Article

Improved Posttransplant Outcomes with HTK-Custodiol when compared to St. Thomas Solution for Preservation of the Cardiac Allograft

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Abbreviations

ATP – Adenosine Triphosphate
CPB time – Cardiopulmonary Bypass time
CPS – Cardiac Preservation Solution
CF-MCS – continuous -flow mechanical circulatory device

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ECC time – Extracorporeal circulation time
ECMO – Extracorporeal Membrane Oxygenation
HTx – Heart Transplantation
ISHLT – International Society of Heart and Lungs Transplant
LR – Logistic Regression
LVAD – Left Ventricular Assist Device
NO – Nitric Oxid
OR – Odds Ratio
OLR – Ordinal Logistic Regression
VAD – Ventricular Assist Device
VIS – Vasoactive Inotropic Score
95%CI – 95% Confidence Interval

Abstract: Introduction: The best choice of cardiac preservation solution (CPS) for protection of the cardiac allograft from cold ischemia damage remains controversial. This retrospective observational study compares an extracellular CS (St Thomas) with an intracellular CPS (HTK-Custodiol) for protection of the cardiac allograft from adverse effects due to diastolic arrest and cold ischemic time. **Methods**: From January 2009 to December 2020, 154 adult HT were performed at our hospital. St. Thomas solution was exclusively applied from 2009 to 2015, and thereafter, HTK-Custodiol alone was used. The 2 CPS were compared on the basis of the following outcomes: posttransplant all-cause mortality, inotropic score, incidence of primary graft dysfunction, and the 1-year rejection score. **Results:** St. Thomas or HTK-Custodiol CPS were applied in n=75 vs n=79 HTx recipients, respectively. Preoperative and intraoperative parameters were not different between groups. Use of HTK-Custodiol was related with the inotropic score in univariate analysis (regression coefficient: -0.69±0.16, p<0.0001). The HTK-Custodiol group showed lower 30-days mortality (2.5 vs 14.7%, p=0,0068), inotropic score (35.7 vs. 98.8; p<0,0001), and mean rejection score (0.13±0.16 vs 0.18± 0.17, p= 0,036). The incidence of primary graft failure requiring transitory ECMO support was not different between groups (12 vs 13%; 0=0.94). In multivariate analysis, use of HTK-Custodiol was associated with 30-days mortality (OR, 95%; 0.15 (0.03-0.71; p=0.0164) and mid-term mortality (HR, 95%: 0.2 (0.069-0.6); p=0.0039).**Conclusion**: In our cohort of HTx recipients, using HTK-Custodiol for CPS was associated with better postoperative outcomes after HTx when compared with St. Thomas.

Keywords: heart transplantation; cardiac preservation solution; inotropic score; acute cellular rejection; all-cause mortality

Introduction

Over the last decades, HTx has been the gold standard of care for well selected advanced heart failure (HF) patients [1]. HTx remains still the first choice for treating advanced HF patients despite an increasing number of patients living with continuous-flow mechanical circulatory support (CF-MCS). One of the reasons favoring HTx as first choice is the superiority of its long-term results when compared to CF-MCS treatment and this may explain the recent increase in the number of HTx candidates on the waitlist even though these patients were likewise eligible for CF-MCS treatment [1].

Successful organ preservation is the key element of cardiac transplantation since it shall maintain the structural integrity and functionality of the cardiac allograft starting with cardioplegic arrest and lasting until release of aortic clamping. Two parameters are determinant of the success of this critical element: the duration of the cold ischemic storage and the preservation solution applied for diastolic cardiac arrest of the cardiac allograft.

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Regarding the duration of cold ischemic time, analysis from the International Society for Heart and Lung Transplantation (ISHLT) indicates that early outcomes are best when 2 to 4 hours of allograft ischemic time are not to exceeded [2,3], although resumption of normal cardiac function even after 13 hours of cold ischemic time has been reported [4].

Overall, multiple CPS [2] have been developed and applied worldwide, and this high number indicates the absence of a one-fits-all cardioplegia CPS. Furthermore, uncertainties remain with respect to the best applicable CPS for standard procedures in cardiac surgery since many CPS have not been tested in head-to-head randomized controlled clinical studies.

In 2015, the University Hospital of Lausanne switched from St. Thomas to HTK-Custodiol CPS for cardiac arrest, procurement and cold ischemic transport. On the basis of unchanged patients' profile in the two-center cohort of HTx recipients in follow-up by the University Hospital of Lausanne and Geneva during the last years, we investigated the impact of these 2 CPS on 30-days mortality, inotropic score, primary graft dysfunction requiring extracorporeal Membrane Oxygenation (ECMO), and 1-year posttransplant rejection score.

Methods

From January 2009 to December 2020, 165 HTx were executed at the Lausanne University Hospital (CHUV) including 11 pediatric cases. The latter were excluded resulting in a study population of 154 adult HTx recipients.

The patients were divided into 2 groups according to the CPS used: St. Thomas solution (N=75) and HTK-Custodiol (N=79) with the former used until 2015 while the latter was applied thereafter.

The study was approved by the Ethic Committee of the Lausanne University hospital (CER 2019-704) and an informed consent was obtained for each patient as required by the study authorizing entity. This study was conducted in accordance with the Declaration of Helsinki and the International Society for Heart and Lung Transplantation (ISHLT) Ethics statement.

Operative strategy

St. Thomas solution was administered at 20ml/kg or more if the heart did not arrest within the first 10 seconds of the infusion. Custodiol was perfused at a dose of 20 to 30 ml/kg in order to achieve a total infusion time of 7 minutes. In both groups, topical cooling with ice-slush was employed during harvest and transport. If allograft ischemic time exceeded 150 min, another 500 ml of either CPS was re-administered upon graft arrival in the operating room.

Cardiac allograft implantation was performed always using the bicaval technique with anastomoses in the following sequence: left atrium, inferior vena cava, superior vena cava, pulmonary artery, and finally the aortic anastomosis.

Clinical evaluation and follow up data

Patients' demographic, clinical, and biological data were obtained from the respective individual health electronic dossiers at the University of Lausanne or Geneva. Clinical parameters and blood withdrawal were realized at the day of transplant operation. Intra-operative, in-hospital postoperative and follow-up data were retrieved from the electronic chart. Primary outcomes were hospital mortality (30-days mortality), vasoactive inotropic score (VIS), primary graft dysfunction requiring ECMO, and rejection score. Secondary outcome was overall mid-term survival.

The VIS score is an acknowledged predictor of outcomes after cardiac surgery (death, cardiac arrest, need for mechanical circulatory support, renal replacement therapy and/or neurological injury) [5] and was calculated according to the Gaies et al. [5]

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formula. In short, on the basis of the continuous documentation of all vasoactive medications in the patient's individual intensive care file, the VIS is calculated using maximal level of each vasoactive substance during the first 48 postoperative hours. The International Society for Heart and Lungs Transplant (ISHLT) histological rejection score was calculated from endomyocardial biopsies obtained during the first year in accordance with the local protocol for posttransplant follow-up.

Statistical methods

Results were expressed as mean and standard deviation (SD) for quantitative variables. For skewed data distributions, the median and interquartile range (IQR) was used. Frequency tables (numbers and percent) were used for summarizing categorical data. In some cases (e.g., waiting time on list), data were log-transformed to normalize their distribution. Mean values of patient groups (Saint-Thomas vs. HTK-Custodiol) were compared by Student test, whereas proportions were compared by the chi-squares test.

The association between the recipient's characteristics and the inotropic score was assessed by linear regression analysis and results were expressed as regression coefficient with standard error (SE). When attempting to predict inotropic score by several covariates, multiple regression (MR) was used.

The prediction of a binary outcome (e.g., 30-day survival) from the recipient's characteristics was carried out by univariate Logistic Regression (LR) analysis. The strength of the association of each covariate with the outcome was quantified by the Odds Ratio (OR) together with its 95% Confidence Interval (95%CI).

The distribution of the rejection score markedly skewed to the right could not be normalized. Therefore, it was categorized into three classes, respectively, equal to 0.0, <0.20 and >0.20, and treated as an ordinal variable. Ordinal Logistic Regression (OLR) analysis was applied to assess the relationship with each recipient's characteristics and the OR with 95%CI was calculated.

The overall survival time was graphically displayed by the Kaplan-Meier (KM) survival curve for both preservation fluids (Saint-Thomas and HTK-Custodiol). The comparison of the two survival curves was done by Cox regression analysis. The same method was used to assess the relationship between survival and covariates related to the recipient. Results were expressed by the Hazard Ratio (HR) and its 95%CI.

Statistical test results were considered significant at the 5% critical level (P<0.05). All calculations were done with SAS version 3.4 (SAS Institute, Cary, NC, USA) and R version 4.1.0.

Results

Baseline patient characteristics are displayed in **Table 1.** Out of the 154 consecutive adult HTx performed in our institution for end stage heart failure from all etiologies, 75 patients (48,7%) received St. Thomas solution and 79 patients (52,3 %) HTK-Custodiol as CPS. Age, etiology of the heart failure, presence of a VAD preoperatively, mean left ventricular ejection fraction (EF), or (and?) CPB time were not different between groups. In the HTK-Custodiol group, females were more frequent (23 vs 10; p= 0,017) and the ischemic time was shorter (172±46 vs 144±40 min p= 0,0008). Donor age was older for the HTK-Custodiol group patients (43,5±14,9 vs 49,2±14,4 years; p=0,038).

Table 1. Comparison of baseline characteristics between St. Thomas and HTK-Custodiol groups.

Variable	Category	Saint Thomas Mean ± SD n (%) (N=75)	HTK-Custodiol Mean ± SD n (%) (N=79)	p-value
Recipient				
Age (years)		51.9 ± 12.1	51.3 ± 12.9	0.76

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Sex	Female	10 (13.3)	23 (29.2)	0.017
Etiology	Ischemic Other	30 (40.0) 45 (60.0)	36 (45.6) 43 (54.4)	0.49
VAD	Yes	24 (32.0)	32 (40.5)	0.27
Diabetes	Yes	13 (17. 3)	21 (26.6)	0.17
eGFR (ml/min/1,73m^2)		50.8 ± 14.3	56.7 ± 20.3	0.079
LVEF (%)		25.0 ± 19.1	28.4 ± 14.4	0.15
VO_2 max (ml/min/kg)		14.1 ± 4.0	18.3 ± 24.2	0.17
PVR (WU)		2.4 ± 1.2	2.3 ± 0.97	0.55
Ischemic time (min)		172 ± 45.5	144 ± 40.2	0.0008
CPB time (min)		154 ± 63.2	157 ± 62.7	0.82
Donor				
Age (years)		43.5 ± 14.9	49.2 ± 14.4	0.038
Sex	Female	25 (40.3)	11 (44)	

SD: standard deviation ; *VAD* : ventricular assist device ; *VO_2 Max* : maximal oxygen consumption; *PVR*: pulmonary vascular resistance ; *WU* :wood units ; *CPB* : cardiopulmonary bypass ; eGFR=estimated glomerular filtration rate ; LVEF= left ventricular ejection fraction.

Regarding outcomes (**Table 2**), 30-days ACM was by trend lower (St. Thomas vs HTK-Custodiol: 11 vs. 2; p=0,068). The rejection score was lower in the HTK-Custodiol group (St. Thomas vs. HTK-Custodiol: 0,18±0,17 vs. 0,13±0,16; p= 0,036) as well as the inotropic score (St. Thomas: 98,8±99,3 vs HTK-Custodiol: 40,5±28; p<0,0001).There was no difference regarding the incidence of primary graft dysfunction requiring postoperative ECMO immediately after transplant surgery or within the first 24 hours (St. Thomas vs HTK-Custodiol: 12 vs 13; p=0,94).

Table 2. Comparison of outcomes between St. Thomas and HTK-Custodiol groups.

Outcome	Category	Saint Thomas Mean ± SD n (%) N=75	HTK Custodiol Mean ± SD n (%) N=79	p-value
Rejection score		0.18 ± 0.17	0.13 ± 0.16	0.036
Histol. reperfusion injury				
Inotropic score	Mean Median (IQR)	98.8 ± 99.3 71.8 (31.8-127)	40.5 ± 28 35.7 (17.5-60.2	<0.0001
Postoperative ECMO	Yes	12 (16)	13 (16.5)	0 .94
30 days mortality	Dead	11 (14.7)	2 (2.5)	0.0068
Follow up (years)	Mean Median (IQR)	7.0 ± 3.9 8.0 (4. 3-12.2)	3.1 ± 1.5 3.0 (1.9-5.7)	<0.0001

SD : standard deviation ; *IQR* : interquartile range ; *ECMO :* extracorporeal membrane oxygenation

At univariate logistic regression analysis (**Table 3**), the strongest risk factors for higher inotropic score was the type of CPS (HTK-Custodiol vs St. Thomas, regression± SE, -0,69±0,16; p<0,001) while ischemic time (regression±SE, 0,008±0,002; p=0,004) and CPB time (regression±SE, 0,004±0,001; p=0,0031) were less important. And multivariate regression analysis confirmed St.Thomas preservation solution (p<0,0001), longer allograft ischemic time (p=0.017), and longer duration of extracorporeal circulation (ECC) (p=0.015) as independent risk factors for increased postoperative inotropic score.

Table 3. Risk factors for Inotropic Score (univariate).

Risk factor	Category	Regression ± SE	p-value
Preoperative (recipient related)			

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Age (years)		-0.0085 ± 0.0077	0.27
Gender	Male *Vs* Female	0.17 ± 0.21	0.42
Etiology	Ischemic *Vs* Other	0.15 ± 0.17	0.37
VAD	Yes *Vs* No	0.17 ± 0.18	0.33
Diabetes	Yes *Vs* No	0.088 ± 0.20	0.67
Renal Function (ml/min/1,73m^2)		-0.015 ± 0.0051	0.77
Ejection Fraction (%)		-0.007 ± 0.0061	0.25
VO_2 Max (ml/min/kg)		0.0013 ± 0.012	0.91
PVR (WU)		0.018 ± 0.084	0.83
Waiting time on list (days)		-0.000123 ± 0.00028	0.66
Log scale		0.057 ± 0.063	0.37
Intraoperative (recipient related)			
Ischemic time (min)		0.0076 ± 0.002	0.0004
CPB time (min)		0.00446 ± 0.00148	0.0031
Log Scale		0.793 ± 0.24	0.0012
Preservation solution	Custodiol *vs* S^t Thomas	-0.69 ± 0.16	<0 .0001

SE: standard error; *VAD*: ventricular assist device; *VO_2 Max*: maximal oxygen consumption; *PVR*: pulmonary vascular resistance; *WU:* Wood units; *CPB*: cardiopulmonary bypass.

Table 4 shows that the type of CPS was the only risk factor for 30-days mortality (HTK-Custodiol vs St. Thomas, OR: 0,15 (0,032–0,71); p=0,016). However, the duration of follow-up for HTK-Custodiol was significantly shorter (St. Thomas vs HTK-Custodiol : 7±3,9 vs 3,1±1,5 years; p<0,001). Overall survival was compared using Cox regression analysis (**Figure 1**). The use of HTK-Custodiol was the only variable associated with improved survival (HTK-Custodiol vs St. Thomas, HR: 0,20 (0,069 -0,6); p=0,0039) (**Table 5**).

Table 4. Risk factors for 30 days mortality (univariate).

Risk factor	**Category**	**OR (95% CI)**	**p-value**
Preoperative (recipient related)			
Age (years)		1.03 (0.97–1.08)	0. 32
Gender	Male *Vs* Female	1.55 (0.33-7.37)	0.58
Etiology	Ischemic *Vs* Other	1.16 (0.37-3.62)	0.80
VAD	Yes *Vs* No	1.10 (0.34-3.55)	0.87
Diabetes	Yes *Vs* No	0.27 (0.034-2.18)	0.22
Renal Function (ml/min/1,73m^2)		0.99 (0.95-1.03)	0.65
Ejection Fraction (%)		1.002 (0.96-1.04)	0.94
VO_2 Max (ml/min/kg)		0 .90 (0.75-1.09)	0.28
PVR (WU)		1.10 (0.65-1.88)	0.72
Waiting time on list (days)		1.00 (0.99-1.002)	0.73
Log scale		1.032 (0.67-1.59)	0.89
Intraoperative (recipient related)			
Ischemic time (min)		1.00 (0.99-1.02)	0.61
CPB time (min)		1.01 (1.00-1.016)	0.06
Log Scale		4.06 (0.85-19.3)	0.07
Preservation solution	Custodiol *vs* S^t Thomas	0.15 (0.032-0.71)	0.0164

OR: odds ratio; *CI:* confidence interval; *VAD*: ventricular assist device; *VO_2 Max*: maximal oxygen consumption; *PVR*: pulmonary vascular resistance; *WU:* Wood units; *CPB*: cardiopulmonary bypass.

Table 5. Risk factors for overall survival.

Risk factor	**Category**	**HR (95% CI)**	**p-value**
Preoperative (recipient related)			

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Age (years)		1.03 (0.99–1.07)	0.11
Gender	Male *Vs* Female	1.38 (0.47-4.00)	0.56
Etiology	Ischemic *Vs* Other	0.95 (0.43-2.06)	0.89
VAD	Yes *Vs* No	0.97 (0.43-2.18)	0.94
Diabetes	Yes *Vs* No	0.63 (0.22-1.82)	0.39
Renal Function (ml/min/1,73m^2)		0.998 (0.97-1.03)	0.90
Ejection Fraction (%)		1.01 (0.98-1.04)	0.46
VO_2 Max (ml/min/kg)		0 .95 (0.86-1.06)	0.36
PVR (WU)		1.07 (0.77-1.50)	0.68
Waiting time on list (days)		0.999 (0.998-1.001)	0.37
Log scale		0.92 (0.71-1.20)	0.55
Intraoperative (recipient related)			
Ischemic time (min)		1.00 (0.99-1.01)	0.94
CPB time (min)		1.005 (0.99-1.01)	0.12
Log Scale		2.16 (0.75-6.26)	0.16
Preservation solution	Custodiol vs St.Thomas	0.20 (0.069-0.6)	0.0039

HR: hazard ratio ; *CI* : confidence interval ; *VAD* : ventricular assist device ; *VO_2 Max* : maximal oxygen consumption; *PVR*: pulmonary vascular resistance ; *WU* :wood units ;*CPB* : cardiopulmonary bypass.

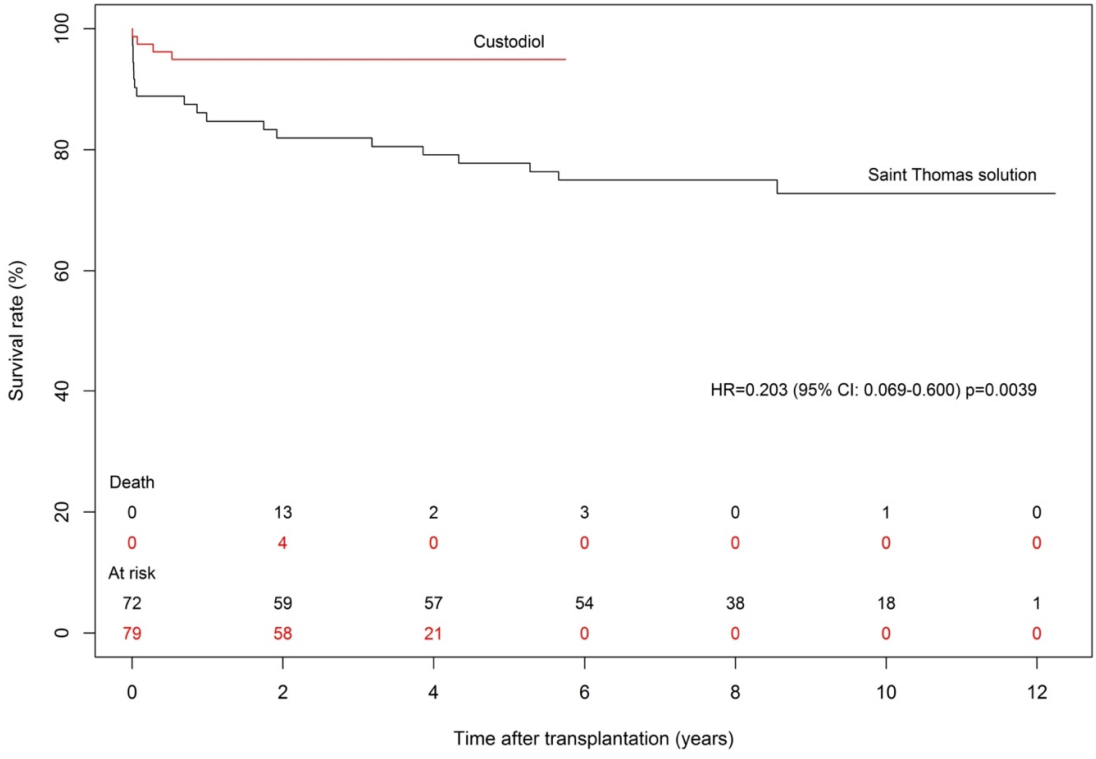

Figure 1. Survival stratified by the type of CPS. The figure displays Kaplan-Meier curves according to the cardiac preservation solution (CPS) received: Saint Thomas solution (black curve) or HTK-Custodiol (red curve) in the overall cohort.

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Discussion

In consecutive HTx recipients, this observational retrospective study compared posttransplant outcomes between patients which had cardiac arrest and cold ischemic transport of their donor heart either by intracellular or extracellular cold preservation solution. Outcomes were overall improved with application of the intracellular CPS as suggested by improved 30 days-survival, lower postoperative inotropic score, and lower 1-year allograft rejection score while the incidence of primary graft failure requiring temporary mechanical support was not different between groups.

More than 5 decades after the first human cardiac transplant surgery, HTx still remains the most promising surgical option for successful long-duration treatment of advanced heart failure patients. In fact, that the number of HTx candidates has continuously increased in the last years confirms sustained acceptance of this therapeutic option worldwide despite the fact that waitlist time for transplant surgery can be long due to the magnitude of potential recipients and the paucity of donors' hearts acceptable for transplantation [1,6,7].

Donor's heart preservation still remains an important issue in transplant surgery since both procurement of the donor's heart in diastolic arrest and the ex vivo transport expose the organ to an important risk of cellular damage. While the search for the best preservation strategy of the donor's heart is still ongoing, minimization of organ injury in order to preserve maximal viability and functionality of the organ has always remained the ultimate goal.

Preservation demands that the highest possible amount of Adenosine Triphosphate (ATP) should be maintained in the donor's heart, however, already diastolic arrest at procurement decreases the cellular ATP levels by 80% [8]. Furthermore, prolonged ex vivo ischemic time can result in extensive myocardial damage even though cooling of the donor's organ to 4°C has been shown to decrease the metabolic demand 10-to-12-fold [9]. Anaerobic glycolysis can maintain marginal generation of energy equivalents in the donor's heart even during cold ischemic storage [10]. However, anaerobic glycolysis results in intracellular acidosis resulting in Na^+ influx through the Na^+/H^+ antiporter and the Na^+/HCO_3^- symporter [11,12]. Na^+ influx not only increases the risk for cellular edema but also drives the sodium-calcium exchanger in the reverse mode resulting in extracellular calcium entry into the cell and, thus, intracellular calcium overload. The latter entails hypercontractility and mitochondrial damage which are considered key pathophysiological elements of ischemia reperfusion injury [13].

Therefore, CPSs contain buffers in order to maintain a stable cellular pH [10] such as bicarbonate in the St. Thomas CPS or histidine in the HTK-Custodiol CPS. The latter provides an additional advantage when compared to bicarbonate since histidine enhances the efficiency of anaerobic glycolysis, thereby adding support to preservation of organ function [14]. This may explain why intracellular buffers may be more effective when compared to extracellular buffers and prevent better from intracellular oedema [15,16].

CPSs, furthermore, distinguish with regard to sodium and potassium concentration classifying CPS into extracellular and intracellular solutions. Extracellular CPSs, such as the Saint Thomas CPS, are characterized by significantly elevated potassium and sodium levels and relatively normal calcium levels. In contrast, intracellular CPSs, such as the HTK-Custodiol CPS, are marked by moderately elevated potassium, relatively low sodium, and very low calcium concentrations. Consequently, extracellular CPSs prevent repolarization of cardiomyocytes while intracellular CPSs prevent action potential generation. These differences can also explain why extracellular CPSs increase the risk for cellular edema and, in particular, impair endothelial function [17]. HTK-Custodiol, however, not only presents a lower risk for cellular edema because of its low sodium content but also because of the component mannitol which acts as a local scavenger protecting from endothelial damage [16,18].

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Nonetheless, the Saint Thomas CPS arrests the donor's heart more rapidly, also due to magnesium at high concentration added to achieve rapid cardiac arrest. Likewise, procainamid hydrochloride in the St. Thomas solution blocks the fast sodium channels preventing repolarization [13,14]. On the other hand, HTK-Custodiol has advantages with regard to metabolic preservation and protection from endothelial damage [16]. Altogether, each CPS has advantages and disadvantages, which is the reason why we compared both CPS against the background of an unchanged donor heart allocation system [19] and unchanged regional posttransplant protocol for the care of HTx recipients over the 2 last decades in Switzerland [19].

Remarkable results of this observational study are the reduced inotropic score, the lower acute cellular rejection score, and the lower 30-days all-cause mortality with the HTK-Custodiol CPS. Solutions with a high concentration of potassium, such as St. Thomas solution, are known to cause toxicity to the vascular endothelium. Carpentier et al. were the first to demonstrate reduced viability and function of endothelial cells after exposure to high potassium concentration solutions [17]. The endothelium is very important as it locally regulates coronary perfusion and cardiac function through the secretion of Nitric Oxid (NO) and vasoactive peptides. The latter have biological functions such as local vasodilation, reactive oxygen species chelation and inhibition of platelet aggregation [17, 20]. Using high potassium concentration CPS should therefore result in more important endothelial dysfunction and, subsequently, more impaired donor's heart function in the immediate postoperative phase [21]. In accordance, in the present study we observed a higher inotropic score in HTx recipients whose donor's heart was arrested and transported with the St Thomas CPS. Although St. Thomas solution is beneficial and still widely used in non-transplant cardiac surgery, our study, like others [16,20] demonstrates that using St. Thomas solution provides worse immediate outcomes after HTx. With regard to current trends in CPS use, most European centers moved from St. Thomas solution to HTK-Custodiol after 2010, and in the United States, in the past years, nearly half of the grafts were stored in the University of Wisconsin solution, one-fourth in Celsior and one fourth in HTK-Custodiol [16].

Regarding the difference in acute rejection score, we cannot exclude that this is a reflection of the improvement of the overall HTx patient care over the last two decades [5, 7, 19, 20]. However, the incidence of histological signs of ischemic reperfusion injury was significantly lower in the HTK-Custodiol group. Reperfusion results in production of ROS and release of damage-associated-molecular-patterns activating the inflammatory, coagulatory, and vasoactive pathways [22, 23]. Subsequently, endothelial cells upregulate their expression of leukocyte adhesion molecules (selectins, ICAM) facilitating leukocyte infiltration across the endothelial barrier into the interstitium where alloantigen presentation can trigger acute rejection [24].

Neither the inotropic score nor the reduced incidence of acute rejection were related with 30-day survival or overall survival while use of HTK-Custodiol was related with less important short- and mid-term all-cause mortality. Application of the HTK-Custodiol was the only predictor that remained significantly related with survival reinforcing the robustness of our finding while we cannot firmly confirm a role of pathomechanisms differently affected by intra- or extracellular CPS.

Limitations

This retrospective longitudinal study of HTx patients suffers from the weakness of retrospective observational studies. However, the data collection was complete and outcome measures were confirmed applying a double strategy: the mortality outcome was confirmed in a local database and the Swiss death registry, the rejection data were confirmed in the local database and the Swiss cohort study, and last but not least, the diagnosis of ischemia-reperfusion injury were confirmed by two independent cardiac pathologists.

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Conclusion

In our regional cohort of consecutive HTx recipients in pre- and posttransplant follow-up by two different tertiary centers, we observed that use of the intracellular HTK-Custodiol CPS was associated with improved outcomes including postoperative inotropic score, rejection score, 30-days mortality and midterm survival. Despite the fact that the present study was not a head-to-head comparison, the results suggest superiority of the intracellular HTK-Custodiol considering that there were no differences between patients' characteristics in both groups, between pre- and post-transplant follow-up, while the national donor heart allocation system remained unchanged during the study period.

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