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Effects of Delayed Hypothermic Machine Perfusion on Kidney Grafts with a Preliminary Period of Static Cold Storage and a Total Cold Ischemia Time of Over 24 Hours

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Background: Hypothermic machine perfusion (HMP) appears to exert a reconditioning effect on the ischemic damage of kidney grafts. However, some concerns still remain about its real effectiveness when it is delayed after a preliminary period of static cold storage (SCS) or with prolonged overall cold ischemia time (CIT).

Material/Methods: The effect of HMP on hemodynamic, metabolic, histological and ultrastructural features of grafts was investigated in 21 single-kidney grafts treated with a delayed HMP after SCS and with a total CIT of over 24 h.

Results: The mean CIT, SCS, and HMP times were 29 h, 12 h, and 18 h, respectively. Longer SCS was associated with higher vascular resistance and lower arterial flow. In the pre- *vs.* post-HMP comparison, a significant decrease in arterial resistances and increase of flow were recorded. The hemodynamic improvement was independent of HMP duration. The perfused grafts retained some metabolic activity, with a statistically significant decrease of pH, pO2, and glucose levels, and increase of lactates in the perfusion liquid, by the end of HMP. Longer SCS was associated with higher pH and greater pO2 decrease during HMP. Light microscopy and transmission electronic microscopy revealed no significant variations in nuclear, cytoplasmic, or ultrastructural damage. SCS, HMP, and CIT were not identified as risk factor for delayed graft function or rejection.

Conclusions: A delayed and extended HMP can recover the graft hemodynamic function, maintain some metabolic activity, and stabilize the accumulated ischemic damage due to a preliminary SCS.

MeSH Keywords: **Cold Ischemia • Kidney Transplantation • Kidneys, Artificial**

Abbreviations: **AR** – acute rejection; **BMI** – body mass index; **CEUS** – contrast-enhanced ultrasound; **CIT** – cold ischemia time; **DBD** – donation after brain death; **DCD** – donation after cardiac death; **DGF** – delayed graft function; **ECD** – extended-criteria donors; **HMP** – hypothermic machine perfusion; **ICU** – Intensive Care Unit; **IQR** – interquartile range; **KT** – kidney transplantation; **SCS** – static cold storage; **TEM** – transmission electronic microscopy; **WIT** – warm ischemia time

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Background

In deceased-donor kidney transplantation (KT), a prolonged cold ischemia time (CIT) has been identified as an independent risk factor for delayed graft function (DGF), acute rejection (AR), and poor graft survival [1,2]. It has been demonstrated that there is a proportional and independent increase in the risk of graft loss and patient mortality for each additional hour of CIT [2]. Furthermore, the extension of donor criteria to meet the transplant demand has led to the inclusion of high-risk categories such as donors after circulatory death (DCD) or donors with advanced age or significant comorbidities, which all show a higher susceptibility to ischemia-reperfusion injury [3]. Thus, to improve the long-term KT outcomes, efforts to minimize CIT have been universally advocated [2].

Thanks to recent technology advances, hypothermic machine perfusion (HMP) has become available in many transplant centers [4]. HMP provides a new strategy of pre-transplant graft management with potential advantages, not only in terms of KT outcome [5,6], but also for KT logistics, optimizing the recipient's preparation and scheduling the surgical procedure [4]. Although recent meta-analyses have verified that HMP compared to static cold storage (SCS) does significantly reduce the incidence of DGF [2,7,8], some heterogeneity among randomized controlled trials does exist, particularly in respect to graft survival. A potential explanation of such differences has been correlated with the modality of HMP used [9]. As a matter of fact, some centers start HMP immediately after procurement [10], while others delay it after a period of SCS [11], usually required during the transfer of the organ from the procurement hospital to the transplant center. Whether such preliminary SCS time still has a detrimental effect on the final KT outcome and whether the HMP improves or stabilizes the already established graft injury has not been fully clarified [9].

Material and Methods

Patient characteristics

During the period October 2017 to June 2018 at the Liver-Kidney Transplant Unit of Udine Academic Hospital, 21 kidney grafts from donation after brain death (DBD), suitable for single-graft transplantation but with an expected CIT over 24 h due to logistic reasons, were prospectively selected for HMP. CIT was defined as the time interval between cross-clamping and graft placement in the abdomen. Expanded-criteria donors (ECD) were not excluded and were defined according to standardized protocols, as follows: donor age >70 years; creatinine clearance <60 mL/min; and presence of at least 2 of the following circumstances: severe hypertension in pharmacological treatment with 2 or more drugs, cardiovascular accident, diabetes mellitus in pharmacological therapy, or presence of proteinuria >1 g/24 h. In such cases, a Remuzzi score ≤4 was required for single-kidney graft allocation. The demographic and clinical characteristics of donors and recipients are summarized in Table 1. Mean donor age was 60±13.4 years, and 47.6% (10 patients) of them were classified as ECD. Three donors were older than 70 years, 50% had arterial hypertension, 20% had chronic ischemic heart disease, 10% had chronic renal failure with proteinuria, 10% had acute renal failure with proteinuria, and 10% had diabetes. In these cases, the median Remuzzi score was 3.5 (2–4). The mean CIT, SCS, and HMP time were 29 h, 12 h, and 18 h, respectively.

Graft management and assessment

Immediately after procurement, all grafts were flushed with 500 mL Celsior preservation solution (Genzyme) and stored for a period of SCS until arrival at the transplant center. Following back-table surgery, the kidneys were managed with overnight HMP using a Life Port Kidney Transporter Machine (Organ recovery Systems, Chicago). Machine perfusion was conducted using 1 L of Kidney Perfusion Solution (KPS-1), a University Wisconsin-derived solution specifically formulated for MP. Graft monitoring during HMP was based on automatic data checking and recording of temperature, flow, vascular resistance, and infusion pressure every 10 s. At the beginning and the end of HMP, samples of the perfusion fluid were collected to measure pH, pO2, glucose, and lactate levels. Moreover, needle biopsies of the grafts were taken immediately before and after HMP and examined on serial hematoxylin and eosin and periodic acid Schiff-stained sections, and assessed by transmission electronic microscopy (TEM). Acute tubular damage was evaluated in terms of cytoplasmic damage (vacuolar degeneration and endo-tubular loss of cytoplasmic debris) and nuclear damage (partial or complete loss of hematoxylinophilia). Cytoplasmic damage was semi-quantitatively scored as less than 30% (+), between 30 and 60% (++), and greater than 60% (+++). Nuclear damage was scored as less than 10% or equal to or greater than 10%. None of the grafts showed nuclear damage greater than 15%. Ultrastructural features were evaluated in terms of glomerular, tubular, and vascular damage. At the time of KT, the recipients were asked to sign an informed consent form for the surgical procedure, which also included back-table graft biopsy.

Surgical procedure and postoperative management

The grafts were kept in HMP until the time of placement into the abdomen with initiation of the warm ischemia time. The details of KT surgical procedure, postoperative management, and follow-up clinical surveillance have already been described elsewhere [12]. A DGF was defined as need for dialysis in the first postoperative week. AR was defined as a biopsy-proven

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Table 1. Donor, graft and recipient characteristics.

	Total (n=21)
Donor and graft characteristics	
Male: Female	12: 9
Age (years)	60.0±13.4
BMI, (kg/m^2)	24 [23–30]
ICU lengh of stay, (days)	4 [2–9]
Amine admistration, (%)	13 (61.9%)
Cause of cerebral death, (%)	
– cerebral hemorrhage	13 (62.0%)
– post-anoxia	4 (19.0%)
– trauma	4 (19.0%)
ECD (%)	10 (47.6%)
Graft weight (gr)	314.5±140.7
CIT, (min)	1766.1±131.2
SCS, (min)	728.9±220.5
HMP, (min)	1064.8±189.5
WIT, (min)	44.8±10.4
Recipient characteristics	
Male: Female	10: 11
Age (years)	56.7±14.7
BMI (kg/m^2)	26.1±3.32
KT waiting list time, (years)	1.81±1.03
Years of dialysis before listing, (%)	
<10 years	18 (85.7%)
≥10 years	3 (14.3%)
Cardiopathy (%)	12 (57.1%)
Diabetes (%)	2 (9.5%)
Arterial vascular disease (%)	8 (38.1%)
Peritoneal dialysis (%)	4 (19.5%)
HLA matching (A, B, DR)	
– no compatibility	0
– 1 locus	1 (4.8%)
– 2 *loci*	7 (33.3%)
– 3 *loci*	5 (23.8%
– 4 *loci*	3 (14.3%)
– 5 *loci*	1 (4.8%)
– 6 *loci*	1 (4.8%)
– 7 *loci*	3 (14.3%)
– 8 *loci*	0

AR – acute rejection; BMI – body mass index; CIT – cold ischemia time; ECD – extended criteria donors; HMP – hypothermic machine perfusion; ICU – Intensive Care Unit; KT – kidney transplantation; SCS – static cold storage; WIT – warm ischemia time.

T cell-mediated rejection within the first 3 months after KT. Standard treatment for AR comprised pulse intravenous steroid therapy followed by a slow oral steroid taper and adjuvant antibody-depleting therapy for severe or steroid-resistant cases.

Statistical analysis

Categorical variables and frequencies were expressed by percentage, while continuous variables were expressed by mean±standard deviation or median [IQR], as appropriate. For categorical variables, cross-tabulations were generated, and the chi-square or Fisher exact test was used to compare distributions. For continuous variables, we used the *t* test or Mann-Whitney test. Pearson or Spearman correlation coefficients were used to explore any correlation between graft parameters and SCS, HMP, and CIT times. The variation rate of hemodynamic and metabolic parameters was calculated using the following formula:

$$(value_{HMP\ end} – value_{HMP\ start}) \times 100 / value_{HMP\ start}.$$

Univariate logistic regression was used to verify whether CIT, SCS, or HMP were significant predictive factors for DGF or AR.

Results

HMP reconditioning effect

The effects of HMP on hemodynamic, metabolic, and histological features rafts are summarized in Table 2. HMP was associated with a significant improvement of graft hemodynamic parameters, by decreasing arterial resistances and increasing the flow. Moreover, the grafts retained some metabolic activity during HMP, as indicated by a statistically significant decrease in pH, pO2, and glucose levels, and increase of lactates, in the perfusion liquid, in the pre- *vs.* post-HMP comparison.

The pathology examination of graft biopsies before and after HMP showed a substantial stabilization of acute tubular injury in terms of nuclear and cytoplasmic damage (Figure 1). From the ultrastructural point of view, post-perfusion samples mainly showed mild endothelial alterations of glomeruli, characterized by swelling of endoluminal capillary walls and/or segmental tubular basolateral labyrinth dilatation (Figure 2).

Table 3 shows the correlations among hemodynamic and metabolic parameters and the different ischemic times. SCS time showed a statistically significant correlation with the initial arterial flow (r –0.488, p 0.024) and vascular resistance (r 0.544, p 0.010). A longer SCS was associated with higher vascular resistance and lower arterial flow, as well as with higher pH and greater pO2 decrease during HMP. HMP duration was not

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Table 2. Reconditioning effect of HMP on graft's hemodynamic, metabolic and cytological features.

	HMP start	HMP end	*p*-Value
Arterial resistance, (mmHg)	0.33 [0.24–0.62]	0.21 [0.18–0.29]	**<0.01**
Mean arterial flow, (ml/min)	70.1±37.7	116.0 ±49.6	**<0.01**
pH	7.25±0.08	7.03±0.04	**0.01**
pO2, (mmHg)	154.8±45.8	51.1±5.1	**0.01**
Lactate levels, (mMol/L)	0.95 [0.3–1]	3.3 [2.6–4.3]	**<0.01**
Glucose levels, (mg/dL)	178.2±12.2	151.1±12.8	**0.01**
Nuclear damage >10%, (%)	3 (14.3%)	3 (14.3%)	0.99
Cytoplasmic damage, (%)			0.31
– (+)	10 (47.6%)	12 (57.2%)	
– (++)	8 (38.1%)	7 (33.3%)	
– (+++)	3 (14.3%)	2 (9.5%)	

HMP – hypothermic machine perfusion; SCS – static cold storage.

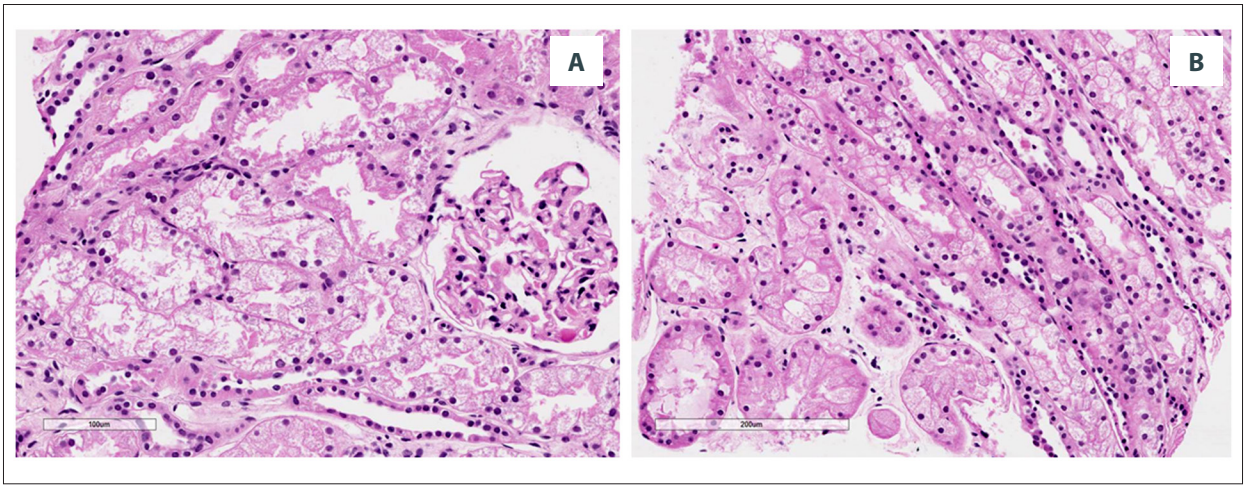

Figure 1. Findings on hematoxylin and eosin stained sections under light microscopy. (**A**) Pre-HMP biopsy: nuclear damage +, cytoplasmic damage +. (**B**) Post-HMP biopsy: nuclear damage +, cytoplasmic damage ++.

significantly correlated with the improvement of hemodynamic parameters, either investigated as HMP end-values or variation rates; these appeared to be independent even from CIT. In terms of metabolic function, the only effect noted was on the lactate levels, in which a longer HMP time was associated with greater variations in lactate levels.

KT outcome

Within the first year after KT, no cases of primary-non-function, graft loss, or patient death were noted. Four recipients (19.0%) developed DGF and 2 (9.5%) developed an episode of biopsy-proven T cell-mediated early rejection. CIT, SCS, and HMP time did not appear to be significant risk factors for these post-KT complications (Table 4).

In all the cases, DGF progressively resolved, with normal renal function recovery within 1 month following transplantation. Three patients received a graft procured from an ECD, with a Remuzzi score of 4, 4, and 1, respectively. The number of dialysis treatment sessions per patients was 9, 5, and 3, and the renal function normalized at 20, 11, and 6 postoperative days (POD), respectively. The dosage of B2-microglobulin (normal value <0.19 mg/l) at the day of first dialysis was 26.6, 18.4, and 23.2 mg/l, respectively, and was associated with increased vascular resistance of the grafts at CEUS. Subsequently, a normalization trend of laboratory and CEUS parameters was observed in all cases. At 1 month after the last dialysis, the B2-microglobulin values were <0.19, 0.65, and <0.19 mg/l, respectively, while graft perfusion and vascular resistance were within normal ranges in all cases. The recipient with a non-ECD graft required 3 dialysis treatments,

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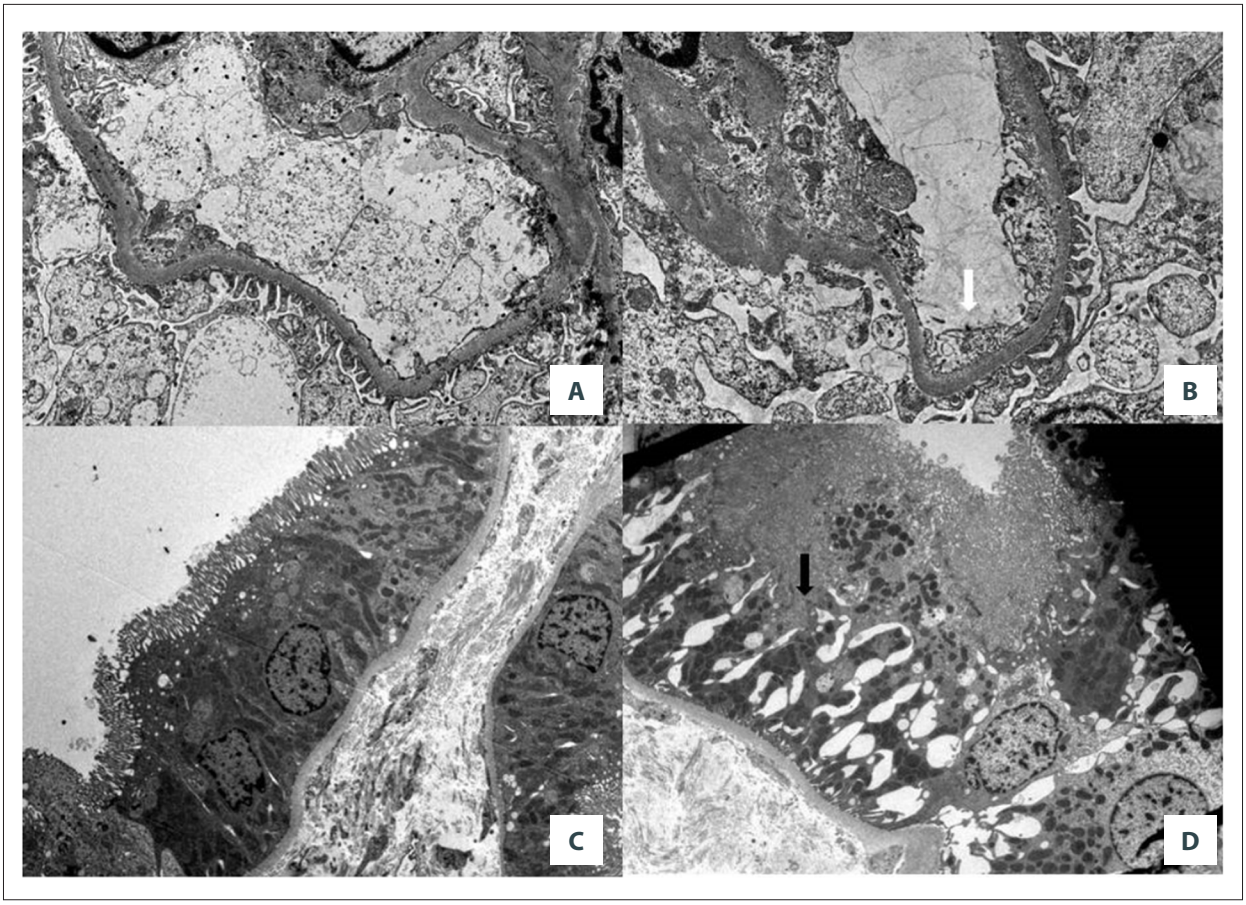

Figure 2. Ultrastructural observation at TEM. Glomerular capillary loops pre-perfusion (**A**) and post-perfusion (**B**) with endothelial swelling (white arrow). Proximal tubular epithelium pre-perfusion (**C**) and post-perfusion (**D**) with basolateral labyrinth dilatation (black arrow).

the starting B2-microglobulin level was 24.5 mg/l, and the vascular resistance of the graft measured by contrast-enhanced ultrasound (CEUS) was 0.80. The graft function normalized at POD 8, and at 1 month after the last dialysis, the B2-microglobulin value was 0.21 mg/l, with normal vascular resistance. The 2 cases of T cell-mediated early rejection were successfully treated with corticosteroids (methylprednisone 250 mg/day for 3 days). None of the patients developed any vascular or urologic complication requiring re-operation. The trend of 24-h diuresis, creatinine serum level, and creatinine clearance are presented in Figures 3–5.

Discussion

The graft injury induced by SCS is a complex phenomenon in which hypoxia triggers a metabolic failure with oxidative stress and inflammatory reaction, that become further magnified during the reperfusion phase [10,13]. Such damage is evident not only in the tubular cells, but also in the endothelial cells of the microvascular system [13]. As a matter of fact, in the present investigation as in previous ones, a significant correlation between SCS time and arterial resistance and flow at the beginning of perfusion was found. Conversely, HMP has been shown to promote normalization of renal hemodynamic parameters [14,15]. Moreover, the vascular resistance trend during HMP has been advocated as a reliable predictor of kidney graft function and risk of DGF/primary non-function [14. 16], with a higher predictive value than graft biopsies scores [16]. The reported advantages rely on a real-time, objective, noninvasive evaluation of the whole organ, which might be productively used in the clinical decision-making process [16,17]. In the present analysis, a significant improvement of arterial resistance and flow during perfusion was observed, although the magnitude of this improvement was not directly correlated with HMP duration. Some experimental studies [18,19] have found that HMP with a duration of 1–4 h can significantly reduce vascular resistance and improve creatinine clearance, compared with SCS alone, and that despite reaching the mean perfusate flow after 2 h of perfusion, vascular resistance values might continue to further improve for up to 6 h [15]. However, another study showed that 4-h HMP after a prolonged period of SCS (14 h) did not have any added advantage over SCS alone but, on the contrary, was

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Table 3. Reconditioning effect of HMP on graft's hemodynamic and metabolic parameters.

	Correlation coefficient		
	SCS	HMP	CIT
Arterial resistance, HMP start	**0.54 (p 0.01)**		
Arterial resistance, HMP end		–0.26 (p 0.25)	0.17 (p 0.46)
Arterial resistance variation rate	–0.35 (p 0.11)	0.24 (p 0.28)	–0.21 (p 0.36)
Arterial flow, HMP start	**–0.49 (p 0.02)**		
Arterial flow, HMP end		0.16 (p 0.48)	–0.33 (p 0.14)
Arterial flow variation rate	0.07 (p 0.75)	–0.09 (p 0.67)	0.17 (p 0.45)
pH, HMP end		–0.14 (p 0.73)	0.05 (p 0.91)
pH variation rate	**0.77 (p 0.02)**	–0.67 (p 0.07)	–0.04 (p 0.93)
pO2, HMP end		–0.35 (p 0.39)	0.09 (p 0.82)
pO2 variation rate	**0.71 (p 0.04)**	–0.24 (p 0.57)	0.59 (p 0.11)
Glucose levels, HMP end		0.03 (p 0.94)	0.40 (p 0.32)
Glucose levels variation rate	0.61 (p 0.10)	–0.06 (p 0.88)	0.46 (p 0.25)
Lactate levels, HMP end		0.20 (p 0.63)	–0.31 (p 0.45)
Lactate levels variation rate	–0.63 (p 0.09)	**0.76 (p 0.03**)	0.24 (p 0.56)

HMP – hypothermic machine perfusion; SCS – static cold storage.

Table 4. Impact of the different phases of cold ischemia on the risk of DGF and graft rejection.

	DGF			Graft rejection		
	OR	95% C.I.	p.	OR	95% C.I.	p.
Total CIT	.999	.992–1.006	0.878	1.001	.993–1.009	0.677
SCS time	.995	.987–1.002	0.199	1.001	.995–1.006	0.737
HMP time	1.005	.997–1.013	0.161	.999	.993–1.006	0.961

DGF – delayed graft function; OR – odds ratio; CIT – cold ischemia time; SCS – static cold storage; HMP – hypothermic machine perfusion.

associated with higher vascular resistance at reperfusion [20]. Overall, very limited data are available, and the heterogeneity of such results shows the necessity to further explore the underlying mechanism regulating graft hemodynamic function. In the present study, the delayed HMP successfully reconditioned the graft vascular resistance and flow, independently of the severity of the pre-existing dysfunction caused by the preliminary SCS period. This effect was maintained even after a prolonged HMP time (mean time: 18 h) and, by the end of HMP, the hemodynamic parameters of the grafts appeared to be independent of CIT. Nonetheless, it was previously reported that an SCS time of over 6 h sustains a negative effect on grafts, despite the combination with a delayed HMP [9], which may even be associated with the development of additional loss of cellular integrity and significant changes in cell morphology [20,21]. Conversely, in a report by Eurotransplant [14], on a series of 336 DBD grafts, the SCS was over 6 h in all cases and the accumulated tubular damage induced by the preliminary SCS actually appeared not to be significantly modified by HMP, but rather was stabilized. Even in terms of graft metabolism, SCS time rather than HMP time showed the greatest impact in the present study. A longer SCS time was associated with greater pH decrease and oxygen consumption during perfusion, as if the perfused graft tried to recover from the metabolic failure accumulated during the SC. Such a result, although just speculative, is a new finding and may further support the potential advantage of oxygenating the perfusate during MP. Of course, by the end of the HMP time, the chemical characteristics of the

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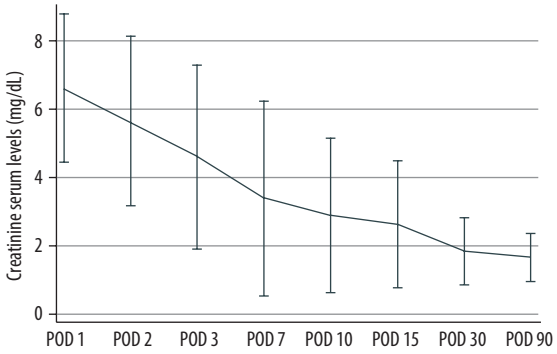

Figure 3. Post-KT trend of creatinine serum levels; POD – postoperative day.

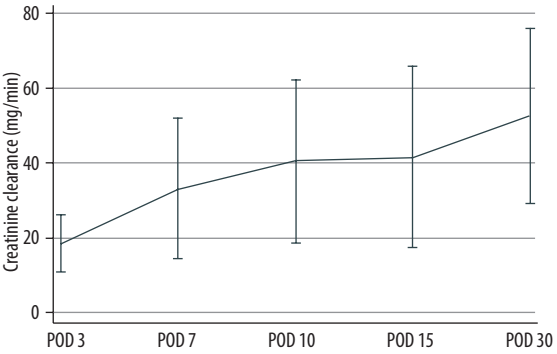

Figure 4. Post-KT trend of creatinine clearance; POD – postoperative day.

perfusate were significantly changed, but this could be expected considering that the shortest HMP time of our series was 9 h. Actually, only the lactate level increase showed a significant correlation with the HMP duration. However, other studies which investigated primary continuous HMP rather than delayed HMP in experimental models, showed a significant decrease in ischemia-reperfusion injury with less accumulation of toxic metabolites, improved electrolytes homoeostasis, and reduced oxidative damage, inflammation, and apoptosis [18].

Clinically, a recent meta-analysis [2] demonstrated that HMP compared with SCS significantly reduced the overall incidence of DGF, regardless of DBD or DCD type, or a total CIT over 24 h. Nevertheless, no significant advantage was found in ECD compared with standard-criteria donors. It may be speculated that since HMP stabilizes the ischemic damage rather promoting its recovery, the intrinsic higher dysfunction grade of ECD may be a greater determinant of the outcome compared to the HMP reconditioning effect. In the meta-analysis, no impact was recorded on the DGF duration or on the incidence of PNF or acute rejection. In the present study, the protective effect of delayed

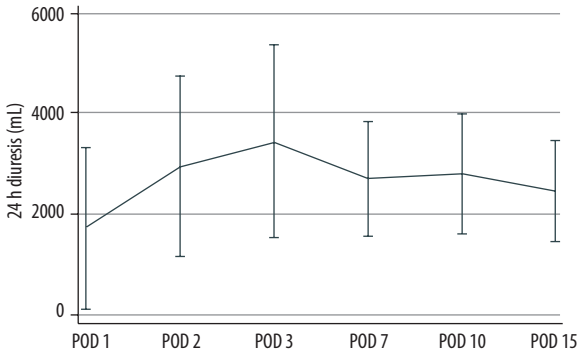

Figure 5. Post-KT trend of 24-h diuresis; POD – postoperative day.

HMP was verified, as the KT outcome was not negatively affected by the prolonged cold ischemia times (SCS, HMP, and CIT). Moreover, the prevalence of post-KT complications were within the ranges reported in the literature [22]. Such results may indirectly provide some new insight into the feasibility of lengthening CIT, if conditioned to the use of HMP, without any additional morbidity. However, it must be noted that none of the grafts in the study reached a CIT longer than 36 h, which is usually identified as the critical time limit [9].

Several limitations of the present study must be mentioned: a limited number of cases; a qualitative rather than quantitative analysis of the ultrastructural features at TEM; a CIT maintained within the upper limit of 36 h; and a follow-up time limited to 1 year after KT.

Conclusions

Kidney graft management based on a preliminary SCS period and a subsequent extended HMP, reaching an overall CIT longer than 24 h, does not appear to negatively affect the immediate- and short-term KT outcomes. The ischemic injury associated with the preliminary SCS is clearly evident at hemodynamic, metabolic, histological, and ultrastructural levels, and the reconditioning effect of HMP mainly results in an improvement of hemodynamic parameters, while the accumulated parenchymal damage tends to stabilize. Moreover, the graft retains some metabolic activity during the perfusion, producing an acidotic environment. Therefore, further studies with oxygenated perfusion machines and with perfusate formulas that can sustain and correct this metabolism are warranted to explore the possibility of further enhancing the graft reconditioning.

Conflicts of interest

None.

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