Experience With Hypothermic Machine Perfusion in Expanded Criteria Donors: Functional Outcomes

M. Ruiz-Hernández[a,*], V. Gómez-Dos Santos[a], D. Díaz-Pérez[a], Á. Fernández-Alcalde[a],
V. Hevia-Palacios[a], S. Álvarez-Rodríguez[a], V. Díez-Nicolás[a], S. Elías-Triviño[b], and F.J. Burgos-Revilla[a]

[a]Urology Department, Ramón y Cajal University Hospital, Surgical Urology and Transplantation Research Group, IRYCIS, Alcalá University, Madrid, Spain; and [b]Nephrology Department, Ramón y Cajal University Hospital, Madrid, Spain

ABSTRACT

Hypothermic machine perfusion (HMP) decreases delayed graft function (DGF) and improves 1-year graft survival in expanded criteria donors (ECDs). Time of HMP could be associated with incidence of DGF.

Objective.   To analyze functional outcomes of ECD grafts preserved totally (local grafts) or partially (imported grafts) with HMP.

Materials and Methods.   We analyzed prospectively collected data from a cohort of first ECD graft receptors, with a minimum follow-up of 6 months. A total of 119 imported and 74 local grafts were included. Local ECD kidneys were preserved with HMP after retrieval. Imported ECD kidneys were preserved with simple cold storage and HMP. Vascular thrombosis, acute rejection, DGF, 1-year glomerular filtration rate, and 1-year graft survival were assessed. Univariate and estimative multivariate logistic regression was applied for analysis of DGF. A Cox proportional hazards model was applied to estimate graft survival.

Results.   DGF occurred in 14 recipients of local grafts and in 33 recipients of imported grafts (28.0 vs 18.1%, $P = .13$); 1-year graft survival was better in the group of local grafts (80.3 vs 91.9%, $P = .03$). No differences in vascular thrombosis (5.9 vs 5.4%, $P = .88$), acute rejection (12.3 vs 9.8%, $P = .91$), or 1-year glomerular filtration rate (41.2 vs 40.5 mL/m/1.73m^2, $P = .87$) were observed. In multivariate analysis, adjusted odds ratio for DGF was 1.20 ($P = .79$) and adjusted hazard ratio for graft survival was 1.93 ($P = .31$).

Conclusions.   There is a trend that complete HMP reduces the risk of DGF and improves 1-year graft survival in ECD kidneys.

KIDNEY transplant is the criterion standard treatment for patients with end-stage renal disease. The number of end-stage renal disease patients is becoming higher and there is a standard criteria donor shortage. Kidneys from expanded criteria donors (ECDs) are currently accepted by many centers as alternatives to extend the graft pool. These kidneys develops delayed graft function (DGF) more frequently and have poorer graft survival [1].

Hypothermic machine perfusion (HMP) reduces the risk of DGF and improves 1- and 3-year graft survival in ECD kidneys compared with simple cold storage (CS) [2,3]. Our group demonstrated that HMP is cost-effective compared with CS [4]. Kidney resistance (RR) and flow during HMP are used as indicators of graft viability because RR at the end of HMP is related to DGF and graft failure [5,6]. However, its prognostic value is poor.

HMP is not widely spread. Some HMP devices are transportable but most of the centers use them locally. Therefore, imported grafts are only partially hypothermic-machine preserved.

*Address correspondence to Mercedes Ruiz Hernández, Urology Department, Ramón y Cajal University Hospital, Surgical Urology and Transplantation Research Group, IRYCIS, Carretera de Colmenar Km 9,100, Madrid 28034, Spain. Tel: 034692258451. E-mail: merh06@gmail.com

The objective of this study was to assess the effect of partial vs total HMP in graft functional outcomes.

MATERIAL AND METHODS
Design, Setting, and Participants

We analyzed prospectively collected data from a cohort of first ECD graft recipients from February 2012 to September 2017. Approval for the study was obtained from the ethics review board. A total of 193 kidney recipients were included in the analysis, with a minimum of 6-month follow-up.

Preservation Method

Kidneys were procured locally or imported into our hospital form another center. Local kidneys were connected to a LifePort Kidney Transporter (Organ Recovery Systems, Chicago, IL, USA) after graft retrieval for HMP. Imported kidneys had a period of CS before they arrived at our center. After bench surgery, they were connected to LifePort Kidney Transporter.

Perfusion Parameters

LifePort calculates RR by dividing the instantaneous pressure by the instantaneous flow. Flow and RR data were collected at 15 and 30 minutes and 1, 2, and 4 hours and at the end of HMP.

Endpoints, Measurements, and Statistical Analysis

The primary endpoint was to assess DGF and 1-year graft survival. DGF was defined as the absence of decrease in serum creatinine level > 10% in the first 48 hours after transplant. Graft loss was defined as the return to dialysis or glomerular filtration rate (GFR) < 15 mL/min/1.73m^2. The secondary endpoints were primary nonfunctioning (PNF), defined as the permanent lack of graft function; 1-year GFR; vascular graft thrombosis; and acute rejection (AR). AR was clinically suspected (good response to treatment) or biopsy-proven.

Continuous variables were expressed as mean and confidence interval or median and range as required; categorical variables were expressed as number and percentage. Endpoints, donors, and recipient variables were assessed for univariate differences between groups by the Wilcoxon signed rank test, t test, or χ^2 test. Multivariate logistic regression was applied to estimate the influence of the kind of HMP (partial vs total) in DGF. A backward strategy was used to construct the regression model [7]. Covariates are shown in Table 1A. The 1-year graft survival rate between groups was analyzed with the log-rank test. A multivariate Cox proportional hazards model was applied to estimate the influence of the kind of HMP in graft survival. A backward strategy was also used [7]. Covariates are shown in Table 1B. All calculations were performed with Stata 14 (StataCorp, College Station, Tex, United States).

RESULTS

From February 2012 to September 2017, a total of 193 kidneys were preserved by HMP: 38.3% (74/193) were local grafts and 61.7% (119/193) were imported grafts.

Donor and recipients characteristics are summarized in Table 2. For baseline characteristics there were differences in donor and recipient age, cold ischemia time, and percentage of HMP. Median donor age was 69.9 years (95% CI, 59.3−78.6) for local grafts and 76.9 years (95% CI,

72.2−82.1) for imported grafts. Median recipient age was 56.1 years (interquartile range [IQR], 49.1−67.9 years) for local grafts and 63.2 years (IQR, 53.5−68.4 years) for imported grafts. Mean cold ischemia time was longer in imported grafts at 18.4 hours (95% CI, 16.0−21.1) vs 16.3 hours (95% CI, 13.7−18.2; $P < .001$). Median percentage of HMP was 0.41% (IQR, 0.30%-0.58%) in imported grafts vs 0.92% (IQR, 0.88%-0.95%) in local grafts ($P < .001$).

For HMP parameters flow increased and RR decreased at the end of perfusion in both groups. Imported grafts showed higher flow and lower RR at the beginning of HMP (Table 2).

Primary Endpoints

DGF occurred in 18.1% (14/74) of recipients of local grafts and in 28.0% (33/119) of recipients of imported grafts, ($P = .13$). Logistic estimative regression analysis also showed no difference in DGF between groups (odds ratio [OR], 1.20; $P = .79$) (Table 1A).

The 1-year graft survival rate was 91.9% in the local donors group and 80.3% in the imported donors group ($P = .03$). In the multivariate estimative Cox proportional hazards model no difference in 1-year graft survival between groups was observed (hazard ratio [HR], 1.93; $P = .31$) (Table 1B).

Secondary Endpoints

PNF did not occur in any grafts in either of the 2 groups. AR occurred in 12.3% (9/74) of recipients of local grafts and in 9.8% (11/119) of recipients of imported grafts ($P = .59$). Vascular thrombosis occurred in 5.4% (4/74) of recipients of local grafts and in 5.9% (7/119) of recipients of imported grafts (5/88, $P = .88$). There was no difference in 1-year patient survival between groups (97.3% vs 96.6%, $P = .78$); 1-year GFR was similar between groups (40.5% vs 41.2%, $P = .87$).

DISCUSSION

ECD represents 75% to 80% of kidney transplant activity in our center. ECD grafts are more susceptible to ischemia-related damage and have worse functional outcomes compared with standard criteria donor grafts [1,8]. Grafts from ECD could better profit from improving preservation techniques, such us preservation with HMP.

Data from the Eurotransplant program showed that HMP could improve outcomes in ECD grafts [2,3,9]. DGF incidence decreased from 29.7% to 22%, and in multivariate logistic regression analysis HMP reduced the risk of DGF compared with CS (OR, 0.46; $P = .047$). PNF incidence decreased from 12% to 3%. One-year graft survival improved from 80% to 90% (adjusted HR, 0.35; $P = .02$) and 3-year graft survival improved from 74.5% to 83.0% (adjusted HR, 0.47; $P = .04$).

In our center, since February 2012 all ECD grafts have been HMP preserved after showing that HMP was cost-effective compared with CS in these kind of grafts [4].

Table 1. Multivariate Analysis. (A): Estimative Logistic Regression Model for Delayed Graft Function; (B): Estimative Cox Proportional Hazards Model for 1-Year Graft Survival.

A	Odds Ratio (95% CI)	P Value	B	Hazard Ratio (95% CI)	P Value
Imported origin	1.20 (0.30–4.66)	.79	Imported origin	1.93 (0.54–6.85)	.31
Time of HMP	0.95 (0.84–1.09)	.48	Donor age	1.06 (1.00–1.12)	.03
Time of CS	1.01 (0.92–1.10)	.91	Time of HMP	1.05 (0.99–1.19)	.40
Donor age	1.03 (0.98–1.07)	.23			

Abbreviations: CS, cold storage; HMP, hypothermic machine perfusion.

However, in Spain CS is the preferred preservation method [10]. In addition, most of the centers use HMP locally, placing the kidney in a hypothermic machine after organ retrieval only if the procurement takes place at the same institution. When the kidney is procured in another center it is placed in HMP after arriving at the transplantation center. This situation was the same for our center. Therefore, we wanted to analyze if there were differences in functional outcomes based on the kind of HMP (totally vs partially used). If our study would have shown differences, it could be beneficial for hypothermic machines to travel between centers.

DGF incidence was 18.1% in local grafts and 28.0% in imported grafts, and 1-year graft survival was 91.9% and 80.35 %, respectively. In both groups, DGF and graft survival was better than those described in the literature [2,9]. In multivariate analysis, there is a trend that the kind of HMP could affect graft outcomes (DGF adjusted OR, 1.20; 1-year graft survival adjusted HR, 1.93). However, the results did not reach statistical significance. This could be explained by 2 facts: first, our small sample of patients and events and second, partial HMP could recondition the kidneys after a period of CS [11].

PNF incidence was 0% in both groups, lower than the incidence reported in other ECD studies. This could be explained by our definition of PNF. Our study considered PNF as permanent lack of graft function excluding vascular thrombosis. Vascular thrombosis occurred in 5.4% of local grafts and in 5.9% of imported grafts. AR incidence was similar to the incidence described by Treckmann et al for the ECD population [2]. One-year GFR was 40.5% in local grafts and 41.2% in imported grafts, which are lower than the GFRs reported by the Eurotransplant program group [2]. HMP mainly affects GFR during the first days after transplant, and

Table 2. Donor and Recipient Characteristics

	Local	Imported	P Value
Donor			
Age, median (IQR), y	62.9 (59.3–78.6)	76.9 (72.2–82.1)	<.001
Sex, men/women, %	54.0/46.0	53.4/46.6	.93
HTA, %	77.0	69.2	.24
DM, %	39.1	26.5	.07
BMI, median (IQR)	27.5 (24.2–30.0)	27.8 (25.7–30.1)	.27
Final Cr, median (IQR), mg/dL	0.74 (0.59–1.02)	0.80 (0.60–0.97)	.75
Glomerulosclerosis, median (IQR), %	7.7 (3.0–11.0)	8.5 (4.2–11.0)	.25
Cold ischemia time, mean (95% CI), h	16.3 (13.7–18.2)	18.4 (16.0–21.1)	<.001
HMP preservation, median (IQR), %	0.92 (0.88–0.95)	0.41 (0.30–0.58)	<.001
RR at first minute, median (IQR)	0.7 (0.4–1.1)	0.6 (0.4–0.8)	.05
RR at end of perfusion, median (IQR)	0.3 (0.2–0.4)	0.3 (0.2–0.4)	.25
Flow at first minute (mL/min), median (IQR)	33.0 (24.0–46.0)	43.0 (29.0–57.0)	.01
Flow at end of perfusion (mL/min), median (IQR)	87.0 (64.0–133.0)	82.0 (62.0–115.0)	.89
Recipient			
Age, median (IQR), y	56.1 (49.1–67.9)	63.2 (53.5–68.4)	.01
Sex, men/women, %	67.6/32.4	74.8/25.1	.28
HTA, %	78.4	84.7	.26
DM, %	25.7	29.7	.55
BMI, median (IQR)	26.5 (23.8–29.8)	27.0 (23.2–29.9)	.88
Peripheral vascular disease, %	24.3	17.1	.22
Heart disease, %	25.7	26.7	.87
Dialysis technique, %			.25
Hemodialysis	47.3	42.0	
Peritoneal dialysis	27.0	21.0	
Pre-emptive	25.7	37.0	
Dialysis time, median (IQR), mo	15.5 (6.4–24.6)	16.9 (8.4–32.5)	.35

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); Cr, creatinine; DM, diabetes mellitus; HMP, hypothermic machine perfusion; HTA, arterial hypertension; IQR, interquartile range; RR, kidney resistance.

GFR at longer follow-up depends mainly on others factors, such as recipient age, comorbidities, and drugs [12].

We also wanted to check if flow and RR during HMP could help us identify better grafts. Flow and RR at the end of perfusion were similar in both groups. The predictive accuracy of RR at the end of perfusion was studied by our group before. We found a C statistic of the receiver operating curve of 0.58 [6], similar to Jochmans et al [5]. Therefore, they should not be used to reject grafts.

CONCLUSIONS

There is a trend that complete preservation reduces DGF and 1-year graft loss, but no statistical significance was found. Currently, we could not recommend transporting machine perfusion devices.

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