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Ex Vivo Heart Perfusion for Cardiac Transplantation Allowing for Prolonged Perfusion Time and Extension of Distance Traveled for Procurement of Donor Hearts: An Initial Experience in the United States

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Background. Scarcity of donor hearts continues to be a challenge for heart transplantation (HT). The recently Food and Drug Administration–approved Organ Care System (OCS; Heart, TransMedics) for ex vivo organ perfusion enables extension of ex situ intervals and thus may expand the donor pool. Because postapproval real-world outcomes of OCS in HT are lacking, we report our initial experience. **Methods.** We retrospectively reviewed consecutive patients who received HT at our institution in the post–Food and Drug Administration approval period from May 1 to October 15, 2022. Patients were divided into 2 groups: OCS versus conventional technique. Baseline characteristics and outcomes were compared. **Results.** A total of 21 patients received HT during this period, 8 using OCS and 13 conventional techniques. All hearts were from donation after brain death donors. The indication for OCS was an expected ischemic time of >4 h. Baseline characteristics in the 2 groups were comparable. The mean distance traveled for heart recovery was significantly higher in the OCS group (OCS, 845 ± 337, versus conventional, 186 ± 188 mi; $P < 0.001$), as was the mean total preservation time (6.5 ± 0.7 versus 2.5 ± 0.7 h; $P < 0.001$). The mean OCS time was 5.1 ± 0.7 h. In-hospital survival in the OCS group was 100% compared with 92.3% in the conventional group ($P = 0.32$). Primary graft dysfunction was similar in both groups (OCS 12.5% versus conventional 15.4%; $P = 0.85$). No patient in the OCS group required venoarterial extracorporeal membrane oxygenation support after transplant compared with 1 in the conventional group (0% versus 7.7%; $P = 0.32$). The mean intensive care unit length of stay after transplant was comparable. **Conclusions.** OCS allowed utilization of donors from extended distances that otherwise would not be considered because ischemic time would be prohibitive by conventional technique.

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Orthotopic heart transplantation (OHT) remains the gold standard for long-term survival in patients with end-stage heart failure despite the advancements in durable mechanical circulatory support. The annual number of HTs is increasing every year, with a record ~3800 transplants performed in 2021 in the United States. However, the number of patients on the waiting list continues to grow, and the demand for OHT in the United States is unmatched by the limited donor pool. Given the continued donor shortage with a high waitlist mortality rate, efforts are being undertaken to maximize donor heart utilization.

The Organ Care System (OCS; TransMedics, Andover, MA) is the first and only ex vivo heart perfusion system by which a donor heart can be maintained in a near-physiological state using the Langendorff's perfusion model allowing for preservation of donor hearts.[1] The technique involves the cannulation of

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the aorta, that upon perfusion, a perfusate passes from the aortic root via the coronary ostia into the coronary artery. This has been previously shown to limit the prolonged cold ischemic time during the transport of donor hearts, which is an independent risk factor for early graft dysfunction and mortality.[2,3]

OCS was initially approved by the Food and Drug Administration (FDA) for transport of donation after brain death for hearts deemed unsuitable for preservation using cold storage method and, more recently, for donation after circulatory death, thus potentially expanding the donor pool for patients awaiting transplant.[4,5] Previous reports have demonstrated the experience of real word utilization of OCS; however, reports from the United States in the postapproval period are lacking.[6,7]

We report our experience in the utilization of OCS for donor heart preservation and compare outcomes with patients undergoing OHT with conventional cold storage technique.

MATERIALS AND METHODS

We retrospectively reviewed all HTs performed at our institution in the post–FDA approval period from May 1 to October 30, 2022. The Institutional Review Board of New York Medical College/Westchester Medical Center approved this study under the "consent exempt" category.

OHT recipients were divided into 2 groups depending on the organ preservation technique, the OCS group and the conventional cold storage group. All hearts were from donors after brain death. The indication for OCS utilization was an expected ischemic time of >4 h.

Transmedics OCS

The OCS is composed of an organ-specific perfusion module with a compact wireless monitor and both disposable and nondisposable parts and has been previously well described. The monitor can display real-time measurements of blood pressure, coronary flow, and aortic pressure.

At the donor transplant center, the first cold ischemic time was initiated at the cross-clamp of ascending aorta. Cold cardioplegia with del Nido solution (500–600 mL depending on donor size in comparison with Custodial Histidine-tryptophan-ketoglutarate solution for conventional transplant) was infused to arrest the heart, and the donor heart was then cannulated and connected to the OCS initiating perfusion and ending the first cold ischemic period (Figure 1, blue bar).

FIGURE 1. Overview of patients using organ care system. Blue denotes first cold ischemic time, red denotes organ care system time, and yellow denotes second cold ischemic time. Case 5 was a status 1 patient on VA-ECMO pretransplant who had primary graft dysfunction requiring continued ECMO for 4 d posttransplant. There was no in-hospital or 30-d mortality in all 8 patients. BMI, body mass index; COD, cause of death; ECMO, extracorporeal membrane oxygen; VA, venoarterial.

The donor heart was then transported to our institution and, in the operating room, was disconnected from the OCS after a second cardioplegia infusion as soon as the preparatory surgery on the recipient was completed for the allograft implantation. Total OCS time concluded with the donor heart being disconnected from the OCS (Figure 1, red bar) and thus initiated the second phase of cold ischemia while the heart was being implanted and lasted until the aortic clamp was opened for reperfusion (Figure 1, yellow bar). Perfusion and metabolic parameters, including lactate levels, were continuously monitored by an experienced perfusionist during the transport period. Surgical technique as well as intra- and postoperative management of patients after OHT, including immunosuppression, were the same in both the OCS and conventional cold storage groups.

Endpoints and Definitions

The primary outcome of the study was in-hospital survival. The secondary outcomes included 30-d graft survival, requirement of venoarterial extracorporeal membrane oxygen (VA-ECMO) support after transplant, primary graft dysfunction (PGD), vasotropic inotropic score (VIS) at 24 and 48 h, and intensive care unit (ICU) length of stay. Severe graft dysfunction was defined as PGD requiring VA-ECMO support as per International Society for Heart and Lung Transplantation guidelines.[8] The VIS was calculated as: dobutamine (μg/kg/min) + 10 × milrinone (μg/kg/min) + dopamine (μg/kg/min) + 100 × epinephrine (μg/kg/min) + 100 × norepinephrine (μg/kg/min) + 10 000 × vasopressin (μg/kg/min) as previously described.[9]

We also compared the total distance, total preservation time, and cold ischemic time in the 2 groups. The total preservation time as defined as the period from cross-clamp of donor heart in the donor chest to the time of reperfusion in the recipient chest, out-of-body time as defined in the PROCEED II Trial.[2] Cold ischemia time was defined as the sum total of the initial retrieval phase (time needed to procure and implant the heart into the OCS—cold ischemic time 1) and the second reimplantation phase (time needed to place the donor heart into the recipient—cold ischemic time 2).

Statistical Analysis

Descriptive statistics were used to describe the demographic and clinical characteristics of the cohorts. Categorical variables are presented as percentages and continuous variables as mean ± standard deviation. Comparisons of continuous variables between groups were performed with *t* tests and of categorical variables by the chi-square test. A *P* value of <0.05 was considered significant. Statistical analysis was performed using JMP version 9.0.1 (SAS Institute Inc., Cary, NC).

RESULTS

Recipient Population

A total of 21 patients underwent OHT during the study period, of which 8 used the OCS, whereas 13 used the conventional cold storage technique.

The mean age of the population was 55.8 ± 11.0 y, with 66.7% men (n = 14). There were no significant differences in the baseline characteristics of recipients in age, body mass index, and history of diabetes (5 ± 10.8 versus 56.2 ± 11.5 y, $P = 0.81$; 27.8 ± 7.5 versus 25.8 ± 4.4 kg/m^2, $P = 0.42$; 37.5% versus 38.5%, $P = 0.46$, in OCS and conventional groups, respectively).

The number of days on the waiting list was similar in both groups (OCS, 10.5 [4–26.75], versus conventional, 10 [2.5–30] d; $P = 0.88$).

Donor Population

The mean donor age and body mass index were also similar in both groups (37.8 ± 9.7 versus 41.8 ± 12.3 y, $P = 0.45$, in the OCS group; 31.5 ± 8.4 versus 27.5 ± 7.5 kg/m^2, $P = 0.27$, in the conventional group). Table 1 demonstrates the baseline characteristics of the population.

Perioperative Data and OCS Parameters

The mean distance traveled for heart recovery was significantly higher in the OCS group (OCS, 845 ± 337 versus conventional, 186 ± 188 mi; $P < 0.001$) with a range of 461 to 1318 mi (Figure 2).

TABLE 1.
Baseline characteristics

	Organ care system, n = 8	Conventional, n = 13	*P*
Recipient characteristics			
Age (y)	55 ± 10.8	56.2 ± 11.5	0.811
Male	5 (62.5%)	9 (69.2%)	0.751
Weight (kg)	93.4 ± 32.1	79.9 ± 14.8	0.205
Height (cm)	182.1 ± 16.9	177.5 ± 9.2	0.446
Body mass index (kg/m^2)	27.8 ± 7.5	25.8 ± 4.4	0.424
Diabetes	3 (37.5%)	5 (38.5%)	0.965
Waiting list time, median d	10.5 (4–26.75)	10 (2.5–30)	0.867
Diagnosis of cardiomyopathy			0.362
Ischemic	3 (37.5%)	6 (46.1%)	
Idiopathic	2 (25%)	4 (30.8%)	
Other	3 (27.5%)	3 (23.1%)	
Blood type			0.780
A	3 (37.5%)	6 (46.1%)	
B	2 (25%)	4 (30.8%)	
0	3 (37.5%)	3 (23.1%)	
AB	0	0	
United Network Organ Sharing status			0.186
1	1 (12.5%)	0	
2	6 (75%)	12 (92.3%)	
3	1 (12.5%)	0	
4	0	0	
5	0	0	
6	0	1 (7.7%)	
Donor characteristics			
Age (y)	37.8 ± 9.7	41.8 ± 12.3	0.458
Male	4 (50%)	10 (76.9%)	0.206
Weight (kg)	97.9 ± 30.7	80.4 ± 19.2	0.123
Height (cm)	175.2 ± 8.6	171.4 ± 7.7	0.300
Body mass index (kg/m^2)	31.5 ± 8.4	27.5 ± 7.5	0.269
Total distance for donor heart, miles	845 ± 337	186 ± 188	<0.001
Cause of death			0.540
Cerebrovascular accident	1 (12.5%)	2 (15.4%)	
Anoxia	4 (50%)	6 (46.1%)	
Head trauma	3 (37.5%)	5 (38.5%)	

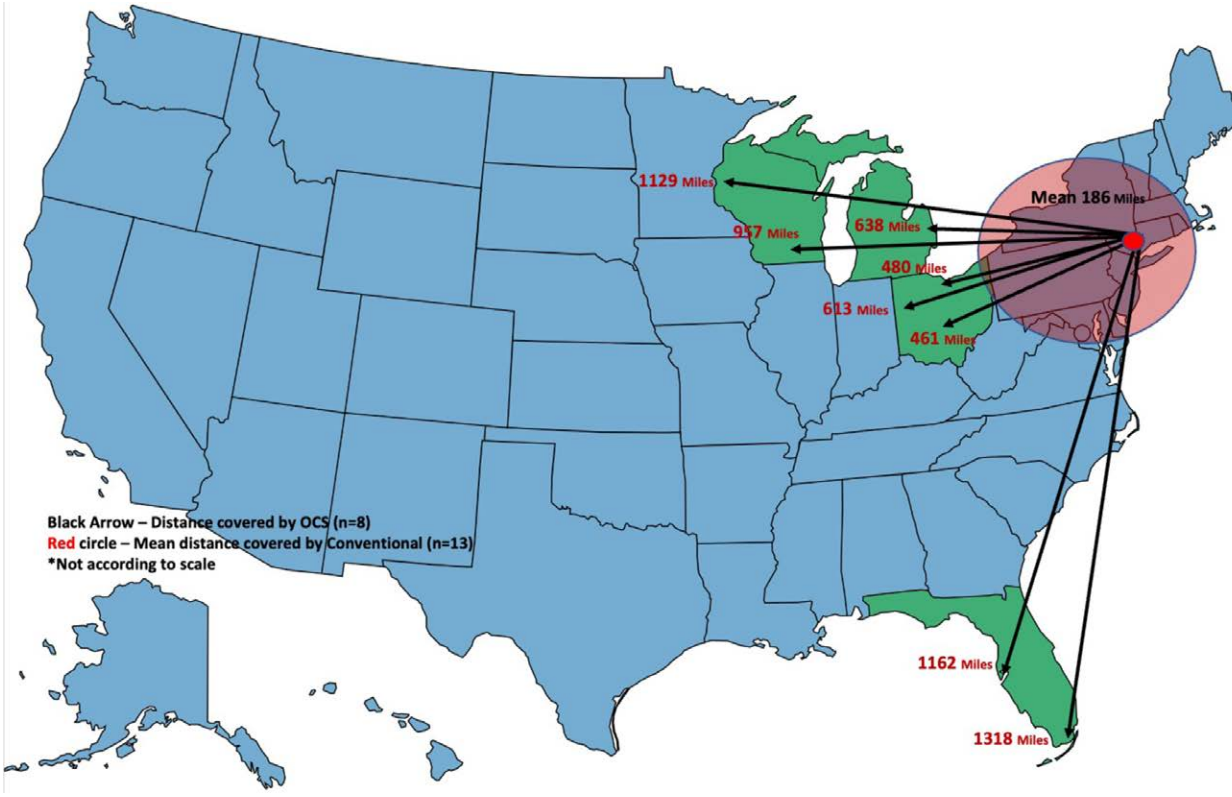

FIGURE 2. Graphical representation of distance traveled using organ care system compared with mean distance traveled using conventional technique. OCS, Organ Care System.

FIGURE 3. Comparison of mean total preservation time and cold ischemic time using the organ care system to conventional technique.

The mean OCS time was 5.1 ± 0.7 h with a range of 4 h and 28 min to 6 h and 45 min. The mean total preservation time was significantly higher in the OCS group (6.5 ± 0.7 versus 2.5 ± 0.7 h; $P < 0.001$) with a significant decrease in the cold ischemic time (1.4 ± 0.6 versus 2.5 ± 0.7 h; $P < 0.001$; Figure 3). The distribution of cold ischemic time and OCS time in all 8 patients using OCS for the donor heart is shown in Figure 1.

Outcomes

Table 2 describes the outcomes of the study cohort. No patients in the OCS group died with an in-hospital survival rate of 100% (n = 8) compared with 92.3% (n = 12) in the conventional group ($P = 0.32$). Posttransplant PGD was similar in

TABLE 2.

Outcomes of primary and secondary endpoints

Outcomes	Total, n = 21	OCS, n = 8	Conventional, n = 13	*P*
Total preservation time, h	4.1 ± 2.1	6.5 ± 0.7	2.5 ± 0.7	<0.001
Cold ischemic time, h	2.1 ± 0.8	1.4 ± 0.6	2.5 ± 0.7	<0.001
In-hospital survival	20 (95.2%)	8 (100%)	12 (92.3%)	0.319
30-d survival	20 (95.2%)	8 (100%)	12 (92.3%)	0.319
VA-ECMO posttransplant	1 (4.7%)	0(0%)	1 (7.7%)	0.319
Primary graft dysfunction	3 (14.3%)	1 (12.5%)	2 (15.4%)	0.853
Severe primary graft dysfunction	2 (9.5%)	1 (12.5%)	1 (7.7%)	0.719
Vasotropic inotropic score, 24 h	7.1 ± 4.1	6.3 ± 4.1	7.6 ± 4.0	0.483
Vasotropic inotropic score, 48 h	4.9 ± 3.4	3.6 ± 2.3	5.7 ± 3.8	0.163
Length of ICU stay, d	8 (5–10)	9 (2.75–21.75)	6 (5–9.5)	0.392

ICU, intensive care unit; OCS, Organ Care System; VA-ECMO, venoarterial extracorporeal membrane oxygen.

both groups (OCS 12.5% [n = 1] versus conventional 15.4% [n = 2]; $P = 0.85$). There was also no difference in severe graft dysfunction (OCS 12.5% [n = 1] versus conventional 7.7% [n = 1]; $P = 0.72$).

No patient in the OCS group required VA-ECMO support after transplant compared with 1 patient requiring VA-ECMO in the conventional group (0% versus 7.7%; $P = 0.32$).

There was a trend for lower VIS at 24 and 36 h respectively in the OCS group but was not statistically significant (OCS, 6.3 ± 4.1, versus conventional, 7.6 ± 4.0 at 24, $P = 0.48$, OCS, 3.6 ± 2.3, versus conventional, 5.7 ± 3.8, $P = 0.16$). The mean ICU length of stay after transplant was also similar in both groups (OCS, 11.6 ± 9.9 d, versus conventional, 8.6 ± 5.9 d; $P = 0.41$).

DISCUSSION

To the best of our knowledge, this is the first report of short-term real-world outcomes with the utilization of OCS in the post–FDA approval period in the United States. The

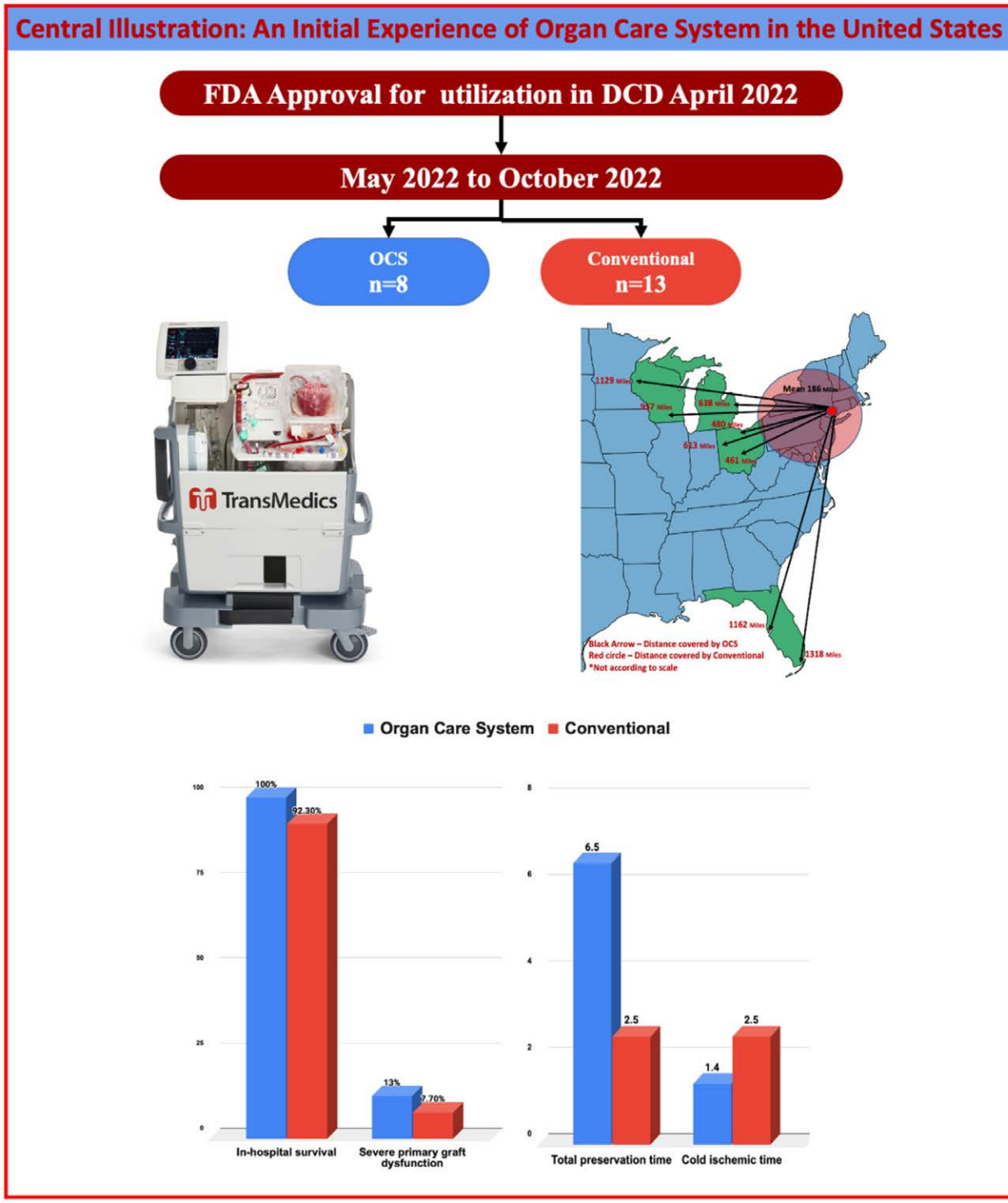

FIGURE 4. Central illustration. DCD, donation after circulatory death; FDA, Food and Drug Administration; OCS, Organ Care System.

major findings of our study are that (Figure 4, central illustration) as follow:

1. The utilization of OCS had similar short-term outcomes, including survival and graft dysfunction, in comparison with conventional cold storage.
2. OCS enabled significantly longer preservation time and extension of distance traveled for procurement while decreasing cold ischemic time.

The field of OHT has developed significant advances in operative technique, postoperative care, and donor management such as utilization of extended criteria donors and the new allocation policy. However, the technique of preservation of donor hearts for prolonged periods remains an unsolved problem and is limited by cold ischemic storage, which confines transplantation to ischemic times <4 h according to the ISHLT guidelines. The total cold ischemic time has been demonstrated to be an independent risk factor for mortality, with an estimated 1.06 increased odds of mortality with every 15-min increase in cold ischemic time.[3]

The utilization of OCS allows a substantial reduction in total cold ischemic time by maintaining the donor heart in a perfused state during transportation. Our study confirms the real-world utilization of OCS, enabling ~5 times the distance covered using conventional cold storage technique with a maximum distance of 1329 mi and total perfusion time of 477 min. This can be crucial in areas with low-density population and significant distance between organ procurement and transplantation sites, with associated worse outcomes for OHT recipients. Furthermore, the ability to travel greater distances can, in fact, expand the donor pool available to our patients.

The utilization of OCS for OHT in comparison with conventional cold storage technique has shown excellent short-term outcomes such as in-hospital survival and graft function. A previous report from Germany demonstrated similar excellent outcomes with the use of OCS with a total preservation time of ~6.4 h.[7] Another single-center series from United Kingdom also reported similar outcomes while decreasing cold ischemic time.[6] In our analysis, we report a real-world single-center experience outside of randomized controlled trials in the United States while showing promising outcomes and the ability to retrieve organs that might not have been available to our patients because of an expected ischemic time of >4 h. We further demonstrate the significant difference in distance that could be covered with the utilization of OCS that has not been previously reported. Our study additionally assessed the VIS that has been associated with adverse outcomes posttransplant.[10,11] In our study, there was a trend toward lower VIS at 24 and 48 h posttransplant in OCS group, suggesting that utilization of OCS was comparable with conventional cold storage while allowing travel to longer distances to procure donor hearts. There was a trend toward longer ICU length of stay in the OCS group; however, post-ICU care after OHT includes a holistic approach and is affected by a multitude of factors.

The OCS, in addition to reducing cold ischemic time and allowing increased preservation time, also allows for the assessment of marginal high-risk hearts. OCS, in particular, can be used for evaluation of the extended criteria donor hearts, such as those with left ventricular hypertrophy, previous donor cardiac arrest, reduced left ventricular ejection fraction, and unknown coronary artery disease because of lack of coronary angiography.[1,12] Furthermore, the use of OCS for donation after circulatory death was recently approved by the FDA, which can also allow an expansion of the donor pool.[5] The OCS also allows for monitoring of metabolic and perfusion parameters during transport, because previous reports, including the PROCEED II trial, have suggested that increasing lactate can be a marker of donor heart dysfunction.[2] Furthermore, the utilization of OCS can possibly decrease the time waiting for donor hearts by allowing the use of an expanded donor pool.

Our study should be interpreted in the context of its limitations, including this being a single-center and retrospective study with small sample size. Furthermore, metabolic and perfusion parameters, such as lactate, coronary perfusion, were not available for this study. Cost effectiveness needs to be further analyzed with a larger cohort of patients given the cost of OCS is approximately an additional $40 000 US dollars compared with typical costs of a single conventional HT while OCS could lower the rate of PGD, which may be associated with better outcomes and cost effectiveness.

CONCLUSION

OHT using OCS allows utilization of donors from extended distances that otherwise would not be considered because ischemic time would be prohibitive by traditional cold storage technique. Despite mean preservation time of up to 7 h and distance traveled of >800 mi, our center's short-term results are promising. The application of OCS can play a key role in expanding the limited donor pool by increasing donor utilization.

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