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Long-term outcomes after heart transplantation using ex vivo allograft perfusion in standard risk donors: A single-center experience

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Abstract

Introduction: The Organ Care System (OCS) is an ex vivo perfusion platform for donor heart preservation. Short/mid-term post-transplant outcomes after its use are comparable to standard cold storage (CS). We evaluated long-term outcomes following its use.

Methods: Between 2011 and 2013, 38 patients from a single center were randomized as a part of the PROCEED II trial to receive allografts preserved with CS ($n = 19$) or OCS ($n = 19$). Endpoints included 8-year survival, survival free from graft-related deaths, freedom from cardiac allograft vasculopathy (CAV), non-fatal major adverse cardiac events (NF-MACE), and rejections.

Results: Eight-year survival was 57.9% in the OCS group and 73.7% in the CS group ($p = .24$). Freedom from CAV was 89.5% in the OCS group and 67.8% in the CS group ($p = .13$). Freedom from NF-MACE was 89.5% in the OCS group and 67.5% in the CS group ($p = .14$). Eight-year survival free from graft-related death was equivalent between the two groups (84.2% vs. 84.2%, $p = .93$). No differences in rejection episodes were observed (all $p > .5$).

Conclusions: In select patients receiving OCS preserved allografts, late post-transplant survival trended lower than those transplanted with an allograft preserved with CS. This is based on a small single-center series, and larger numbers are needed to confirm these findings.

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AUTHOR CONTRIBUTIONS

Jon A. Kobashigawa and Fardad Esmailian were involved in the study conceptualization and design. Qiudong Chen, Amy Roach, and Tahli Singer-Englar conducted the data analysis and interpretation and drafted the manuscript. Dominic Emerson, Dominick Megna, Danny Ramzy, Pedro Catarino, Jignesh K. Patel, Michelle Kittleson, Lawrence Czer, Joanna Chikwe, and Fardad Esmailian were involved in the data interpretation and manuscript writing/review. All authors reviewed and edited the final manuscript.

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

Keywords

heart (allograft) function/dysfunction; heart disease; organ perfusion and preservation; patient survival

1 INTRODUCTION

Orthotopic heart transplantation (OHT) is currently the gold standard for the treatment of refractory end-stage heart failure. Post-transplant outcomes have significantly improved due to advances in surgical technique, donor allocation, immunosuppression, and post-operative care. However, donor availability remains a major limitation.[1] Although the number of OHT has increased over the last decade, the waiting list continues to grow as demand far exceeds the supply, with a 42.6% increase from 2008 to 2019.[2] Compared to other organ transplants, one major constraint unique to OHT is the heart's heightened sensitivity to ischemic damage. Conventional cold storage (CS) of donor hearts during transportation uses cooling to reduce metabolic activity. However, this does not completely eliminate ongoing myocardial injury as low-level anaerobic processes continue on a cellular level.[3] Prolonged ischemic time of greater than 4–6 h is associated with increased early graft dysfunction and recipient mortality.[4] Consequently, this results in limited organ sharing between geographic regions and underutilization of available donor organs.

The Organ Care System (OCS) (TransMedics, Andover, MA, USA) is currently the only commercially available ex vivo normothermic organ perfusion platform for donor hearts and recently received premarket approval from the Food and Drug Administration. Using oxygenated and nutrient-enriched donor blood, it was designed to maintain the donor heart in a warm, beating, and perfused state during transport. At the same time, ongoing monitoring of the hemodynamic profile and metabolic activity of the donor heart is made possible by using parameters such as aortic pressure, coronary flow, temperature, oxygen saturation, hematocrit, and lactate. The safety and effectiveness of the OCS was first established in two single-arm, non-randomized studies.[5,6] Subsequently, PROCEED II (Clinical Trial Number NCT00855712) was the first pivotal randomized clinical trial that established non-inferior short-term clinical outcomes of OCS in standard criteria donors as compared to conventional CS.[7] Data on long-term outcomes after OCS use for graft preservation remain scarce in existing literatures. Therefore, we sought to evaluate long-term outcomes of patients transplanted with allografts preserved using the OCS versus standard CS.

2 MATERIALS AND METHODS

2.1 Data source

We longitudinally followed patients who were enrolled from a single center into the multi-center PROCEED II trial (Clinical Trial Number NCT00855712) between 2011 and 2013. Details regarding the study protocol, inclusion/exclusion criteria, and donor criteria were previously described.[7] Briefly, PROCEED II was a non-inferiority trial aimed to assess short-term outcomes of the OCS compared with standard CS of human donor hearts for

transplantation. It randomized 130 patients to either the OCS group (n = 67) or the CS group (n = 63). The primary endpoint was 30-day patient and graft survival, with a 10% non-inferiority margin. No significant differences in short-term outcomes were detected between the two groups. From our center, we enrolled 38 patients into the PROCEED II trial, randomized to receive transplantation with donor hearts preserved with either standard CS (n = 19) or the OCS (n = 19). No cross-over occurred in our cohort. Median follow up time was 8.42 (interquartile range [IQR] 2.08–9.45) years for the entire cohort and 92.1% complete. The study was performed in strict compliance with the ethical standards set forth by the World Medical Association, as stated in the Declaration of Helsinki, as well as the International Society for Heart and Lung Transplantation (ISHLT)'s Statement on Transplant Ethics. All patients provided written informed consent to participate in the initial PROCEED II trial. Follow-up information was obtained retrospectively and waiver of informed consent was obtained under a separate protocol. Both study protocols were approved by our Institutional Review Board.

2.2 Study endpoints

The primary endpoint was 8-year overall survival. Freedom from cardiac graft-related death up to 8 years was also assessed. Secondary endpoints included 8-year freedom from cardiac allograft vasculopathy (CAV), freedom from non-fatal major adverse cardiac events (NF-MACE: myocardial infarction, new congestive heart failure, percutaneous coronary intervention, implantable cardioverter defibrillator [ICD]/pacemaker implant, stroke), freedom from rejections (any-treated rejection [ATR], acute cellular rejection [ACR], antibody-mediated rejection [AMR], and biopsy negative rejection [BNR]). CAV was defined as any stenosis ≥30% by invasive angiography and was screened at 6 weeks and 1 year after transplantation, then every year thereafter, and at the time of any clinical indication. The determination of ACR and AMR followed the ISHLT grading system.[8–10] They were identified based on the pathological findings of endomyocardial biopsy (EMB) after transplantation, which was performed once a week for the first month, twice a week for the second month, once a month from months 3 to 6, and once every other month from months 7 to 12 after transplantation. After the first year, EMB was performed only if clinically indicated. Additionally, in select low-risk patients, Allomap (CareDx Inc., San Francisco, CA, USA) was used instead of EMB for rejection surveillance between post-transplantation months 7 and 12. Patients were considered low risk if they had normal ejection fraction, no donor-specific antibody, and no previous episode of AMR or ACR. The detailed management of induction, maintenance, and rejection therapy at our center was previously described.[11]

Graft total preservation time and ischemic time were also compared between the two groups. Total graft preservation time was defined as the period between the arrest of the donor heart in the donor chest and graft reperfusion in the recipient chest. Total ischemic time refers to the length of time that the donor heart was kept on ice and without any blood supply. In the CS group, total ischemic time was equivalent to total graft preservation time.

2.3 Statistical analysis

Categorical variables were expressed as group percentages, and continuous variables were expressed as either mean +/− standard deviation or median with IQR depending on overall distribution. The Shapiro–Wilk test was used to test for normal distribution of continuous variables. Between-group differences in continuous variables were evaluated using unpaired Student *t*-tests if normally distributed or Wilcoxon signed-rank test when the normality assumption was violated. Between-group differences in categorical variables were assessed using chi-square test or Fisher's exact test when expected counts per cell were less than 5. A *p*-value less than or equal to .05 was considered statistically significant. Overall survival was determined using Kaplan–Meier estimates, and compared between strata using log-rank tests. Patients who had not died were censored upon the last date that they were known to be alive via follow-up assessment. Survival free from graft-related death was estimated using competing risk analysis, with death from causes unrelated to the cardiac graft as a competing risk. The cumulative incidences of non-fatal outcomes, such as CAV, NF-MACE, and rejections, were estimated with death as a competing risk and compared between strata using the Gray's test. All statistical analyses were performed using SAS software, Version 9.4 (SAS Institute Inc., Cary, NC, USA).

3 RESULTS

Baseline recipient and donor characteristics are listed in Table 1. Patients in the CS group had significantly older recipient age (59.9 ± 11.8 years vs. 51.9 ± 11.8 years, $p = .04$) and numerically higher proportion of status 1A patients (84.2% vs. 52.6%, $p = .10$). There were no differences in prior sternotomy (52.6% vs. 52.6%, $p = 1.0$), pre-transplant mechanical circulatory support use (21.1% vs. 31.6%, $p = .71$), sensitization status (as evidenced by baseline panel reactive antibody > 10%) (36.8% vs. 21.1%, $p = .48$), or percentage of recipients with ischemic cardiomyopathy (47.4% vs. 31.6%, $p = .46$) between the CS and OCS group. There were no multi-organ transplants in this cohort. Total graft out-of-body time was longer for the OCS group (361 ± 96 min vs. 207 ± 50 min, $p < .001$), while cold ischemic time was shorter for the OCS group (134 ± 45 min vs. 207 ± 50 min, $p < .001$).

At 8 years, there was a trend towards lower overall survival in the OCS group (57.9%, 95% confidence interval [CI] 26.7–79.7 vs. 73.7%, 95% CI 41.6–90.0, $p = .24$) (Table 2, Figure 1). Detailed causes of early and late mortality in both study arms and select donor and recipient characteristics are described in Table 3. Eight deaths occurred in the OCS group within 8 years following transplant. Three early mortalities, occurring on post-operative day (POD) 3–33, were all graft related. The remaining deaths took place between POD 229 and 2561: two patients died due to complications of malignancy, two patients had multi-organ failure due to CMV infection, and one died of unknown etiology. In comparison, there were five mortalities in the CS group. Three were related to the cardiac graft, including two cases of rejection and one case of sudden cardiac arrest at home with unknown cause, and all took place at least >6 months after transplant. Eight-year survival free from cardiac graft-related death, with other causes of death as a competing risk, was 84.2% for both the CS group and the OCS group (95% CI 64.5–96.3 vs. 64.5–96.3, $p = .93$) (Figure 1, insert).

Among the three early mortalities in the OCS group, one patient (49 years, female, status 2 at listing) with familial dilated cardiomyopathy had severe primary graft dysfunction. The donor was a 49-year-old male with normal left ventricular ejection fraction (60%) and coronary angiogram. The patient had minimal ventricular function after weaning from cardiopulmonary bypass (CPB) and was placed on venoarterial extracorporeal membrane oxygenation (VA-ECMO). On POD 3, she underwent total artificial heart implantation and ECMO decannulation. Immediately afterwards, she developed disseminated intravascular coagulation with extensive thrombosis in the aorta and right atrium. The total artificial heart had to be explanted, and she was unable to be placed back on VA-ECMO and expired. The second patient (55 years, male) had suspected severe allergic reaction to protamine and blood products transfusion. He had a history of valvular cardiomyopathy with previous mechanical aortic and mitral valve replacements and an ascending aortic aneurysm. After redo-sternotomy, heart transplantation, and ascending aortic replacement, donor graft function was initially excellent upon weaning from CPB. However, after infusion of protamine and additional blood products, graft function immediately deteriorated necessitating reinstitution of CPB. Significant thrombus was discovered in the left atrium, left ventricle, ascending and descending aorta that required additional cooling and removal, but the transplanted heart had minimal function. He was placed on VA-ECMO and intra-aortic balloon pump but had no meaningful neurological recovery and was subsequently declared brain dead on POD 5. The third patient (38 years, male) developed cardiac arrest secondary to cardiac tamponade. His transplantation and post-operative course were uncomplicated. He underwent an EMB on POD 13 and was discharged home on POD 14 with therapeutic Lovenox injections due to significant history of antiphospholipid syndrome and hypercoagulable state. On POD 15, he was readmitted with cardiac tamponade leading to cardiac arrest. Despite emergent surgical evacuation, he developed anoxic brain injury and subsequently died 33 days after the initial transplant.

Eight-year freedom from CAV was 89.5% in the OCS group and 67.8% in the CS group ($p = .13$), and freedom from NF-MACE was 89.5% in the OCS group and 67.5% in the CS group ($p = .14$) (Figure S1). Regarding specific causes of NF-MACE, two patients developed new congestive heart failure in the OCS group. In the CS group, three patients required permanent pacemaker or ICD insertion, and two patients developed new congestive heart failure with reduced ejection fraction. Otherwise, 8-year incidence of post-transplant rejections was similar between the two groups (Figure S2).

4 DISCUSSION

There is a lack of long-term data on outcomes after OCS use for cardiac allograft preservation. At our institution, we demonstrated that 8-year survival was numerically lower in the OCS group compared to the CS group. This difference in late survival was primarily driven by mortalities that were unrelated to the cardiac graft, as survival free from graft-related deaths was similar. Additionally, we found that freedom from CAV and NF-MACE trended higher in those who received donor hearts preserved with OCS.

The OCS has significant potential for reducing cold ischemia time, thereby minimizing myocardial damage and reducing constraints of procurement distances to improve donor

utilization.[12] PROCEED II, a randomized, prospective, non-inferiority, open-label, multi-center trial, demonstrated comparable 30-day patient/graft survival, cardiac-related serious adverse events, and severe rejection in patients undergoing OHT with standard risk donor hearts preserved on the OCS compared to conventional CS. At the same time, OCS allowed significantly longer preservation (out-of-body) time, but shorter cold ischemic time.[7] Several other single-center studies also evaluated short and intermediate outcomes following the use of OCS to preserve standard criteria donor grafts. Koerner et al. evaluated post-transplant survival after implantation of standard criteria donor grafts preserved with OCS ($n = 29$) versus CS ($n = 130$) in a prospective, nonrandomized study. Two-year survival was 89% and 79% for OCS and CS group, respectively ($p = .19$).[13] In an earlier study from our institution using the same cohort of patients as the current investigation, Chan et al. demonstrated that 2-year survival was 72.2% in patients transplanted with an allograft preserved with the OCS and 81.6% in patients who received an allograft preserved with standard CS ($p = .38$).[14]

In the current study, we have demonstrated a trend toward lower overall survival at 8 years following transplant when OCS was used for donor allograft preservation. When causes of mortality were evaluated in detail, it showed that this difference in late survival was primarily driven by mortalities that were unrelated to the cardiac graft. Only three deaths in the OCS group were graft-related and all occurred early in the post-operative period (POD 3–33). The remaining deaths (5/8, 62.5%) took place at least 6 months following transplant and were due to complications from either CMV infection or malignancy. These late mortalities were more likely associated with chronic immunosuppression rather than graft preservation on the OCS. Subsequently, when survival free from graft-related death was analyzed with other causes of death as a competing risk, there was no longer a difference, with equal estimated 8-year survival of 84.2% versus 84.2% ($p = .93$) in the OCS and CS group.

Although the primary interest of our study was long-term outcomes following OCS use, the three early mortalities in the OCS group warrant further attention. One patient developed severe PGD, and the cause for this was not clear. She lacked any discernable risk factors for post-transplant complications (e.g., status 2 listing, no pre-transplant mechanical circulatory support use, no prior sternotomy, standard-risk donor with short ischemic time). Sub-optimal graft preservation on the OCS was also unlikely, as graft perfusion during transport was carefully monitored using serial lactate measurements under the PROCEED II study protocol.[7] In the second patient, severe allergic reaction to protamine and additional blood products given intra-operatively were likely associated with his subsequent mortality, as the initial graft function after weaning from CPB was excellent. In the third patient, cardiac tamponade most likely developed because of bleeding after EMB due to therapeutic anticoagulation.

At 8 years, we also noted that OCS use was associated with a trend toward greater freedom from CAV (89.5% vs. 67.8%, $p = .13$) and NF-MACE (89.5% vs. 67.5%, $p = .14$). Although patients were randomized to the OCS or CS group, it is important to note that even after randomization, recipients in the OCS group were significantly younger (59.9 ± 11.8 years vs. 51.9 ± 11.8 years, $p = .04$) and had numerically lower proportion of status 1A patients at transplant (52.6% vs. 84.2%, $p = .10$) than the CS group. It is possible that these differences

in baseline characteristics contributed to the observed difference in post-transplant CAV and NF-MACE. Additionally, since the OCS group had significantly shorter cold ischemic time, it is possible that this protected against the development of CAV. Ischemic-reperfusion injury has been showed to be associated with the development of CAV due to endothelial damage, and graft ischemic time > 240 min has been shown to be a predictor of the development of CAV.[15–17] Importantly, CAV was defined using any stenosis ≥30% on angiography in our study instead of the ISHLT standardized nomenclature.[18]

Several limitations exist in this study. First and foremost, the sample size of the existing analysis is small and may be underpowered to detect any significant differences between the groups. The PROCEED II trial randomized 130 patients at 20 centers, and our cohort only represented 38 participants of the trial at one center. Larger numbers will be needed to confirm these findings. Second, our study population is carefully selected based on the inclusion and exclusion criteria of the PROCEED II trial.[7] From the recipient standpoint, patients with ventilator dependency and dialysis-dependent renal failure at the time of transplant were excluded, and no multi-organ transplants were performed in our cohort. We still have no knowledge of outcomes of the use of OCS in these recipient populations. From the donor standpoint, donor hearts were only selected if donor age was less than 60 years old, with ejection fraction > 40% and left ventricular inter ventricular septum and posterior wall thickness < 1.3 cm.[7] Mean donor age in our cohort was 30.9 ± 13.1 in the OCS group and 31.8 ± 13.5 in the CS group, and only one donor in each group had a history of diabetes. Therefore, only standard risk donors were used. Favorable donor characteristics should also be considered when interpreting the results of this study. Since PROCEED II, many published or ongoing investigations sought to evaluate the use of OCS in extended-criteria donors and donors after circulatory death.[19–25] In these scenarios, besides minimizing cold ischemic time, the OCS provided additional benefits of allowing resuscitation and careful assessment of graft quality before definitive transplantation. Thus, it is important to note that the results of the current study only apply to standard risks donors, and no inference regarding extended-criteria donors can be made.

5 CONCLUSION

In carefully selected patients undergoing heart transplant using standard risk donors, OCS use for allograft preservation is associated with a trend toward lower overall survival at 8 years. This difference was primarily driven by late mortalities that seemed unrelated to the cardiac graft, and 8-year survival free from graft-related deaths was similar. These results are based on a small single-center series, and larger numbers are needed to confirm these findings.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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CONFLICT OF INTERESTS

Fardad Esmailian received research grants from TransMedics. Jon A. Kobashigawa served on the steering committee for the OCS PROCEED II trial and the EXPAND trial, and is a co-primary investigator for these studies, and received study grants from TransMedics. The remaining authors have no conflict of interests to disclose.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

REFERENCES

1. Khush KK, Potena L, Cherikh WS, et al. The International Thoracic Organ Transplant Registry of the International Society for Heart and Lung Transplantation: 37th adult heart transplantation report-2020; focus on deceased donor characteristics. J Heart Lung Transplant. 2020;39(10):1003–1015. [PubMed: 32811772]
2. Colvin M, Smith JM, Ahn Y, et al. OPTN/SRTR 2019 Annual Data Report: heart. Am J Transplant. 2021;21(Suppl 2):356–440. [PubMed: 33595196]
3. Buckberg GD, Brazier JR, Nelson RL, Myron Goldstein S, McConnell DH, Cooper N. Studies of the effects of hypothermia on regional myocardial blood flow and metabolism during cardiopulmonary bypass: I. The adequately perfused beating, fibrillating, and arrested heart. J Thorac Cardiovasc Surg. 1977;73(1):87–94. [PubMed: 831012]
4. Chambers DC, Yusen RD, Cherikh WS, et al. The Registry of the International Society for Heart and Lung Transplantation: thirty-fourth Adult Lung And Heart-Lung Transplantation Report —2017; focus theme: allograft ischemic time. J Heart Lung Transplant. 2017;36(10):1047–1059. [PubMed: 28784324]
5. Tenderich G, El-Banayosy A, Rosengard B, et al. 10: prospective multi-center European trial to evaluate the safety and performance of the Organ Care System for heart transplants (PROTECT). J Heart Lung Transplant. 2007;26(2):S64.
6. McCurry K, Jeevanandam V, Mihaljevic T, et al. 294: prospective multi-center safety and effectiveness evaluation of the Organ Care System device for cardiac use (PROCEED). J Heart Lung Transplant. 2008;27(2):S166.
7. Ardehali A, Esmailian F, Deng M, et al. Ex-vivo perfusion of donor hearts for human heart transplantation (PROCEED II): a prospective, open-label, multicentre, randomised non-inferiority trial. Lancet. 2015;385(9987):2577–2584. [PubMed: 25888086]
8. Billingham ME, Cary NR, Hammond ME, et al. A working formulation for the standardization of nomenclature in the diagnosis of heart and lung rejection: Heart Rejection Study Group. The International Society for Heart Transplantation. J Heart Transplant. 1990;9(6):587–593. [PubMed: 2277293]
9. Stewart S, Winters GL, Fishbein MC, et al. Revision of the 1990 working formulation for the standardization of nomenclature in the diagnosis of heart rejection. J Heart Lung Transplant. 2005;24(11):1710–1720. [PubMed: 16297770]
10. Kobashigawa J, Crespo-Leiro MG, Ensminger SM, et al. Report from a consensus conference on antibody-mediated rejection in heart transplantation. J Heart Lung Transplant. 2011;30(3):252–269. [PubMed: 21300295]
11. Chang DH, Youn JC, Dilibero D, Patel JK, Kobashigawa JA. Heart transplant immunosuppression strategies at Cedars-Sinai Medical Center. Int J Heart Fail. 2021;3(1):15. 10.36628/ijhf.2020.0034 [PubMed: 36263111]
12. Ozeki T, Kwon MH, Gu J, et al. Heart preservation using continuous ex vivo perfusion improves viability and functional recovery. Circ J. 2007;71(1):153–159. [PubMed: 17186994]
13. Koerner MM, Ghodsizad A, Schulz U, El Banayosy A, Koerfer R, Tenderich G. Normothermic ex vivo allograft blood perfusion in clinical heart transplantation. Heart Surg Forum. 2014;17(3):E141–E145. [PubMed: 25002389]

14. Chan JL, Kobashigawa JA, Reich HJ, et al. Intermediate outcomes with ex-vivo allograft perfusion for heart transplantation. J Heart Lung Transplant. 2017;36(3):258–263. [PubMed: 27646064]
15. Ramzy D, Rao V, Brahm J, Miriuka S, Delgado D, Ross HJ. Cardiac allograft vasculopathy: a review. Can J Surg. 2005;48(4):319–327. [PubMed: 16149368]
16. Kevelaitis E, Nyborg NC, Menasché P. Coronary endothelial dysfunction of isolated hearts subjected to prolonged cold storage: patterns and contributing factors. J Heart Lung Transplant. 1999;18(3):239–247. [PubMed: 10328150]
17. Lim JY, Jung SH, Kim MS, et al. Cardiac allograft vasculopathy after heart transplantation: is it really ominous? Clin Transplant. 2017;31(2):e12883.
18. Mehra MR, Crespo-Leiro MG, Dipchand A, et al. International Society for Heart and Lung Transplantation working formulation of a standardized nomenclature for cardiac allograft vasculopathy-2010. J Heart Lung Transplant. 2010;29(7):717–727. [PubMed: 20620917]
19. Schroder JN, D'Alessandro D, Esmailian F, et al. Successful utilization of extended criteria donor (ECD) hearts for transplantation - results of the OCS™ heart EXPAND trial to evaluate the effectiveness and safety of the OCS heart system to preserve and assess ECD hearts for transplantation. J Heart Lung Transplant. 2019;38(4):S42.
20. García Sáez D, Zych B, Sabashnikov A, et al. Evaluation of the organ care system in heart transplantation with an adverse donor/recipient profile. Ann Thorac Surg. 2014;98(6):2099–2105. discussion 2105–2106. [PubMed: 25443013]
21. Sáez DG, Bowles CT, Maunz OK, et al. Donor circulatory death heart transplantation with adverse donor and recipient risk profile. J Heart Lung Transplant. 2017;36(4):S16.
22. Sponga S, Ferrara V, Beltrami AP, et al. Ex-vivo perfusion on marginal donors in heart transplantation: clinical results and pathological findings. J Heart Lung Transplant. 2019;38(4):S42–S43.
23. Iyer A, Gao L, Doyle A, et al. Normothermic ex vivo perfusion provides superior organ preservation and enables viability assessment of hearts from DCD donors. Am J Transplant. 2015;15(2):371–380. [PubMed: 25612491]
24. Dhital KK, Iyer A, Connellan M, et al. Adult heart transplantation with distant procurement and ex-vivo preservation of donor hearts after circulatory death: a case series. Lancet. 2015;385(9987):2585–2591. [PubMed: 25888085]
25. TransMedics Clinical trial to evaluate the safety and effectiveness of the portable Organ Care System (OCSTM) heart for resuscitation, preservation and assessment of hearts from donors after circulatory death (DCD heart trial). clinicaltrials.gov; 2020. Accessed August 9, 2021. https://clinicaltrials.gov/ct2/show/NCT03831048

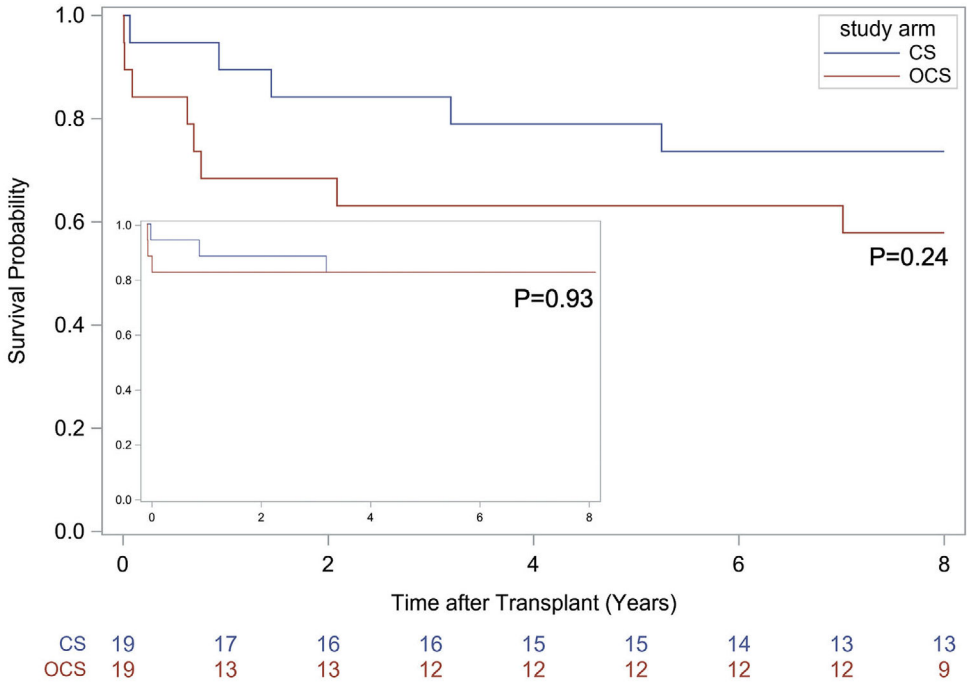

FIGURE 1.

Overall survival (main figure) and survival free from graft-related death (insert) after heart transplantation. CS, cold storage; OCS, Organ Care System

TABLE 1

Baseline recipient and donor characteristics

	Organ Care System (*n* = 19)	**Cold storage (*n* = 19)**	***p*-value**
Recipient characteristics			
Age	51.9 ± 11.8	59.9 ± 11.8	.04
Body mass index	26.2 ± 5.9	23.1 ± 4.2	.08
Gender: female	26.3 (5)	36.8 (7)	.73
Ischemic cardiomyopathy	26.3 (5)	42.1 (8)	.60
Ventricular assist device	31.6 (6)	21.1 (4)	.71
Diabetes	21.1 (4)	31.6 (6)	.71
Hypertension	52.6 (10)	57.9 (11)	1.00
Sensitization	21.1 (4)	36.8 (7)	.48
Pre-transplant blood transfusions	47.4 (9)	47.4 (9)	1.00
Prior sternotomy	52.6 (10)	52.6 (10)	1.00
Status 1A at transplant	52.6 (10)	84.2 (16)	.10
Donor characteristics			
Age	30.9 ± 13.1	31.8 ± 13.5	.42
Body mass index	27.0 ± 3.7	25.8 ± 4.9	.19
Gender: female	21.1 (4)	31.6 (6)	.71
Race			
White	31.6 (6)	42.1 (8)	.74
Hispanic	21.1 (4)	47.4 (9)	.17
African American	26.3 (5)	10.5 (2)	.40
Other	21.1 (4)	0 (0)	.11
Cause of death			
Head trauma	63.2 (12)	57.9 (11)	.99
Anoxia	26.3 (5)	21.1 (4)	.99
Cerebrovascular accident/stroke	10.5 (2)	21.1 (4)	.66
Diabetes	5.3 (1)	5.3 (1)	1.00
Hypertension	5.3 (1)	21.1 (4)	.66
Vasoactive medication requirements			
Dopamine	0 (0)	10.5 (2)	.49

	Organ Care System (n = 19)	Cold storage (n = 19)	p-value
Vasopressin	5.3 (1)	5.3 (1)	1.00
Nitroprusside	0 (19)	5.3 (1)	.99
Donor/recipient BMI ratio	1.2 ± .3	1.0 ± .3	.06
Female donor/male recipient	5.3 (1)	15.8 (3)	.60

TABLE 2

Post-transplantation survival, freedom from adverse events, and freedom from rejections at 8-years

	Organ Care System (*n* = 19)		Cold storage (*n* = 19)		
	Percentage	**95% CI**	**Percentage**	**95% CI**	***p*-value**
Overall survival	57.9	26.7–79.7	73.7	41.6–90.0	.24
Survival free from graft-related death	84.2	64.5–96.3	84.2	64.4–96.3	.93
Freedom from CAV	89.5	70.8–98.4	67.8	46.1–87.6	.13
Freedom from NF-MACE	89.5	70.8–98.4	67.5	45.8–87.4	.14
Freedom from ATR	63.2	41.7–84.2	63.2	41.8–84.2	.85
Freedom from ACR	79.0	58.2–93.8	73.7	52.5–90.9	.74
Freedom from AMR	94.7	97.9–99.7	94.7	97.9–99.7	.98
Freedom from BNR	84.2	64.3–96.3	84.2	64.4–96.3	.94

Abbreviations: ACR, acute cellular rejections; AMR, antibody-mediated rejections; ATR, any-treated rejection; BNR, biopsy negative rejections; CAV, cardiac allograft vasculopathy; CI, confidence interval; NF-MACE, non-fatal major adverse cardiac events.

TABLE 3

Causes of early and late mortality

Subject	Study arm	Recipient age (years)	Donor age (years)	Cause ofdeath	Total graft preservation time(min)	Total ischemic time(min)	Days after transplant	Graft-related death
1	OCS	49	49	Severe primary graft dysfunction	375	123	3	Yes
2	OCS	55	45	Massive intracardiac and intravascular thrombosis after separation from CPB, suspected severe protamine reaction and transfusion reaction	542	294	5	Yes
3	OCS	38	22	Cardiac arrest due to cardiac tamponade with development of anoxic brain injury despite emergent sternotomy and evacuation	365	105	33	Yes
4	OCS	63	35	Unknown	312	124	229	No
5	OCS	57	18	CMV infection	315	146	252	No
6	OCS	56	48	CMV infection	272	130	278	No
7	OCS	68	51	Respiratory failure from metastatic urothelial carcinoma to lung	206	92	761	No
8	OCS	54	45	Left temporal artery hematoma following surgical resection of malignant facial squamous cell carcinoma with resulting midline shift and neurological compromise	268	120	2561	No
9	CS	59	21	Sudden cardiac arrest at home of unclear cause with subsequent development of diffuse cerebral edema/ anoxic brain injury	280	280	25	Yes
10	CS	54	28	Recurrent acute cellular rejections and CAV due to medication non-compliance	167	167	341	Yes
11	CS	76	37	CMV infection	178	178	527	No
12	CS	58	18	Recurrent antibody-mediated rejections	181	181	1167	Yes
13	CS	67	29	Unknown	158	158	1916	No

Abbreviations: CAV, cardiac allograft vasculopathy; CMV, cytomegalovirus; CPB, cardiopulmonary bypass; CS, cold storage; OCS, Organ Care System.