances in Organ Care System technology, protocols have since been updated to better understand and improve myocardial perfusion and protection with this technique.

In conclusion, our findings show that the clinical outcomes of donor hearts adequately preserved with the Organ Care System platform are non-inferior to the outcomes of those preserved with standard cold storage. Evaluation of the metabolic assessment capability of the Organ Care System requires further study.

***Panel*: Research in context**

Systematic review

We search PubMed, the Cochrane Library, and SCOPUS on Nov 15, 2014, with the search term "ex-vivo heart perfusion", for reports of ex-vivo heart perfusion. Several experimental reports[11–13] have used continuous infusion drips of glucose, fatty acids, insulin, heparin, steroids and antibiotics to maintain a steady state of metabolism of the donor heart ex vivo. The feasibility of ex-vivo heart perfusion for 12 h has been shown with recovery of cardiac function and preservation of endothelial cell function.[14] We identified several reports[20–22] that described the use of the Organ Care System in human heart transplantation.

Interpretation

The Organ Care System is the only clinical ex-vivo heart transplant platform that can maintain the donor heart in a warm, beating, near-physiological state ex vivo. The PROCEED II trial is the first clinical trial to assess the efficacy and safety of this new technology in human heart transplantation. Our study shows that the short-term outcomes of donor hearts adequately preserved with the Organ Care System platform are similar to those of hearts preserved with standard cold storage. These findings will provide a foundation for future studies of ex-vivo heart perfusion.

Contributors

AA and JK participated in the study design, data interpretation, data analysis, and writing of the manuscript. All other authors participated in the trial steering committee meetings, data collection, and review of the final manuscript.

The PROCEED II trial investigators

David Baran (St Barnabas Heart Center, Newark Beth Israel Medical Center, Newark, NJ, USA); Ugolino Livi and Giorgio Guzzi (Ospedale Santa Maria della Misericordia, Udine, Italy); Steven Tsui (Papworth Hospital NHS Foundation Trust, Cambridge, UK); Andre Simon (Royal Brompton and Harefield NHS Trust, Harefield Hospital, Middlesex, UK); and Joren Madsen, (Massachusetts General Hospital, Boston, MA, USA).

Declaration of interests
AA received funds for PROCEED II trial expenses from UCLA Medical Center, and fees for travel expenses from Transmedics. FE has received personal fees from Transmedics. MC has received fees for consultancy from Sunshine Heart, Thoratec, and Maquet. JK has received grants and personal fees from Transmedics. ES has served on a scientific advisory board for Transmedics. EH has received honoraria and fees for travel expenses from Transmedics. YN has received personal fees from Transmedics and Thoratec. RP has worked in the Transmedics pathology core laboratory. MD, DM, MZ, and PL declare no competing interests.

Acknowledgments
This study was funded by Transmedics. This study was presented in part at the Annual Meeting of the International Society of Heart and Lung Transplantation; San Diego, CA, USA; April 10–13, 2014.

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