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Comparison of Custodiol vs warm blood cardioplegia and conditioning of donor hearts during transportation with the organ care system

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Abstract

Objectives: Cold crystalloid cardioplegia for donor heart harvesting and cold ischemic storage conditions during the transportation is the standard of care during heart transplantation procedure. Organ care system (OCS) was introduced for more prolonged and reliable ex vivo organ management. This study evaluated the two different techniques used for myocardial preservation during the procurement and transportation of the heart using the OCS.

Methods: We performed prospective analysis of 43 patients with heart failure undergoing heart transplantation and using the OCS for donor organ transport. Donor hearts were arrested using blood cardioplegia and conditioning ($n = 30$) or standard Custodiol (SC) solution ($n = 13$). Perfusion and cardiac function parameters were continuously monitored while the donor hearts were perfused in the OCS. Impact of preservation techniques on biochemical parameters and clinical outcomes were evaluated.

Results: All donor hearts had stable perfusion and lactate characteristics in the OCS, with similar measures between the two groups at the beginning of the ex vivo perfusion. Ex vivo heart perfusion mean ending concentration of Interleukin (IL)-6 and IL-8 was significantly lower in the blood cardioplegia group compared to the standard care group. Clinical outcomes were comparable between the two groups of patients.

Conclusions: The use of blood cardioplegia and conditioning could be a safe method for myocardial protection in distant procurement and preservation of donor hearts in the OCS.

KEYWORDS
blood cardioplegia, ex vivo perfusion, heart transplantation, interleukin

1 | INTRODUCTION

Despite improvements of mechanical circulatory support in recent years, heart transplantation remains the approach most likely to improve survival and quality of life in patients with end-stage heart failure.[1] Success in heart transplant depends on the quality of the donor heart, procurement, preservation and storage of the graft, the complexity of the operation and, duration of graft ischemia.[2] Some determinants of successful transplant outcomes are difficult or even impossible to modify, such as the recipient comorbidities or the quality of the donor heart. On the other hand, it might be possible to improve clinical outcomes by modifying determinants related to procurement and preservation of the graft.

In 2012, we initiated the first heart transplant program in Kazakhstan. Alongside initiatives to increase the donor pool, we sought ways to improve patient outcomes to mitigate the realities of a small donor pool and the long distances over which donor hearts are transported in our country (often >1000 km).[3] In this context, the organ care system (Transmedics, OCS) is used at our center and it allows normothermic, beating, perfused ex vivo donor heart preservation and thus has the potential to reduce the risk related to time-dependent ischemic injury to the donor heart during cold storage.[4] The OCS also allows ex-situ assessment or improvement of nonstandard donor hearts, or resuscitation of DCD hearts.[5] The results of the PROCEED II study demonstrated a significant reduction in cold ischemic time for the OCS relative to standard cold storage donor preservation. The standard approach for donor heart harvesting is to use of custodiol cardioplegic solution for arresting the heart, followed by reanimation of the heart in the OCS.

We hypothesized that warm blood cardioplegia would better mimic physiologic conditions. Cardioplegia solution using the donor's blood in combination with blood conditioning with levosimendan and hemofiltration might have a positive impact on heart function during longer period of ex vivo organ care.

2 | METHODS

2.1 | Participants and procedure

This prospective study was approved by the local regional bioethics committee. The study was conducted under good clinical practice protocols. In this study, we performed analysis of prospectively collected data at our center. Between May 2014 and September 2017, 43 patients with heart failure underwent heart transplantation at our institution, and we used the OCS for donor heart preservation in all cases. Eligible recipients were at least 18 years of age and had to be on the heart-transplant waiting list at our center. Of these, we arrested the donor hearts before explant and before implant using blood cardioplegia and conditioning in 30 cases and in 13 cases, we used standard Custodiol solution for cardioplegia (standard care group). The study received approval through the responsible ethics committee at our institution and all patients provided written informed consent to be part of this study and to allow their data to be used for the analysis.

2.2 | Procedures

All patients underwent orthotopic heart transplantation. After the donor heart was dissected, a double-outlet needle was inserted in the donor's ascending aorta and secured with a 4-0 polypropylene purse-string suture. According to standard procedures for the Transmedics device, 500 ml of priming solution was added to the OCS. After the donor was heparinized (300 IU/kg), the donor blood (1200–1500 mL) was collected before antegrade cardioplegia and before cross clamping of the aorta. 10,000 IU of heparin was added to the blood collection bag and this was used to prime the perfusion module. In the blood cardioplegia group, a portion of the normothermic blood (500-750 mL) was collected retrogradely for initial dose of cardioplegia. In the standard care group, 1000 mL of standard Custodiol solution (cooled to 4 degrees of Celsius) was used. In both groups, the aorta and pulmonary artery of the donor heart were cannulated and heart connected to the OCS. In the OCS, oxygenated blood was pumped into the aorta, perfusing the coronary arteries. The coronary sinus flow then passes through the tricuspid valve (as both the superior and inferior vena cavae are sutured closed) and is ejected by the right ventricle into a pulmonary artery catheter and returned to the blood reservoir. Then, the heart is reanimated to normal sinus rhythm. The pump flow and solution flow rates of the OCS were adjusted to maintain the mean aortic pressure between 60 mmHg and 90 mmHg and coronary blood flow between 650 mL/min and 850 mL/min. According to standard protocol, samples were taken in the OCS before the donor heart was connected to the OCS. These included donor lactate (CG4+, within 30 minutes of blood collection), baseline OCS lactate and chemistries (CG8+, during priming). Hourly arterial and venous lactates were monitored throughout during OCS time. Periodic arterial chemistry samples were taken during OCS time (approximately every 20-30 minutes). Samples were collected from the arterial and venous sampling port of OCS. The samples were analyzed with a handheld lactate analyzer (i-STAT, Abbott Diagnostics, East Windsor, NJ). At the beginning and end of ex vivo heart perfusion, venous blood samples were taken to assess interleukin (IL)-6 and IL-8 levels (Bio-Rad, Model 680; Model 680 Microplate Reader). Upon arrival at our center, the donor heart were arrested with approximately one liter of normothermic blood cardioplegia in the blood cardioplegia group or Custodiol solution in the standard care group and were disconnected from the OCS for implantation into the recipient. Transplantation and preoperative care proceeded according to the standard procedures of our center in both groups.[5] The solution we used in the blood cardioplegia group consisted of blood and crystalloid solution at the ratio of 5:1 and a cardioplegia pressure of 150 mmHg. The crystalloid solution in the blood cardioplegia group contained KCl 4% (30 mL), $MgSO_4$ 25% (10 mL), $NaHCO_3$ 4% (13 ml), Mannitol 15% (6.5 ml), and Lidocaine 2% (2 ml) with blood up to a total volume of 600 ml. In the blood cardioplegia group only, the graft was conditioned with Levosimendan 45 μg/kg (using body weight of donor) while in the OCS and

hemofiltration with a blood flow of 200 to 300 ml/h was applied in the OCS to protect and improve donor heart function. Between 100 to 200 mL/hour of plasma was collected and Sterofundin isotonic solution was used to replace the plasma. It was used due to its positive inotropic effect by increasing calcium sensitivity of myocytes by binding to cardiac troponin C in a calcium-dependent manner.

Outcomes of interest were the ex vivo heart perfusion mean change in IL-6 and IL-8 concentration from baseline, ischemic time, perfusion time, hemodynamic measurements, and lactate levels. We defined total preservation time as the heart perfusion time while in the OCS. Total ischemic time was defined as the time from donor heart explant to recipient implantation minus time in OCS. We also collected electrophysiological data, data on perioperative parameters, including OCS perfusion measures, IL-6, IL-8 and lactate trends. Postoperative recovery and follow-up were defined as inotrope dose, length of stay in the intensive care unit, TDI parameters and extracorporeal membrane oxygenation duration (if used).

2.2.1 | Statistical analysis

Continuous data are expressed as mean ± standard deviation for continuous data, unless otherwise specified. Categorical data are expressed as counts and proportions. Where possible, a two-sample independent *t*-test was used to compare the means. Statistical analyses were performed using SPSS system for statistics.

3 | RESULTS

3.1 | Recipient and donor population

The donor and recipient characteristics and risk factors are shown in Table 1. In the recipient group, the median age is slightly higher in the standard care group compared to the blood cardioplegia group. Other prognostic risk factors at baseline were similar between the two groups, including gender, body mass index, ILs in donor and proportion of patients who were on a ventricular assist device at the time of transplant.

TABLE 1 The donor and recipient characteristics and risk factors

Donor characteristics	BC (*n* = 30)	SC (*n* = 13)	*P* value
Age, y	39 ± 11	43 ± 15.5	.2
Male, n (%)	22 (74)	9 (75)	.95
BMI, kg/m^2	22.4 ± 1.6	22.6 ± 2.5	.08
Cause of death CVA, n (%)	22 (74)	9 (75)	.95
Other cause of death, n (%)	8 (26)	4 (25)	.96
Median LVEF, range	62 (57-65)	63 (59-67)	
Recipient characteristics	**BC (*n* = 30)**	**SC (*n* = 13)**	***P* value**
Age, y	35 ± 15	40 ± 12	.45
Male	89.4% (26 of 30)	75% (9 of 13)	.51
BMI, kg/m^2	22.6 ± 2.5	22.8 ± 4	.1
NICM, n (%)	73.6% (22 of 30)	50% (6 of 13)	.27
Other	26.3% (8 of 30)	50% (6 of 13)	.25
UNOS 1A+	42.1 (12 of 30)%	33.3% (4 of 13)	.74
Implanted VAD, n (%)	52.6% (15 of 30)	41.6% (5 of 13)	.66

Abbreviations: BC, blood cardioplegia; CVA, cerebrovascular accident; LVEF, left ventricular ejection fraction; BMI, body mass index; NICM, non-ischaemic cardiomyopathy; UNOS, United Network for Organ Sharing; SC, standard Custodiol; VAD, ventricular assist device.
Data are expressed as mean ± standard deviation unless otherwise noted.

3.2 | Electrophysiological findings; OCS data

Ischemic times and perfusion times of donor hearts in the OCS are shown in Figure 1. Mean (±standard deviation) total ischemic time was 75.2 (±22) minutes in the blood cardioplegia group compared to 82.9 (±8.4) minutes in the standard care group. Mean ex vivo perfusion time was 282.5 ± 86.7 minutes in the blood cardioplegia group compared to 247.4 ± 88.4 minutes in the standard care group (*P* = .87). Time of sinus rhythm restoration in OCS and in recipient was significantly lower in blood cardioplegia group Table 2.

All donor hearts had stable perfusion and biochemical characteristics in the OCS and measures were similar between the two groups (Figure 2). Starting concentration of IL-6 and IL-8 were no statistical differences between groups. Ex vivo heart perfusion mean ending concentration of IL-6 and IL-8 was significantly lower in the blood cardioplegia group compared to the standard care group 1493 ng/ml (SD = 529.3) vs 2866 ng/mL (SD = 601.2);(*P* = .01), 989 ng/mL (SD = 453.6) vs 1274 ng/mL (SD = 423.4) (*P* = .05) (Figure 3).

Mean venous lactate at the start of perfusion was 2.7 mmol/L (SD = 0.7) in the blood cardioplegia group and 3.2 mmol/L (SD = 0.8) in the standard care group (*P* = 0.1). At the end of perfusion, the mean venous lactate was lower in the blood cardioplegia group 4.1 mmol/L (SD = 1.9) compared to the standard care group 8.8 mmol/l (SD = 2.1) (*P* = .001) (Figure 4).

3.3 | Postoperative recovery

Median ICU stay was 11 days (range, 4-40 days) in the blood cardioplegia group and 19 days (range, 5–42) in the standard care group. Median time on ECMO who received mechanical support was 29.5 hours (29.5 ± 28.4 hours, *n* = 6) in the blood cardioplegia group compared to 78.4 hours (78.4 ± 89 hours, *n* = 8) in the standard care group (*P* = .02). Inotrope dose within 72 hours was significantly lower in the blood cardioplegia group see Table 3.

3.4 | Survival and graft failure

All patients were alive on the 30th day post implant in both groups. Primary graft failure incidence was 3% (*n* = 1) in blood cardioplegia group and 8% (*n* = 1) in the standard care group. One patient

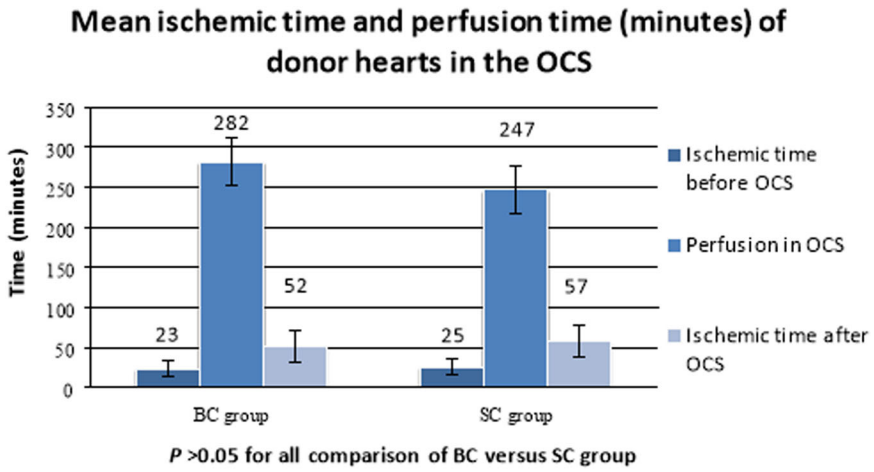

FIGURE 1 Mean ischemic time and perfusion time (minutes) of donor hearts in the OCS ($P > .05$ for all comparison of BC vs SC group). BC, blood cardioplegia; OCS, organ care system; SC, standard Custodiol

TABLE 2 Time of sinus rhythm restoration (Data are mean−S.D.)

	BC group (n = 30)	*SC group (n = 13)*	*P value*
Time of sinus rhythm restoration in OCS (min)	2.6 ± 1.4	8.5 ± 5.8	.04
Time of sinus rhythm restoration in recipient (min)	3.2 ± 2.1	7.3 ± 7.1	.02

Abbreviations: BC, blood cardioplegia; OCS, Organ care system; SC, standard Custodiol.

developed right ventricular dysfunction 1 month after implant in the standard care group, and one patient in the blood cardioplegia group.

4 | DISCUSSION

The OCS has been used to prolong out-of-body time in some cases, expanding possibilities for organ procurement from distant sites.[6] This is an important consideration for centers such as which are forced to reckon with long transport distances and increasing rates of mechanical assist devices and fully artificial mechanical support device use in donor recipients.

In this context, we hypothesized that blood cardioplegia could provide near-physiologic conditions (oxygenated environment, normothermic) and could result in favorable patient outcomes. The ischemic time between explant from donor and implant to the OCS is generally between 20 to 30 minutes, and a single dose of blood cardioplegia has a similar duration of action. In contrast, Custodiol has a longer duration of action and could still be active when the heart is reanimated in the OCS, with unknown effects. In this sense, Custodiol is an intracellular cardioplegic solution which is high in potassium content and can cause arrest related to membrane depolarization. Results of several studies have shown favorable results for the use of blood cardioplegia using measurements such as cardiac enzymes metabolic response.[7] The use of induction and reperfusion blood cardioplegia is associated with lower prevalence of post-transplantation right heart insufficiency, arrhythmias, and evidence of ischemia when compared with standard crystalloid cardioplegia.[8-11] Adoption of this method of myocardial protection might be indicated to control early morbidity, particularly when poor donor organs are used in high-risk transplant recipients.

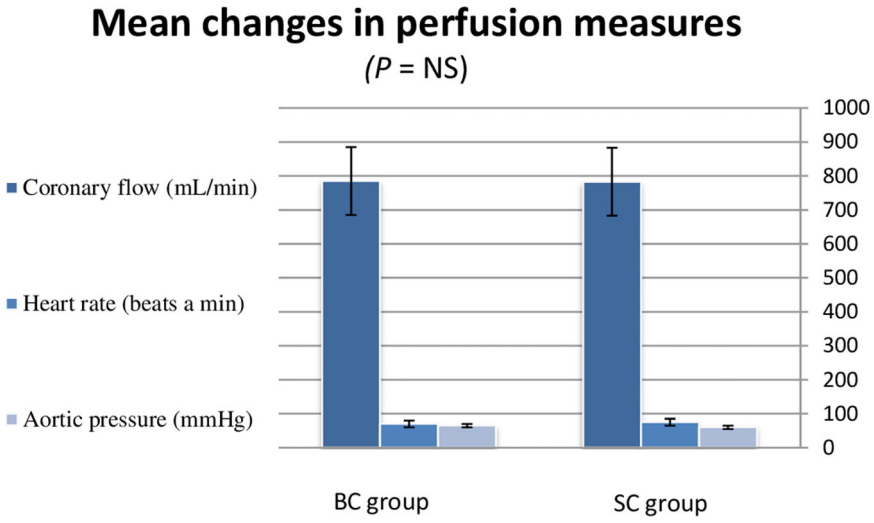

FIGURE 2 Mean changes in perfusion measures: Coronary flow (mL/min), Heart rate (beats a minute), Aortic pressure (mmHg) in OCS Heart (P = NS). OCS, organ care system

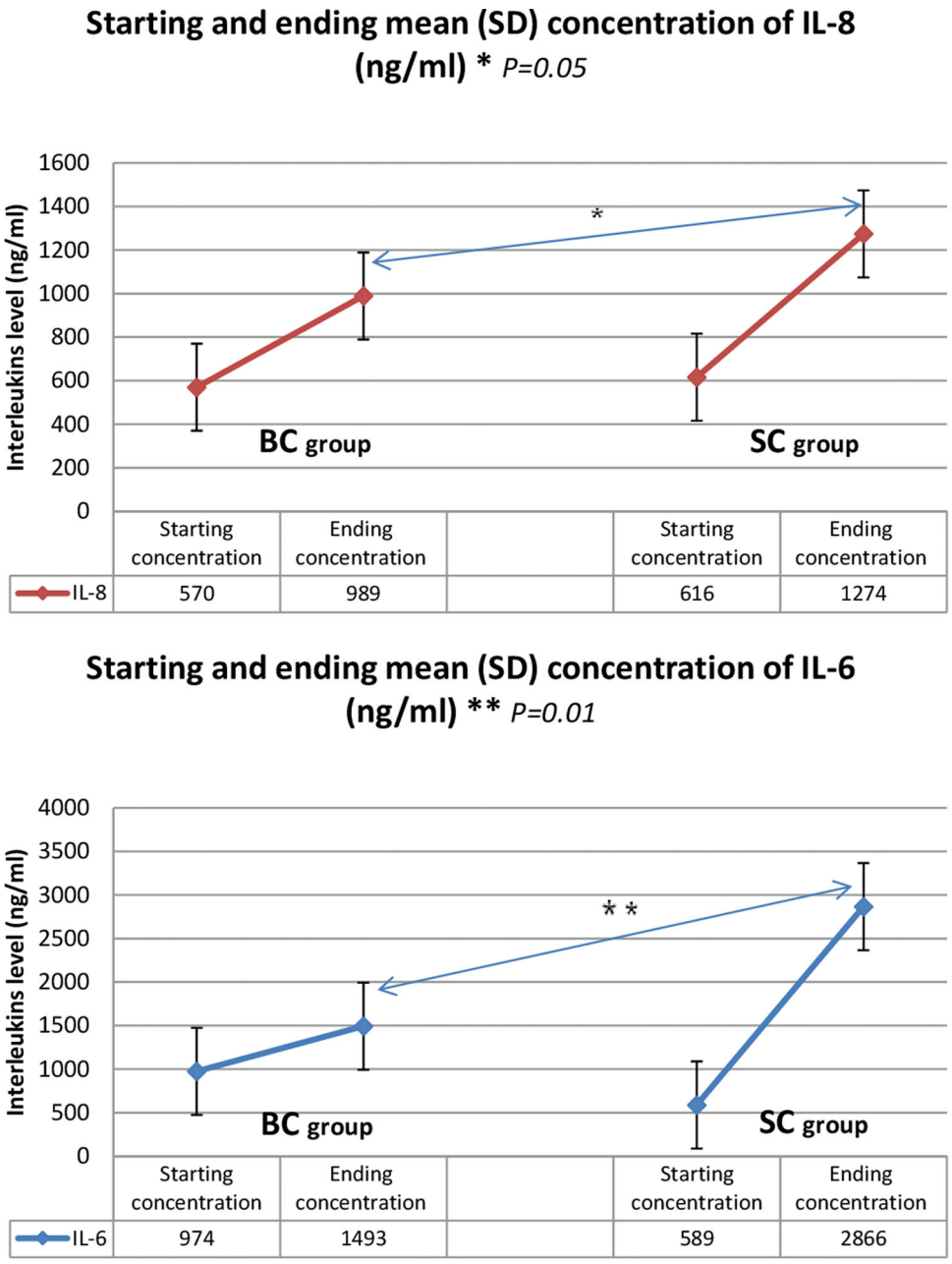

FIGURE 3 Starting and ending mean (SD) concentration of IL-6, 8 (ng/ml) in the organ care system (ng/ml). IL, Interleukin

In addition, Custodiol must be perfused under hypothermic conditions (4°C), lowering the heart temperature to 15°C. But during isolated hypothermia, different ion constellations may lead to cellular edema and impaired electrical activity and to heart fibrillation. Before the onset of cardiac arrest, the energy consumption is increased.[12-14] This may cause adverse effects related to the temperature gradient because in the OCS, the donor heart is transported at 34°C.

It has been demonstrated that the duration of cold ischemia negatively impacts the outcome of transplanted patients and thus can adversely affect organ viability. Peritransplant injury of endothelium after brain death may initiate immunological processes that accelerate graft arteriopathy.[15] The interleukins are a class of cytokines that are produced by leukocytes and have been shown to play important roles in immunological and inflammatory responses. Interleukins 6 and 8 are common cytokines involved in inflammation. IL-6 is an anti-inflammatory cytokine, which plays an important role in inducing acute phase reactions and controlling local and systemic acute inflammatory responses.[16,17] In addition, recent research suggests that lactate level before removal of graft from the OCS is a powerful predictor of graft failure.[18] In our Center, we often use donor hearts with high venous lactate (>5 mmol/l) because of the severe shortage of donor organs in our country.[19]

There is some evidence suggesting that ultrafiltration (UF) can lead to significant reduction in circulating inflammatory mediators and reduces blood loss and transfusion requirements.[20] UF provides

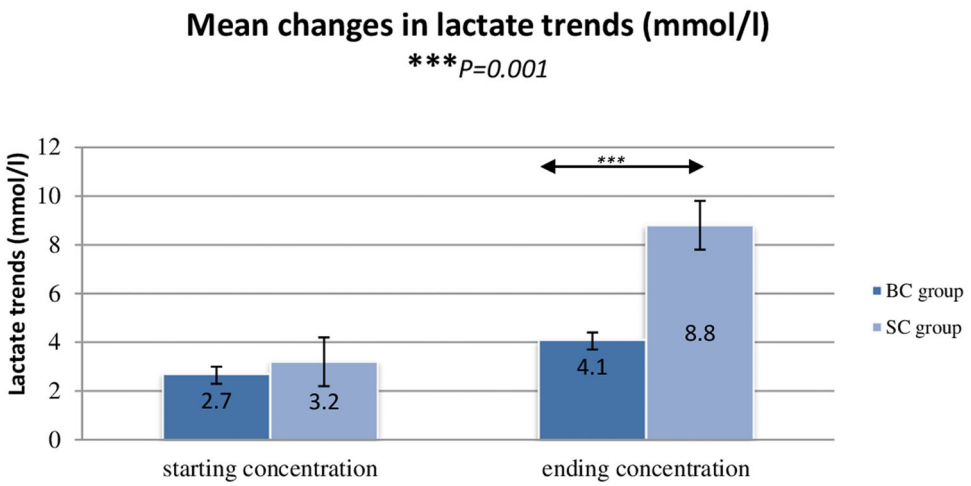

FIGURE 4 Mean changes in lactate trends (mmol/L). *P*-value represents the difference of change over time (test)

TABLE 3 Tissue Myocardial Doppler (at day 7), ICU length of stay, Inotrope dose, and ECMO duration

	Blood cardioplegia group (n = 30)	*Custodiol group (n = 13)*	*P value*
S^1LV lateral (cm/s) TMD	10 ± 1.6	9.2 ± 1.8	.73
S^1LV medial (cm/s) TMD	8.93 ± 1.35	8.58 ± 1.6	.60
S^1RV (cm/s)TMD	10 ± 2.66	8.95 ± 1.96	.36
LVEF (%)TMD	61.4 ± 2.31	57.5 ± 7.9	.001
ICU length of stay, d	11.7 ± 10.3	19.6 ± 13	.44
Inotrope Dose, mcg/kg/min IV			
24 h	6.5 ± 1.9	6.5 ± 1.7	
Dobutamine	1.75 ± 1.25	1.8 ± 1.3	.74
Milrinone			.90
48 h	6.0 ± 2.6	6.8 ± 1.3	
Dobutamine			.39
	0.2 (*n* = 1)	0.3 (n = 1)	
Milrinone			
72 h	3.6 (±0.8)	5.4 (±2.7)	
Dobutamine			.05
	0.2 (*n* = 1)	0.2 (*n* = 1)	
Milrinone			
ECMO duration, h	29.5 ± 28.4 *n* = 6	78.4 ± 89 *n* = 8	.002

Abbreviations: ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit; LVEF, left ventricular ejection fraction; S^1LV, myocardial velocity associated with isovolumic contraction of left ventricle; S^1RV, myocardial velocity associated with isovolumic contraction of right ventricle; TMD, tissue myocardial Doppler.
Data are expressed as mean ± *standard deviation.*

its potential advantages, with improvements in hemodynamic, pulmonary, coagulation, and other organ functions. Decrease of blood transfusion requirements, as well as reduced total body water and blood loss after the surgery, are additional benefits of UF.[21,22] Modified ultrafiltration (MUF) leads to a significant reduction of lipopolysaccharide-binding protein and terminal complement complex and was associated with reduced blood loss and postoperative lactate concentrations shortly after surgery.[23] MUF can be effective in removing cytokines and adhesion molecules.[24] Smaller molecules, such as IL-6, IL-10, tumor necrosis factor (TNF), and endothelin 1 have been shown to be filtered with UF.[25]

In our small cohort, the patient outcomes—survival and incidence of serious cardiac-related adverse events at 30 days post implant—were acceptable and demonstrate the feasibility of blood cardioplegia use with the OCS. Lactate trends at the end of ex vivo heart perfusion, inotrope dose at 72 hours and time of sinus rhythm restoration in OCS were statistically significantly higher in the standard care group. Other outcomes, such as OCS perfusion measures and length of ICU stay, were all within the expected range for our center. There was a lower mean ECMO duration in the blood cardioplegia group relative to the standard care group. We commonly use ECMO after heart transplant, during the postoperative recovery period, to reduce the reperfusion time.

Our analysis has several limitations. This is a single center report. Lack of randomization and small sample size are another limitations, and additional studies, ideally with randomized controlled design, are needed to evaluate the impact of procurement technique and conditioning of the donor heart during transportation might have on outcomes, especially with long ex vivo times during long-distance transportation. Our observations, while preliminary, show mean ex vivo heart perfusion ending concentration of IL-6 and IL-8 were significantly lower in the blood cardioplegia group compared to the standard care group. The use of blood cardioplegia and conditioning could be a safe method for myocardial protection in distant procurement and preservation of donor hearts in the OCS. The

independent effects of blood cardioplegia and Levosimendan are not possible to separate in this study. We can only make comments about the observations we have seen with the combination of blood cardioplegia, Levosimendan, and ultrafiltration. For future research, it will be important to separate these interventions and determine their impact individually.

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