foscarnet (*20*), failed to resolve acute reinfection without sequelae. Whether ganciclovir alone or in combination with foscarnet would have prevented histologic progression if given earlier, before recurrent hepatitis developed, or had aborted fulminant hepatitis, is entirely speculative. The value of ganciclovir therapy in acute HBV allograft recurrence can not be determined by anecdotal reports alone and requires a controlled trial.

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Received 5 April 1994.
Accepted 13 May 1994.

RENAL HEMODYNAMIC EFFECTS OF CYCLOSPORINE TREATMENT IN PATIENTS WITH CHRONIC UVEITIS AND NORMAL NATIVE KIDNEYS

Cyclosporine represents the drug of choice in transplant recipients (*1, 2*) and its clinical indications have been recently extended to various immune disorders such as LES, glomerulopathies, psoriasis, and uveitis (*3–7*).

Renal toxicity is a major concern in the use of the drug. Both glomerular and interstitial alterations have been described following long-term treatment with high or moderate CsA doses (*8, 9*). Recent data have suggested that these effects are associated with profound renal hemodynamic changes that may represent an early stage of cyclosporine toxicity (*10, 11*). No information is available on the renal hemodynamic regulation in humans with normal renal function undergoing long-term low-dose CsA treatment.

Six subjects, 5 male and 1 female, age from 24 to 55 years

(mean ± SE = 41±2 years) and body mass index (BMI)* of 25±2 were studied. Participants had proliferative chronic uveitis and were being treated with cyclosporine Sandoz (Milan, Italy) at a dosage of 1.5–4 mg/kg/day, as monotherapy or in combination with low doses of steroids (from 12.5 to 25 mg/day). The mean duration of CsA therapy was 7±4 months, ranging from 2 to 18 months. Five normal subjects ranging in age from 26 to 37 years (mean ± SE = 31±2 years) with a BMI 25±3, were tested as controls. All subjects consumed a weight-maintaining diet providing 200/250 g of carbohydrate/day for at least 3 days before the study and 70–90 g of protein/day for at least 7 days prior to the study. With the exception of CsA and steroid in the study group, no subject was taking any medication and none had a past medical history of renal, cardiovascular, or other systemic disease. The purpose and potential risks of the study were explained to all subjects and voluntary consent was obtained prior to their participation.

Studies were performed at 8:00 A.M. after a 12-hr overnight fast. The last oral dose of CsA was assumed 12-hr prior to the study. Inulin and paraaminohippurate (PAH) clearances were performed as previously described (*12*). Following a 50-min equilibration period, three consecutive 30-min control urine collections were obtained. An intravenous amino acid (AA) infusion was started (Solamin 7.5%, Pierrel, Milan, Italy) at a rate of 0.044 ml/kg/min for 150 min. Urine was collected at 50-min intervals throughout the study. Blood samples were obtained at 50-min intervals for determination of inulin, PAH, hormones, and amino acid concentrations. Inulin and PAH concentrations in plasma and urine were determined with colorimetric methods (*12*). Plasma amino acid levels were assessed by use of cation exchange chromatography methods performed with a Beckman 6300 amino acid analyzer (Beckman, Palo Alto, CA), after deproteinization of plasma samples with a 5% sulfosalicylic acid solution. Plasma insulin and glucagon levels were determined by standard RIA methods.

Within each study, observations from the control period (mean of 3 determinations) were averaged and compared with subsequent clearance periods by use of paired *t* test analysis. Differences between CsA subjects and controls were obtained by use of the two-way analysis of variance for repeated measures, using basal values as a covariate. Glomerular filtration rate (GFR) and renal plasma flow (RPF) were calculated as the clearances of inulin and PAH, respectively, using standard formulas U·V/P, and were normalized for 1.73 m^2 of surface area (SA). Mean arterial blood pressure (MABP) was calculated in mmHg, as MABP = (P syst-P diast)/3+P diast. The renal blood flow (RBF) was calculated as RBF = RPF/(1-Htc), and total renal vascular resistance (RVR) was estimated as RVR = MABP/RBF, in mmHg/ml min^{-1}.

In CsA-treated patients basal GFR averaged 61±4 ml/min 1.73 m^2 SA. In response to amino acid administration GFR did not change and averaged 57±6, 57±6, and 50±5 ml/min at 50, 100, and 150 min, respectively. Basal RPF averaged 357±57 ml/min 1.73 m^2SA; in response to amino acid infusion a significant rise (P<0.01) was observed that averaged 410±68, 449±59, and 485±62, at 50, 100, and 150 min, respectively. In controls, basal GFR and RPF averaged 82±11 and 406±53 ml/min 1.73 m^2 (P = NS vs. CsA). Following amino acid infusion both GFR and RPF rose significantly: GFR averaged 92±2, 92±5, and 89±6 ml/1.73 m^2 min at 50, 100, and 150 min (Fig. 1); RPF averaged 457±80, 444±67, and 517±68 ml/1.73 m^2 min at 50, 100, and 150 min, respectively (P<0.01 vs. basal) (Fig. 2).

Basal filtration fraction (FF) was slightly, although not significantly, lower in CsA patients (0.17±0.02) than in controls (0.20±0.01). During amino acid administration FF declined significantly in CsA patients (0.14±0.01, 0.13±0.02, and 0.11±0.05 at 50, 100, and 150 min, respectively). This is at variance with data in controls in whom AA administration did not induce any significant variation in FF (0.21±0.04, 0.22±0.02, and 0.17±0.02 at 50, 100, and 150 min, respectively) (P<0.05 vs. CsA).

Basal mean arterial blood pressure (MABP) averaged 106±5 and 89±4 mmHg in CsA patients and controls, respec-

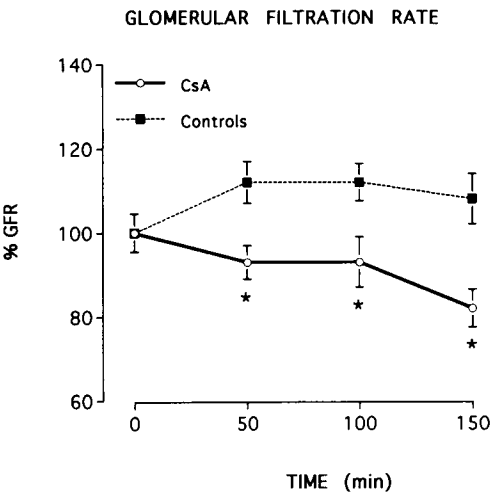

FIGURE 1. Time course of percentage changes of GFR vs. basal in controls (solid squares) and CsA-treated patients (open circles). Values are mean ± SEM; (*) $P < 0.05$ vs. controls.

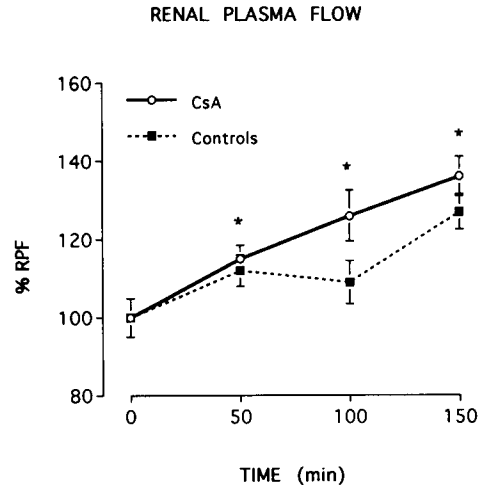

FIGURE 2. Time course of percentage changes of RPF vs. basal in controls (solid squares) and CsA-treated patients (open circles). Values are mean ± SEM; (*) $P < 0.01$ vs. basal.

* Abbreviations: AA, amino acid; BMI, body mass index; FF, filtration fraction; GFR, glomerular filtration rate; MABP, mean arterial blood pressure; PAH, paraaminohippurate; RBF, renal blood flow; RPF, renal plasma flow; RVR, renal vascular resistance; SA, surface area.

tively ($P<0.05$ vs. CsA). Following AA infusion MABP did not change significantly in both CsA (106±7, 105±6, 106±7) and in controls (93±3, 91±5, 93±3) at 50, 100, and 150 min, respectively). Basal heart rate was 69±2 in CsA and 68±1 bpm in controls and did not change significantly during AA infusion.

Basal renal vascular resistance was significantly increased in CsA patients in comparison with controls and averaged 0.227±0.058 vs. 0.122±0.012 mmHg/ml min ($P<0.01$). During amino acid infusion RVR declined significantly in both study groups. However, the delta in RVR was significantly greater in CsA patients than in controls (0.078±0.005 vs. 0.021±0.003 mmHg/ml/min, [$P<0.01$ vs. CsA]).

Basal plasma insulin and glucagon levels were similar in the two study groups and averaged 5±2 vs. 6±1 μU/ml and 164±22 vs. 148±32 pg/ml, respectively. Amino acid administration induced a similar rise in both groups, insulin averaged 12±3 and 13±2 μU/ml ($P<0.01$), and glucagon rose to 234±39 and 272±47 pg/ml in CsA and controls, respectively ($P<0.01$).

Basal plasma amino acid levels were similar in the two study groups: following AA infusion a two-fold rise in plasma AA concentrations was observed in both study groups (Table 1).

Cyclosporine has significantly improved allograft survival in organ transplantation (*1, 2*). Recently it has been successfully employed in treatment of various autoimmune diseases (*3, 7*). Side effects are nephrotoxicity and hypertension (*8, 9*). It has been suggested that renal toxicity may not be reversible and may cause progressive decline in renal function. CsA induces complex ultrastructural changes, such as glomerular ischemia and sclerosis, obliterative arteriolopathy, tubular atrophy, and fibrosis (*8, 9*). Several studies have also shown significant renal hemodynamic abnormalities in CsA-treated humans and animals (*10, 11, 13*). In humans, a significant decline in GFR has been observed following both acute (*10*) and chronic (*5*) CsA administration. The decline in RPF is less pronounced, and as a result FF is significantly reduced. In CsA treated transplant recipients acute sodium depletion induces an abnormal decline in GFR and urea clearances, which again suggests an altered renal hemodynamic regulation (*11*).

Recent studies have also shown that in CsA-treated transplant recipients the administration of each therapeutic dose of CsA is associated with a transient 10–20% decline in GFR and FF. We have investigated renal hemodynamic effects of an intravenous balanced amino acid administration in patients with normal native kidney in treatment with low-dose (1.6–4 mg/kg/day) CsA. In normal subjects, an amino acid infusion designed to increase two-fold plasma amino acid levels induces a 15–20% rise in GFR and RPF (*12*).

Nunley et al. (*14*) have demonstrated that renal functional reserve to a meat meal is lost in transplant recipients maintained on CsA but not in patients on conventional therapy. In CsA patients the response to amino acid administration is impaired. During hyperaminoacidemia the rise in RPF is similar to controls—in contrast, no change in GFR is observed, thus leading to a significant decline in FF with no residual RFR. To our knowledge, the response to amino acid administration in CsA-treated patients with normal native kidneys is unusual and is not observed in glomerular diseases (*15*), diabetes (*16*), hypertension (*17*), chronic renal insufficiency (*18*), or renal allograft recipients (*14*). In fact, in the abovementioned conditions variations in GFR always parallel those of RPF with no significant effects on FF.

The present results, however, cannot be explained by qualitative and/or quantitative differences in the amino acid profile or glucagon/insulin responses induced by hyperaminoacidemia (*12*), which were similar in the two study groups.

In the basal state, CsA patients showed a moderate, although not significant, decline in FF in comparison with controls. Following amino acid administration, GFR does not rise and FF declines significantly, thus indicating a condition of filtration disequilibrium, which may be ascribed to the abovementioned CsA-mediated constriction of the afferent glomerular arterioles (*19*).

Several questions arise from the present observations, such as whether the hemodynamic effects of CsA are either dose- or time-dependent. Furthermore, it may be relevant to test the effect of calcium channel blockers, which selectively vasodilate preglomerular arteriole and have been shown to ameliorate or prevent the CsA-induced nephrotoxicity (*20*).

In conclusion, patients with long-term low-dose CsA treatment are characterized by a complex alteration of renal hemodynamic regulation that may represent an early sign of CsA nephrotoxicity.

TABLE 1. Plasma amino acid levels (nmol/ml) in controls and in CsA-treated patients in the basal state and following 150 min of amino acid infusion (study) (mean ± SEM).

	Controls		CsA	
	Basal	Study	Basal	Study
Thr	145±8	226±14*[a]	104±5	256±15*
Ser	119±4	165±10*	84±4	175±14*
Glu	582±55	479±93	533±92	527±123
Gly	213±10	794±56*	198±9	997±55*
Ala	382±26	449±35*	349±29	463±52*
Cit	50±4	73±10*	47±6	74±6*
Val	254±11	515±21*	179±15	551±31*
Cys	54±2	39±2	49±5	29±1
Met	35±1	299±28*	34±2	377±13*
Ileu	76±4	214±13*	64±4	230±10*
Leu	142±7	344±17*	115±9	369±9*
Tyr	70±4	88±9	72±3	125±31*
Phen	59±2	235±17*	62±5	318±31*
$NH4^+$	234±32	292±45	250±36	277±77
Hlys	129±21	190±35*	113±5	191±22*
Orn	121±11	212±19*	105±16	313±90*
Lys	202±8	381±24*	196±17	466±32*
His	99±5	245±15*	79±2	298±3*
3Mhis	1±1	3±1	5±2	5±2
Arg	116±13	350±21*	153±17	443±30*
Gluconeog.	1442±100	2113±210*	1269±80	2418±99*
Essen.	1151±34	2777±143*	1014±47	3192±81*
Not Essen.	1570±70	2319±192*	1412±95	2820±208*
BCAA	472±19	1074±51*	359±27	1150±35*
Total	2720±140	5096±390*	2426±60	6012±200*

[a] (*) $P < 0.01$ vs. basal.

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Received 22 December 1993.
Accepted 10 May 1994.

A NOVEL APPROACH TO THE DRAINAGE OF LOCULATED PERIRENAL ALLOGRAFT LYMPHOCELES

DUAL SCOPE LAPAROSCOPY

Periallograft lymphocele is a relatively common occurrence following renal transplantation. Its incidence has been reported at 0.6–18% (*1*). Lymphoceles arise from egress of lymph from either severed lymphatics adjacent to the iliac vessels—or, alternatively, from nonligated lymphatics in the hilum of the renal allograft. Lymph is then retained in the retroperitoneal space by the intact peritoneum. Most lymphoceles are asymptomatic (*2*, *3*) and do not require therapy. However, some can cause a mass effect resulting in a variety of manifestations. These include unilateral peripheral edema, deep vein thrombosis, persistent wound drainage, bladder displacement, ureteral obstruction and hydronephrosis, frequency, urgency, discomfort, or pain.

Symptomatic lymphoceles require drainage. Simple percutaneous drainage may be diagnostically useful. However, it is not considered an efficacious treatment, with a recurrence rate of 77% (*4*). Peritoneal fenestration with internal drainage is the usual treatment. Recurrence is uncommon following internal drainage (*5*). This operation can be performed either through a lower midline incision or via the transplant incision. In either case a large window is created in the peritoneum allowing lymph to drain freely into the peritoneal space where it is reabsorbed. Omentum may be placed into the lymphocele cavity to maintain patency of the peritoneal fenestration.

Recently, with the popularization of minimally invasive surgery, numerous authors have reported the successful laparoscopic internal drainage of simple large lymphoceles (*6–13*). This problem is ideally suited for laparoscopic surgery. The location of the lymphocele is usually easily determined by a bulge in the peritoneum, which can then be incised. More problematic are multiple small or loculated lymphoceles. Elevation of the recipient iliac vessels during the transplant operation, distorsion of the vascular anatomy