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THE UW SOLUTION FOR CANINE KIDNEY PRESERVATION

ITS SPECIFIC EFFECT ON RENAL HEMODYNAMICS AND MICROVASCULATURE[1]

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The preservation effects of UW solution on renal hemodynamics and microvascular systems were studied in canine kidney autografts. In 72-hr UW-preserved kidneys, the microvessels of both cortex and medulla were completely visualized with silicon rubber compound 1 hr after reperfusion. Histology also showed extremely well-preserved arterioglomerular and tubular systems. These results were correlated with good renal blood flow, prompt recovery of posttransplant graft function, and 100% two-week survival of dogs. In contrast, kidneys preserved for 72 hr with Euro-Collins solution showed necrotic and obstructive changes of the microvasculature and deterioration of renal hemodynamics. In 120-hr UW-preserved kidneys, the microcirculation of the medullary region became poor after reflow when there was fairly intact perfusion of the cortical region, indicating an ischemia-related intrarenal blood flow maldistribution. The 120-hr kidneys subsequently failed in spite of having a good blood flow and morphologically well-maintained microvasculature after reperfusion. These data demonstrated that much, but not all, of the beneficial effect of UW solution in kidney preservation might be attributed to its remarkable protection of renal microvasculature. Correction of intrarenal blood maldistribution caused by a discrepancy in tolerance to ischemia of the vascular and tubular systems might be important in successfully preserving the kidney for 120 hr.

The University of Wisconsin solution, developed by Belzer and his associates has had a major impact on organ preservation (*1*). Ploeg et al. (*2, 3*) have reported a 100% success rate with canine kidney grafts autotransplanted after 72-hr simple cold storage with UW solution as compared with 0% survival in Euro-Collins (EC)* solution. The beneficial effect of UW solution has been attributed to its prevention of cell swelling and tissue edema that occur during cold perfusion and storage (*1, 4*).

The cortical hypoperfusion following unclamping has been considered to play a critical role in the course of postischemic acute tubular necrosis of preserved kidneys (*5, 6*). The hypoperfusion of revascularized organs following prolonged ischemia might be a consequence of the deterioration in the integrity of the organs' microcirculation (*7, 8*). Therefore, the mechanism of protection of UW solution on renal autografts was investigated with special attention to renal hemodynamics and microvasculature.

MATERIALS AND METHODS

Animals and operative procedures. A group of mongrel dogs of either sex, weighing 18–22 kg, were randomly divided into five groups (Table 1). For the determination of animal survival and posttransplant graft function, 18 animals were used and 32 were used for analyses of histopathology and microvasculature of grafts at the end of cold storage, at 1-hr graft reperfusion, or in controls. After an overnight fast, animals were anesthetized with 20 mg/kg of intravenous sodium pentobarbital supplemented with 10 mg/kg ketamine and 0.05 mg/kg pancuronium. Animals were intubated and placed on a ventilator with an oxygen and room air mixture, 50% of FiO_2, under 5 cm H_2O of positive end-expiratory pressure.

Through a midline abdominal incision, the left kidney and the left ureter were dissected free, and 1.25 g mannitol and 10 mg furosemide were given intravenously. The left kidney was removed 15 min after drug administration and was transferred immediately into an ice-filled basin. Initial flushing of the graft was with 200 ml of cold heparinized lactated Ringer's solution, which was followed with 200 ml of cold preservation solution—EC solution or UW solution. The graft was placed in a sterile bag that was filled with the same preservation solution, and stored in a refrigerator until transplantation.

Anesthesia for autotransplantation was carried out as for the nephrectomy. After 72 or 120 hr of preservation, the renal autograft was placed in the right pelvic location. Vascular reconstruction was with end-to-end anastomosis of the renal artery to the external iliac artery and end-to-side anastomosis of the renal vein to the common iliac vein. Immediately after the graft revascularization and contralateral nephrectomy, 1.25 g mannitol and 10 mg furosemide were given intravenously. A polyethylene catheter was introduced into the graft ureter for urine measurement. In animals studied for survival, the catheter was removed subsequently and ureteroneocystostomy was performed. The electrolyte infusion was restricted to 30–40 ml/kg/hr during nephrectomy and transplantation. Cephalosporin 1 g was given intraoperatively and for 3 postoperative days. Neither infusion nor diuretics was given to the animals postoperatively. Animals were fed from the next morning.

Graft function. Graft function was estimated by urine output and serial measurements of serum creatinine (Cr) at days 0, 1, 2, 3, 5, 7, 9, 12, and 15. Animals were killed on the 15th postoperative day.

Renal blood flow measurement. Measurement of total renal blood flow was with an ultrasonic blood flowmeter (Model T-201, Transonic System Inc.) (*9*). In 12 randomly selected animals, the left renal arterial flow was measured just before the left kidney was removed. For the measurement of posttransplant renal blood flow, a probe was placed at the external iliac artery 1.0 cm proximal to the arterial anastomosis. Postoperative measurements were performed at 0.5, 1, 2 and 3 hr after graft revascularization, and the results were expressed as ml/min/g of wet graft weight.

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* Abbreviation: EC, Euro-Collins.

Analysis of renal microvasculature. Thirty-two kidneys from 32 animals were used for the analysis of renal microvasculature with a Microfil technique (*7, 10*). Four kidneys were from normal animals, 16 were studied at the end of cold preservation, and 12 were studied after graft revascularization (Table 1). Immediately after the graft was flushed with 50 ml of heparinized warm saline via the renal artery, the Microfil silicon rubber compound (Canton Biological Medical Company, Denver, CO) was infused slowly for 10–15 min at 100 cm of hydrostatic pressure until the compound drained freely through the renal vein. The midportion of the graft was sliced into five pieces 0.5 cm wide, and fixed with a graded series of alcohol for 7 days. Tissues were cleared with methylsalicylate solution for an additional 24–48 hr, and 5 micrographs per slice were exposed under a stereoscopic dissecting microscope. Filling of renal microvasculature with silicon rubber compound was graded from the micrographs from 0 (severe defect) to 4 (excellent filling) without knowledge of duration of preservation, type of preservation fluid, or any other experimental details.

Histologic studies. Animals that died within 15 days were immediately autopsied. All of the animals that survived for 15 days were killed at this time. A part of the kidney was obtained for microvasculature study. Tissues were fixed with 10% of formalin and stained with hematoxylin-eosin. Histopathologic changes of the graft were examined blindly.

TABLE 1. Experimental groups and the number of animals used

Group	Preservation fluid and time	Survival and blood flow study	Microfil[a] and histological study—1 hr reflow	End of ischemia
1	EC-72[b]	6	4	4
2	UW-72[c]	6	4	4
3	EC-120	—	—	4
4	UW-120	6	4	4
Control	—	—	4	—

[a] Another 4 animals were used as the normal control for the Microfil study.

[b] Kidneys were preserved for 72 hr with Euro-Collins' solution.

[c] Kidneys were preserved for 72 hr with University of Wisconsin Solution.

TABLE 2. Survival time of dogs after kidney autotransplantation

Group	Survival (days)	Mean survival (days)	*P* values
1	3,4,5,6,12,15	7.50±4.85	$P<0.01$[a]
2	15,15,15,15,15,15[b]	15.00±0.00	$P<0.001$[c]
4	2,3,5,5,6,15	6.00±4.65	

[a] Comparison between groups 1 and 2.

[b] This dog was sacrificed with a high serum creatinine level at posttransplant day 15.

[c] Comparison between groups 2 and 4.

Statistical analysis. Values were expressed as the mean ± SD. Student's *t* test, paired or unpaired, was used for the comparison of group means, and a *P* value less than 0.05 was considered significant.

RESULTS

Animal survival. As shown in Table 2, all 6 of the dogs in group 2 lived for 15 days. In contrast, in group 1 and 4, only one of 6 dogs (17%) survived in each group. Autopsy of these

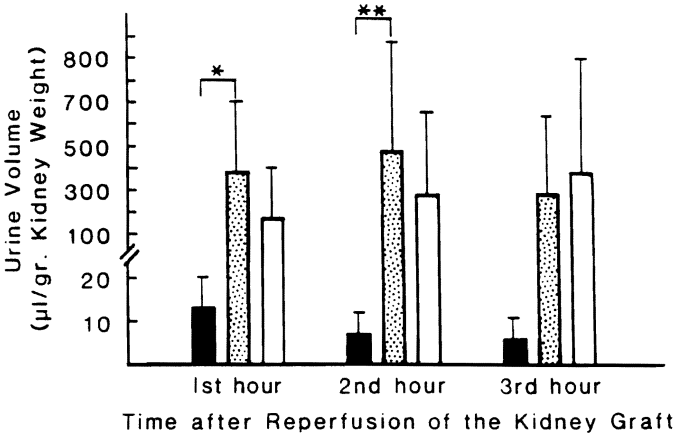

FIGURE 1. Urine production of the kidney autograft during 3 hours reperfusion period. Group 1: EC-72 Group 2: UW-72 Group 3: UW-120; *p <0.02; **p <0.05.

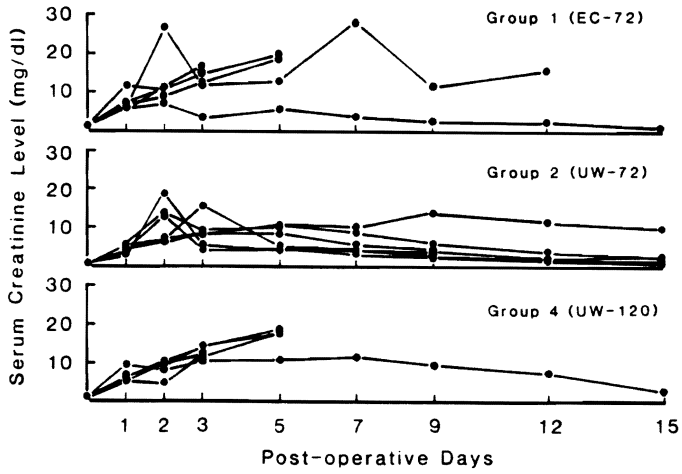

FIGURE 2. Changes of serum creatinine level after kidney autotransplantation.

TABLE 3. Total renal blood flow before donor nephrectomy and after kidney autotransplantation (ml/min/g kidney weight)[a]

Group	Before nephrectomy	Time after reperfusion of kidney grafts			
		0.5 Hr	1.0 Hr	2.0 Hr	3.0 Hr
1	4.76±0.85	1.46±1.06	1.34±0.97	1.30±0.94	1.27±0.60
	(134±15)[b]	(120±11)	(119±22)	(124±19)	(124±6)
2	4.76±0.85	2.55±0.98[c]*	2.89±1.00**	2.89±1.33*	2.00±0.28**
	(134±15)	(119±15)	(124±10)	(126±8)	(125±7)
4	4.76±0.85	1.90±0.76	2.43±1.14	2.17±0.68	1.82±0.44
	(134±15)	(126±26)	(125±21)	(128±25)	(134±26)

[a] There is no significant difference between groups 1 and 4 and groups 2 and 4. All values are presented as mean ± SD.

[b] Mean arterial blood pressure (mmHg) at the time of measuring blood flow.

[c] * $P<0.05$; ** $P<0.02$; as compared with group 1.

dogs showed edematous and congestive kidney grafts accompanied by some ascites and hemorrhagic lung edema, suggesting the progressive uremia caused by primary nonfunctioning kidney grafts.

The kidneys in the dogs that survived for 15 days showed only compensatory hypertrophy. No animals died of infection or complications related to surgery.

Graft function. The urine output during the 3 hr after unclamping is shown in Fig. 1. The average urine volume was 8.85±2.30 (SD), 385±360, and 278±353 μl/hr/g Kidney weight in groups 1, 2, and 4, respectively. The remarkable superiority of the UW preservation in terms of urine excretion was evident even after 5 days preservation (Fig. 1). The serum creatinine levels rose in all animals, but in group 2 these began to fall within 1 week except for one dog (Fig. 2). In contrast, the creatinine levels remained high in most of the animals of groups 1 and 4 until death from renal failure within 6 postoperative days.

Renal blood flow. Immediately after renal unclamping, all kidneys became pink and tense, suggesting a good initial blood supply. However, in group 1, the firmness of the kidneys decreased gradually in the first 30 min after unclamping. In groups 2 and 4, kidneys maintained good color and turgor for the 3-hr observation period. Renal blood flow was severely decreased in all experimental groups 30 min after unclamping (Table 3). However, flow was restored significantly better in groups 2 and 4 1–3 hr after unclamping than in group 1.

Renal microvascular structures. As shown in Figure 3B and Table 4, the entire microvascular systems of kidney graft in group 2 were extremely well visualized with Microfil, not only during the 72 hr of cold storage with UW but after unclamping. In contrast, significant cortical hypoperfusion of the EC grafts in group 1 was already apparent in the subcapsular and the outer zones during the 72 hr cold storage and was augmented and extended into the inner zone after reperfusion (Fig. 3A). Although no significant difference between the EC and UW kidneys could be demonstrated in the medullary region during the cold ischemic period, the silicon rubber filling was totally obstructed in the EC kidneys 1 hr after unclamping.

FIGURE 3. Dissecting photomicrographs of renal vascular architectures filled with silicon rubber compound at one hour after reperfusion of the grafts (original magnification: ×40). (A) 72 hour EC group: Notice complete filling defect of subcapsular cortex and medulla. Patchy distribution of a vascular area, irregular and deformed pattern of interlobular artery and glomerulus can be seen. (B) 72 hour UW group: The capillary networks of both cortex and medulla are fully filled with silicon rubber. (C) 120 hour group: Notice poorly perfused medullar vascular bundles, whereas inner cortical glomerular and capillary systems are still fairly intact.

TABLE 4. Morphological evaluation of silicon rubber filling in renal microvasculatures after cold storage and following autotransplantation

Group	Time at perfusion	Subcapsular cortex	Outer cortex	Inner cortex	Outer medulla	Inner medulla
Normal Control	Postnephrectomy	2.9±0.5	3.2±0.6	3.6±0.5	3.6±0.5	3.2±0.8
1	EC-72[b]	1.7±0.8[d]	2.1±1.0[d]	3.2±0.6	2.7±1.3	1.5±1.4
	EC-72-1[c]	1.4±0.7[d]	1.4±0.7[d]	1.6±0.7[d]	0.0±0.0[d]	0.0±0.0[e]
2	UW-72[b]	3.8±0.4[d]	3.7±0.5[d]	3.8±0.4	2.8±1.0	1.9±1.0
	UW-72-1[c]	3.0±0.7[d]	3.1±0.7[d]	3.4±0.7[d]	2.9±0.9[d,e]	2.1±1.0[e]
3	EC-120	1.0±0.9[d]	1.6±1.0[f]	2.6±1.1[f]	1.6±1.0	1.0±0.8
4	UW-120	2.5±0.7[d]	2.9±0.7[f]	3.4±0.5[f]	2.6±0.8	1.9±1.1
	UW-120-1	2.2±1.0	2.7±0.5	2.8±0.4	1.8±0.8[e]	0.8±0.7[e]

[a] Eight sections of each group were examined with a blind method, and overall filling grade was determined by using a scoring system as follows; 4—excellent; 3—good; 2—fair; 1—poor; 0—filling defect. All values are presented as mean ± SD.

[b] After 72-hour cold storage with Euro-Collin's solution or UW solution.

[c] At 1 hour reflow after 72 hours cold storage with Euro-Collins solution or UW solution.

[d] $P<0.0001$.

[e] $P<0.005$.

[f] $P<0.05$.

When cold ischemic time was extended to 120 hr under EC, deterioration of both cortical and medullar microcirculation was obvious even prior to reperfusion in the kidneys of group 3. In the UW kidneys of group 4, significant medullary hypoperfusion could be seen only after reperfusion—and this at a time when cortical perfusion of the inner zone was still fairly well maintained. This suggested that UW solution could not protect the medullary microcirculation from reperfusion injury following 120-hr cold ischemia.

Histology. No significant difference between the groups could be detected morphologically in kidney grafts prior to revascularization. However, major abnormalities, including vacuolation of tubular epithelial cells and sludging of interlobular arteries and glomeruli, were evident in group 1 as early as 1 hr after unclamping. As shown in Figure 4A, there were necrotic changes of the arterial muscular layer concomitant with the narrowing and obstruction of the vascular lumens. Kidneys of group 2 had well-maintained vascular and tubular structures. Even in the UW kidneys of group 4, (Fig. 4 B and C) the entire vascular structure was quite intact after 120-hr preservation, suggesting that the UW solution was especially protective of the renal vascular muscular layer.

The kidney grafts taken from long survivors at postoperative day 15 were histologically normal or nearly so.

DISCUSSION

The possibility that kidneys can suffer from ongoing postperfusion injury after a period of devascularization has been widely recognized. Anaise et al. (*11*) have demonstrated a close correlation between pretransplant cortex perfusion indices and subsequent graft function. Our study supports this concept in that protection of the integrity of the renal cortical microcirculation was a crucial determinant of posttransplant graft function and animal survival. By the end of 72 hr of preservation with EC solution, the microvasculature of kidneys was already so damaged structurally that cortical hypoperfusion was inevitable. The principal morphologic damage was concentrated in the muscle layer. Kidneys preserved with UW did not show these changes at 72 hr, and evidence of damage was not florid even after 120 hr.

With both kinds of solution, the extent of "circulatory crisis" became evident only after reperfusion. The vascular damage we have documented could explain many of the characteristics of a failed graft, including increased permeability of the glomerular capillary systems, a decreased plasma flow followed by intraglomerular sludge formation, and finally complete obstruction of cortical circulation (the "no-reflow" phenomenon) (*5, 7, 12*). When ongoing cortical ischemia is imposed as a result of a damaged vascular system, a decrease in glomerular filtration rate and urine production, tubular cast formation, tubular obstruction, and back leaking follow. Disturbances in oxygen and substrate delivery make such changes irreversible (*13–15*).

The central hypothesis that our studies support is that some or even much of the value of the UW solution can be explained by its protection of the microcirculation and the consequent prompt relief of ischemia after revascularization. Many efforts have been made to achieve the latter objective by peritransplant volume expansion or by giving drugs such as dopamine, lidocaine, and prostaglandins (*16–19*). However, even if such efforts to achieve efficient reperfusion are successful, there are limits to what can be expected. These limits are imposed by the ischemic damage to the parenchymal cells themselves, the consequent intracellular energy crisis that is produced, and the variable creation of a self-perpetuating injury cycle (*20, 21*). Our data with the UW preserved kidneys are consistent with this interpretation. The renal blood flow and urine production were the same after 72- and 120-hr preservation, yet the life-supporting capability of the kidneys at these two points was vastly different.

How much UW solution increases the tolerance of the microvascular system of grafts to ischemia, as opposed to its protective effect on parenchymal tissues, could be a key distinction as attempts are made to extend cold storage limits even further. This distinction has been made particularly clearly in hepatic grafts (*22–25*). The essential components of the UW solution have been said to be the impermeants, lactobionate and raffinose, or possibly lipid peroxide scavengers such as glutathione (*4*). Other cytoprotective agents—including calcium antagonists, prostaglandins, or ATP-Mgcl2 (*6, 21, 26*) could be synergistically effective by virtue of their prevention of cell membrane degradation, provision of energy source for tubular cells, or even correction of postischemic intrarenal blood maldistribution.

Flow maldistribution of the preserved kidney has received considerable attention (*27–29*). Yamamoto and his colleagues (*29*) have stressed that the decrease in blood flow to the outer

FIGURE 4. Light photomicrographs of renal cortex at one hour after reperfusion. (A) 72 hour EC group (H&E; original magnification: ×40): Sludging of glomerulus and interlobular artery (arrow) can be seen. Notice the necrotic change of medial and endothelial cells of interlobular artery. (B) 72 hour UW group (H&E; original magnification: ×30): Completely preserved microvasculatures. Notice the integrity of interlobular artery (arrow) is intact. (C) 120 hour UW group (H&E; original magnification: ×30): Glomerulus and afferent arteriole (arrow) are still well maintained and patent.

stripe of the medulla is caused primarily by swelling of tubular epithelial cells rather than of vascular cells. Outer medullary tubular cells, especially those of the thick ascending limb of Henle's loop probably are the most sensitive to ischemia, since they normally operate on the verge of anoxia (*14*). Our results were consistent with Yamamoto's theory because the circulatory crisis after renal reflow was greatest in the medullary region. With the EC kidneys, the vulnerability of vascular bundles in the outer medullary zone seemed to be primarily attributable to the hypoperfused inner cortical glomeruli that provide the blood supply to the outer medulla from efferent vessels of their juxtamedullary apparatus (*10*). Thus, in the EC kidneys, the fundamental failure seemed to be of the microvasculature.

In contrast, in the 120-hr UW kidneys, there was a major discrepancy between perfusion of the cortex and medulla, as seen with the silicon rubber studies. Here it might be suggested that, in spite of good reperfusion, the proximal tubules degenerated from pure ischemic effects and secondarily compressed the adjacent vascular bundles including their drainage veins. Clarification of such seemingly esoteric details of mechanisms of tissue injury could help in planning therapeutic strategies.

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