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The Association of Tacrolimus Formulation on Cerebral Blood Flow and Cognitive Function

Irisa Mahaparn, MD,[1] Rebecca J. Lepping, PhD,[2,3] Robert N. Montgomery, PhD,[4] Rishav Mukherjee, MSc,[4] Sandra A. Billinger, PhD,[2] William M. Brooks, PhD,[2,3] and Aditi Gupta, MD[1,2,3]

Background. Calcineurin inhibitors are inherent vasoconstrictors. Cerebral vasoconstriction can reduce cerebral blood flow (CBF), and negatively impact cerebrovascular response (CVR) to exercise, and cognitive function. The once-daily extended-release (LCP) tacrolimus has fewer side effects than the immediate-release (IR) tacrolimus. The role of calcineurin inhibitors on CBF and the impact of specific formulations of tacrolimus on CBF, CVR, and cognitive function are unknown. In this pilot study, we evaluated whether changing from IR tacrolimus to LCP tacrolimus modulates CBF, CVR, or cognitive function in kidney transplant (KT) recipients. **Methods.** We randomized (2:1) 30 stable KT recipients on IR tacrolimus to intervention (switch to LCP tacrolimus) and control (continue IR tacrolimus) arms. We measured CBF, CVR, and cognitive function at baseline and at 12 wk. We used ANCOVA to evaluate changes in outcome variables, with baseline values and study arm as covariates. We used descriptive statistics with mean changes in outcome variables to compare the 2 groups. **Results.** Participants were 51 ± 13 y old. There was no difference in plasma tacrolimus levels at baseline and at 12 wk in the 2 arms. The changes in CBF, resting middle cerebral artery velocity, CVR, and cognitive function were more favorable in the intervention arm than in the control group. **Conclusions.** Changing IR tacrolimus to LCP tacrolimus may improve CBF, cerebrovascular dynamics, and cognitive function in KT recipients. Larger studies are needed to confirm these results.

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[1] Department of Internal Medicine, University of Kansas Medical Center, Kansas City, KS.

[2] Department of Neurology, University of Kansas Medical Center, Kansas City, KS.

[3] Hoglund Biomedical Imaging Center, University of Kansas Medical Center, Kansas City, KS.

[4] Department of Biostatistics and Data Science, University of Kansas Medical Center, Kansas City, KS.

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Correspondence: Aditi Gupta, MD, Division of Nephrology and Hypertension, Department of Internal Medicine and Department of Neurology, Hoglund Biomedical Imaging Center, 3901 Rainbow Blvd, Mail Stop 3002, Kansas City, KS 66160. (agupta@kumc.edu).

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Neurotoxicity is a common side effect of CNIs such as tacrolimus, which are commonly used by kidney transplant (KT) recipients. Mild symptoms such as tremors, neuralgia, and peripheral neuropathy are common. Severe symptoms such as psychosis, hallucinations, blindness, seizures, cerebellar ataxia, motor weakness, or leukoencephalopathy can also occur. Neurotoxic side effects of tacrolimus are dose-dependent and are most prominent during peak concentrations.[1] Compared with immediate-release (IR) tacrolimus, the once-daily extended-release (LCP) tacrolimus formulation has a lower maximum serum concentration, less intrapatient variability of serum levels, a similar area under the curve, and lower dose-related side effects including tremors.[2-4]

Tacrolimus is an inherent vasoconstrictor.[5-9] Cerebral vasoconstriction can decrease cerebral blood flow (CBF), and affect cerebrovascular response (CVR) to exercise, and cognitive function. Given the brain's lack of oxygen stores and need for adequate oxygen,[10,11] increase in oxygen delivery via increase in CBF is necessary to meet the brain's metabolic requirements. Inability to increase CBF can impact long-term cerebrovascular outcomes. Indeed, lower CBF is associated with faster cognitive decline.[12] We have previously shown that CBF decreases after KT,[13] CVR to exercise is impaired in KT recipients,[14] and there is a high prevalence of cognitive impairment in KT recipients.[15] Furthermore, liver transplant recipients on CNI-sparing regimens have better cognitive function than patients who are on CNIs.[16] Tacrolimus has also been associated with posterior reversible leukoencephalopathy syndrome potentially from hypoperfusion injury to the brain.[17]

These data suggest that CNI-induced vasoconstriction could contribute to cognitive impairment in KT recipients. In this pilot study, we assessed whether conversion from IR tacrolimus to LCP tacrolimus changes CBF, cerebrovascular kinetics, or cognitive function.

MATERIALS AND METHODS

We conducted an open-label, single-center, single-blinded, 2:1 randomized, proof-of-concept trial in adult KT recipients. The study was approved by the institutional review board and all participants signed informed consent before study procedures. KT recipients were enrolled in the posttransplant clinic of a large academic transplant center. Patients on IR tacrolimus were enrolled if they had a stable estimated glomerular filtration rate with a serum creatinine of <3 mg/dl, were transplanted at least 3 mo ago, and were English speaking. Exclusion criteria were simultaneous dual organ transplant, acute stroke, concussion, traumatic brain injury or diagnosis of dementia, current use of antipsychotics or antiepileptics, oxygen dependency, uncontrolled blood pressure, hearing or visual impairment, inability to exercise on a recumbent stepper, or undergoing an MRI scan.

The baseline visit included vascular assessment with a brain MRI to assess CBF, transcranial Doppler (TCD) to measure the dynamic regulation of CBF and blood pressure in response to exercise, pulse wave velocity (PWV) to measure arterial stiffness, and cognitive function assessment.[18] After the baseline visit, the 30 enrolled patients were randomized to the intervention versus control arm in a 2:1 ratio. The 20 patients in the intervention arm switched IR tacrolimus to LCP tacrolimus, whereas the 10 in the control arm continued IR tacrolimus. All participants maintained the same serum tacrolimus goal through levels. There were no dose changes made for the control arm. Brain MRI, TCD, PWV, and cognitive function assessments were repeated at 12 wk to compare changes from baseline in the 2 arms. Tacrolimus levels, other laboratory data, demographic data, and medical history were obtained from the patients' medical records. Study personnel performing and analyzing MRI, TCD, and PWV data were blinded to randomization.

Cerebral Blood Flow

CBF data were acquired using pseudocontinuous arterial spin labeling perfusion MRI using a 3-dimensional gradient and spin echo sequence developed by the University of Southern California.[19,20] A high-resolution noncontrast structural MRI of the brain was acquired using a 3-dimensional magnetization-prepared rapid acquisition gradient echo sequence for segmentation of brain regions of interest. Image quantification was completed through the University of Kansas Alzheimer's Disease Neuroimaging Core using methods we have previously described.[21] Using methods adapted from the Laboratory of Functional MRI Technology CBF Preprocess and Quantify packages for CBF calculation (loftlab.org, ver. February 2019), pseudocontinuous arterial spin labeling images were realigned to the first image separately for labeled and control frames and smoothed, and CBF (mL/100 g tissue) was calculated by subtracting the control images from the label images.[22] The high-resolution magnetization-prepared rapid acquisition gradient echo images were segmented into volumetric anatomic brain regions using FreeSurfer 6.0.[23-25] CBF images were coregistered with the FreeSurfer anatomic data, and regional CBF values were obtained by multiplying the FreeSurfer regional and total gray matter masks with the CBF image and calculating an average CBF value over the number of voxels included in each mask. The technicians analyzing brain MRI were blinded to the patient randomization for study arm assignment. Although regional CBF was assessed to investigate regional variations in CBF, the total gray matter was chosen a priori as the primary variable of interest.

Cerebrovascular Response to Exercise

We used TCD to measure the mean middle cerebral artery velocity (MCA_V) at rest and during an acute bout of moderate-intensity exercise. The MCA was identified using practice standards for probe positioning and orientation, depth selection, and flow direction to ensure accuracy. We used the experimental protocol we have published previously.[26] Briefly, beat-to-beat heart rate (HR), mean arterial pressure (MAP), MCA_V, and end-tidal carbon dioxide were measured at rest and at steady-state moderate-intensity exercise defined as 45%–55% of HR reserve (calculated using the Karvonen formula), as components of cerebrovascular kinetics.[27] Patients completed 2 exercise bouts and data points were averaged to optimize signal-to-noise ratio. MCA_V response to exercise was calculated as the change in mean beat-to-beat MCA_V from rest to steady-state moderate-intensity exercise. MCA_V kinetics response profile was measured using 3 s time-binned means over the entire rest and exercise bout with a monoexponential model,[18]

$$MCA_V(t) = BL + Amp\left(1e^{(tTD)/\tau}\right)$$

where MCA_V (t) is the MCA_V at any point in time, BL is the baseline resting MCA_V before starting exercise, TD is the time delay preceding the exponential increase in MCA_V, Amp is the peak amplitude of the response, and tau (τ) is the time constant. Terms used in the analysis are described in Table S1 (SDC, http://links.lww.com/TXD/A552).

Pulse Wave Velocity

Pulse wave velocity (PWV) was measured using SphygmoCor Xcel, a noninvasive diagnostic tool for the clinical assessment of central arterial pressures and indices of arterial stiffness.[28]

Cognitive Function Assessment

We used a battery of standard neuropsychological tests that included the Mini-Mental State Exam (MMSE), Montreal Cognitive Assessment (MoCA), trail making A and B, logical memory I and II, digit symbol, digit span forward and backward, category fluency, block design, Stroop Interference, and free recall to assess cognitive function. Trained study staff performed the cognitive assessments in a private room. A priori, we chose the trail making A and B tests as our primary endpoints based on previous work demonstrating changes in trail making test scores with changes in CBF flow in hemodialysis patients.[29]

Statistical Analysis

Baseline patient characteristics were summarized using the means, SDs for continuous variables, and frequencies and percentages for categorical variables. The changes in CBF, cerebrovascular kinetics, and neuropsychological tests were compared

in the 2 groups. We used an ANCOVA model to estimate the effect of the intervention. The ANCOVA models included values for the outcome variables at baseline and the study arm as covariates. Because vasoconstrictive effects of tacrolimus are likely dose-dependent, we included change in tacrolimus level as a covariate in our ANCOVA models in our sensitivity analysis. Additionally, given the small sample size we used Wilcoxon rank sum tests on the change from baseline to 12 wk as another sensitivity analysis. Because this was a pilot study and not powered to assess statistically significant differences at the level of $P < 0.05$, we examined trends in difference in change of outcome variables from baseline to 12 wk in the 2 groups.[30]

RESULTS

Baseline characteristics of study participants are presented in Table 1. Most of the patients were White (80%) and male (60%). There were more women in the intervention arm than in the control arm. Causes for kidney failure included diabetes, glomerulonephritis, and autosomal dominant polycystic kidney disease. Most patients (73%) were on dialysis before KT. All patients were on standard immunosuppression with IR tacrolimus and mycophenolic acid, with or without prednisone, per institutional protocol. There was no significant (at the level of $P < 0.05$) difference in serum tacrolimus trough levels at baseline in the intervention arm (7.7 ± 1.8 ng/ml) and the control arm (8.9 ± 2.9 ng/ml). Levels at 12 wk were also not different in the intervention arm (6.4 ± 1.8 ng/ml) and the control arm (8.0 ± 2.9 ng/ml). The change in serum tacrolimus levels from baseline to 12-wk assessment in the intervention (−1.1 ± 2.6 ng/ml) arm was similar to that in the control arm (−1.1 ± 3.9 ng/ml) (Table 2 and Table S2, SDC, http://links.lww.com/TXD/A552).

Cerebral Blood Flow

CBF data were analyzed for 27 patients who completed both baseline and 12-wk assessments. Three patients were excluded from the analysis as 1 patient could not complete the MRI at the baseline visit and another 2 could not complete it at the 12-wk assessment because of claustrophobia. At 12 wk, the CBF in the control arm decreased by −7.2 ± 11.4 mL/100 g tissue (Table 3). Conversely, there was an increase of 1.5 ± 10.4 mL/100 g tissue in CBF in the intervention arm. The difference in CBF between the 2 arms was

TABLE 1.

Baseline demographics

Variable	Intervention (n = 20)	Control (n = 10)	All patients (n = 30)	*P*
Age, mean ± SD, y	52.0 ± 9.9	47.9 ± 17.4	50.6 ± 12.8	0.56
Male sex, n (%)	6 (30.0)	6 (60.0)	18 (60.0)	0.14
Education, n (%)				0.09
High school diploma	2 (10.0)	1 (10.0)	3 (10.0)	
Some college	11 (55.0)	6 (60.0)	17 (56.7)	
4-y degree	6 (30.0)	0 (0)	6 (20.0)	
Graduate school	1 (5.0)	3 (30.0)	4 (13.3)	
Race, n (%)				0.63
White	16 (80.0)	8 (80.0)	24 (80.0)	
Black or African American	2 (10.0)	0 (0)	2 (6.7)	
Other	2 (10.0)	2 (20.0)	4 (13.3)	
BMI, mean ± SD, kg/m^2	28.3 ± 4.7	28.4 ± 5.4	28.3 ± 4.9	0.91
SBP, mean ± SD mm Hg	134 ± 12.8	130 ± 15.7	133 ± 13.7	0.43
DBP, mean ± SD, mm Hg	81.6 ± 8.3	70.0 ± 11.3	77.7 ± 10.7	0.01[a]
Dialysis before KT, n (%)	14 (70.0)	8 (80.0)	22 (73.3)	0.99
Time since transplant, mean ± SD, y	5.4 (4.4)	3.8 (2.7)	4.9 (3.9)	0.37
Primary cause of ESKD, n (%)				0.56
Diabetes	3 (15.0)	0 (0)	3 (10.0)	
Glomerulonephritis	5 (25.0)	2 (20.0)	7 (23.3)	
Hypertension	1 (5.0)	1 (10.0)	2 (6.7)	
ADPKD	6 (30.0)	2 (20.0)	8 (26.7)	
Other	4 (20.0)	5 (50.0)	9 (30.0)	
Unknown	1 (5.0)	0 (0)	1 (3.3)	
Medical history, n (%)				
Angioplasty or CABG	0 (0)	1 (10.0)	2 (6.6)	0.33
Atrial fibrillation	1 (5.0)	2 (20.0)	3 (10.0)	0.25
Diabetes	6 (30.0)	3 (30.0)	9 (30.0)	1.00
Hypertension	17 (85.0)	10 (100)	27 (90.0)	0.53
Dyslipidemia	13 (65.0)	8 (80.0)	21 (70.0)	0.68
Seizures	2 (10.0)	0 (0)	2 (6.7)	0.54
Depression	7 (35.0)	2 (20.0)	9 (30.0)	0.68
Smoking	2 (10.0)	1 (10.0)	3 (10.0)	1.00

The *P* values were calculated using Fisher exact test for categorical variables and Wilcoxon ranked sum tests for continuous variables.

[a]$P<0.05$.

ADPKD, autosomal dominant polycystic kidney disease; BMI, body mass index; CABG, coronary artery bypass graft; DBP, diastolic blood pressure; ESKD, end-stage kidney disease; KT, kidney transplant; SBP, systolic blood pressure.

TABLE 2.

Tacrolimus levels at baseline and 12 wk in the intervention and control arms

	Intervention (n = 20)			Control (n = 10)			
	Baseline	12 wk	Change	Baseline	12 wk	Change	*P*
Tacrolimus level, ng/mL	7.7 ± 1.8	6.4 ± 1.8	−1.1 ± 2.6	8.9 ± 2.2	8.0 ± 2.9	−1.1 ± 3.9	0.15

The *P* values were calculated using ANCOVA adjusted for baseline tacrolimus level.

TABLE 3.

Cerebral blood flow at baseline and at 12 wk in the intervention and control arms

	Intervention, mean ± SD (n = 18)			Control, mean ± SD (n = 9)			
Brain region	Baseline	12 wk	Change	Baseline	12 wk	Change	*P*
Total gray matter	73.2 ± 9.1	75.1 ± 9.2	1.5 ± 10.4	76.4 ± 19.1	70.0 ± 15.4	−7.2 ± 11.4	0.08
Anterior cingulate cortex	76.3 ± 12.0	78.4 ± 11.8	1.7 ± 13.6	82.1 ± 20.7	78.5 ± 17.5	−4.8 ± 9.7	0.46
Caudate	50.8 ± 9.6	53.4 ± 10.3	2.1 ± 12.7	63.0 ± 31.8	46.8 ± 16.2	−18.3 ± 35.4	0.18
Frontal	92.5 ± 13.5	95.1 ± 13.5	2.0 ± 16.1	99.9 ± 29.8	88.0 ± 20.1	−13.1 ± 19.6	0.08
Middle frontal gyrus	107 ± 16.5	109 ± 16.9	1.4 ± 18.1	111 ± 31.9	101 ± 26.2	−10.9 ± 15.6	0.12
Hippocampus	41.2 ± 6.5	43.2 ± 7.3	1.8 ± 8.3	45.0 ± 14.1	37.6 ± 11.7	−7.8 ± 11.3	0.04[a]
Primary motor cortex	101 ± 16.9	104 ± 14.5	1.4 ± 17.2	111 ± 30.8	101 ± 24.8	−11.8 ± 21.3	0.25
Posterior cingulate cortex	92.1 ± 12.3	94.4 ± 12.7	1.5 ± 14.7	92.4 ± 23.0	93.6 ± 12.8	−5.6 ± 16.9	0.14
Pallidum	36.4 ± 6.7	38.2 ± 8.6	2.0 ± 10.4	43.2 ± 12.1	34.1 ± 8.9	−10.4 ± 15.4	0.31
Parietal	97.8 ± 14.7	102 ± 15.5	3.4 ± 16.4	98.6 ± 26.6	96.0 ± 27.2	−3.5 ± 8.8	0.27
Precuneus	88.9 ± 11.7	88.7 ± 16.7	−0.2 ± 14.2	95.2 ± 27.1	87.5 ± 23.1	−7.8 ± 14.6	0.20
Putamen	48.1 ± 9.4	48.4 ± 9.2	0.3 ± 14.3	57.4 ± 12.3	47.0 ± 11.8	−10.4 ± 14.3	0.58
Subparietal	98.5 ± 18.2	103 ± 20.4	3.4 ± 20.6	98.1 ± 30.4	96.6 ± 30.4	−1.9 ± 8.0	0.46
Temporal	57.3 ± 7.31	60.8 ± 8.8	3.0 ± 12.0	58.9 ± 14.9	53.3 ± 13.3	−6.0 ± 9.6	0.06
Thalamus	57.4 ± 10.1	61.9 ± 13.4	4.4 ± 10.8	59.9 ± 18.5	50.7 ± 14.4	−10.1 ± 15.3	0.002[a]

The *P* values were calculated using ANCOVA.
[a]$P < 0.05$.

statistically significant in the hippocampus ($P = 0.04$) and thalamus ($P = 0.002$).

Cerebrovascular Response to Exercise and Components of Cerebrovascular Kinetics

TCD data were analyzed in 27 patients. Three patients were excluded from the analysis as MCA signal could not be detected in 2 patients in the intervention arm and 1 in the control arm during their baseline visit. For another 3 patients, only right-sided readings were analyzed as left MCA_V could not be measured reliably. HR and MAP could not be assessed for 1 patient who had premature ventricular contractions during a baseline visit and for another patient who could not get an accurate EKG. The change in resting MCA_V was lower in the intervention group but did not reach statistical significance ($P = 0.42$). Similarly, the decrease in CVR (Table 4). The decrease in CVR was smaller for the intervention arm compared with the control arm, but the difference in the 2 arms did not reach statistical significance at $P < 0.05$ ($P = 0.72$).

TABLE 4.

Measurements of cerebrovascular response to exercise and components of cerebrovascular kinetics at baseline and 12 wk in the intervention and control arms

	Intervention, mean ± SD (n = 19)			Control, mean ± SD (n = 7)			
Variable	Baseline	12 wk	Change	Baseline	12 wk	Change	*P*
Resting MCA_V, cm/s	60.7 ± 12.4	58.8 ± 10.7	−1.8 ± 8.8	55.6 ± 16.1	51.9 ± 13.3	−3.7 ± 12.1	0.42
Resting HR, bpm	79 ± 11	77 ± 11	−1.9 ± 8.2	73 ± 11	73 ± 11	−0.92 ± 4.7	0.95
Resting MAP, mm Hg	101.0 ± 24.8	103.0 ± 21.3	1.4 ± 18.6	87.8 ± 13.7	89.9 ± 20.7	2.1 ± 19.9	0.51
Resting $P_{ET}CO_2$, mm Hg	32.4 ± 3.10	33.1 ± 3.5	0.75 ± 4.7	33.7 ± 3.29	32.4 ± 3.3	−1.4 ± 3.1	0.53
CVR, cm/s	9.0 ± 4.3	9.0 ± 4.7	−0.4 ± 4.8	12.4 ± 5.9	10.9 ± 2.3	−1.5 ± 4.9	0.71
Time delay, s	32.3 ± 31.5	19.3 ± 47.9	−13.0 ± 50.6	44.4 ± 43.5	49.0 ± 32.5	4.6 ± 56.9	0.17
Amplitude, cm/s	9.3 ± 3.2	9.6 ± 4.3	0.3 ± 5.5	12.6 ± 5.6	10.6 ± 3.0	−2.0 ± 6.1	0.62
Time constant, τ, s	36.3 ± 17.4	47.6 ± 47.5	11.3 ± 42.8	38.8 ± 26.5	47.2 ± 58.1	8.4 ± 61.7	0.93
Steady-state HR, bpm	118 ± 18	112 ± 22	1.3 ± 21.3	105 ± 19	102 ± 20	−0.8 ± 18.2	0.46
Steady-state MAP, mm Hg	124 ± 26	125 ± 26	1.3 ± 20.2	110 ± 15	110 ± 28	−0.7 ± 18.2	0.59
Steady-state $P_{ET}CO_2$, mm Hg	34.8 ± 4.3	35.8 ± 3.45	0.9 ± 4.88	38.8 ± 4.5	37.8 ± 3.9	−1.0 ± 2.7	0.71
Work rate, watts	83.1 ± 16.5	83.1 ± 16.8	0.9 ± 15.1	90.0 ± 20.6	88.9 ± 23.3	−1.1 ± 10.5	0.93

The *P* values were calculated using ANCOVA.
CVR, cerebrovascular response; HR, heart rate; MAP, mean arterial pressure; MCA_V, middle cerebral artery velocity; $P_{ET}CO_2$, end-tidal carbon dioxide.

Pulse Wave Velocity

Seven patients, 4 from the intervention arm and 3 from the control arm, were unable to complete PWV assessment. The increase in PWV was numerically smaller in the intervention arm (0.4 ± 1.9 cm/s) than in the control arm (1.0 ± 3.3 cm/s) (Table 5). There was no difference in the change in augmentation index between the intervention and control arms.

Cognitive Function

Twenty-nine patients completed both the baseline and 12-wk cognitive function assessments. Improvement in test scores for trail making A and B, digit symbol, MoCA, Stroop interference, and free recall and to a lesser degree, logical memory I A and II A and category fluency animals were greater in the intervention arm than in the control arm (Table 6). MMSE scores decreased in both arms, but the decrease in the intervention arm was smaller than in the control arm. Digit span forward, category fluency vegetables, and block design showed a greater improvement in the control arm.

The sensitivity analysis with adjustment for serum tacrolimus levels and the Wilcoxon rank sum tests did not significantly change the above associations significantly (Tables S3, SDC, http://links.lww.com/TXD/A552–S6, SDC, http://links.lww.com/TXD/A552). Including change in tacrolimus led to a change in the estimated direction of the between-group difference in 5 variables (Table S4, SDC, http://links.lww.com/TXD/A552: Resting HR, Time constant, Steady-State MAP, Work Rate; Table S6, SDC, http://links.lww.com/TXD/A552: Digit Span backward), but outside of these variables it had little effect, especially on the outcome variables used to justify the conclusions of the study.

DISCUSSION

In this proof-of-concept pilot study, we examined whether changing IR tacrolimus to LCP tacrolimus can improve CBF. We found that CBF in the total gray matter as well as all predefined areas of the brain decreased in the control arm at 12 wk. Conversely, CBF increased in the intervention arm. We have previously shown that CBF decreased after a KT.[13] It is possible that this decrease in CBF is related to the use of CNIs after KT. Low CBF is associated with cognitive impairment[31] and brain atrophy[32] and is a risk factor for future dementia. Lowering CBF caused by tacrolimus can have adverse long-term consequences.

We also assessed change in CVR and cognitive function with change in tacrolimus formulation. The resting MCAv and CVR remained stable in the intervention arm but decreased in the control arm. Furthermore, the increase in aortic augmented pressure was more in the control arm. We have previously shown that CVR is blunted in KT recipients.[14] Low CVR is

TABLE 5.

Pulse wave velocity, augmentation index, and aortic augmented pressure at baseline and 12 wk in the intervention and control arms

	Intervention, mean ± SD (n=16)			Control, mean ± SD (n=7)			
Variable	**Baseline**	**12 wk**	**Change**	**Baseline**	**12 wk**	**Change**	***P***
PWV, cm/s	8.2 ± 2.2	8.6 ± 1.7	0.4 ± 1.9	8.7 ± 2.2	9.7 ± 2.9	1.0 ± 3.3	0.30
AIx	21.4 ± 9.2	23.9 ± 7.4	2.6 ± 10.0	19.0 ± 9.9	21.6 ± 7.3	2.6 ± 5.7	0.64
AAP, mm Hg	8.4 ± 4.0	9 ± 3.3	0.6 ± 4.4	8.4 ± 7.0	9.7 ± 5.3	1.3 ± 3.5	0.63
AIx75	19 ± 7.5	21.2 ± 5.9	2.3 ± 7.5	14.6 ± 10.2	15.6 ± 8.5	1.1 ± 6.6	0.20

The *P* values were calculated using ANCOVA.
AAP, aortic augmented pressure; AIx, augmentation index; AIx75, augmentation index corrected for heart rate of 75 beats per min; PWV, pulse wave velocity.

TABLE 6.

Neuropsychological test scores at baseline and 12 wk in the intervention and control arms

	Intervention, mean ± SD (n = 20)			Control, mean ± SD (n = 9)			
Neuropsychological test	**Baseline**	**12 wk**	**Change in score**	**Baseline**	**12 wk**	**Change in score**	***P***
MMSE	28.4 ± 0.9	28.2 ± 1.6	−0.2 ± 1.5	28.9 ± 1.2	28.3 ± 1.8	−0.6 ± 1.2	0.64
MoCA	24.9 ± 2.3	26.2 ± 2.4	1.3 ± 2.4	26.4 ± 2.5	26.9 ± 1.7	0.4 ± 1.3	0.93
Trail making A, s	27.3 ± 8.4	24.2 ± 5.0	−3.1 ± 5.7	24.7 ± 5.5	22.1 ± 3.1	−2.4 ± 5.1	0.37
Trail making B, s	74.2 ± 26.0	65.3 ± 17.8	−8.8 ± 24.6	62.0 ± 11.6	59.7 ± 18.7	−2.7 ± 14.3	0.85
Logical memory IA	10.7 ± 2.7	12.0 ± 3.1	1.4 ± 2.9	10.3 ± 4.0	11.4 ± 5.3	1.2 ± 2.6	0.86
Logical memory IIA	9.8 ± 3.7	11.5 ± 3.4	1.7 ± 4.0	9.9 ± 4.1	11.3 ± 5.0	1.4 ± 2.9	0.87
Digit symbol	53.8 ± 12.0	56.3 ± 11.4	2.5 ± 5.4	56.4 ± 8.8	58.4 ± 7.7	2.0 ± 4.1	0.97
Digit span forward	8.9 ± 1.9	9.1 ± 2.0	0.2 ± 1.1	9.1 ± 2.3	9.4 ± 1.8	0.3 ± 0.9	0.66
Digit span backward	6.0 ± 2.2	6.2 ± 2.2	0.2 ± 1.4	7.6 ± 2.8	7.8 ± 2.3	0.2 ± 1.6	0.42
Category fluency animal	20.6 ± 5.9	22.6 ± 4.8	2.0 ± 5.4	19 ± 5.0	20.7 ± 3.0	1.7 ± 3.8	0.39
Category fluency vegetables	14.7 ± 3.4	13.6 ± 3.6	−1.2 ± 2.8	12.2 ± 3.1	14.4 ± 2.1	2.2 ± 2.6	0.03[a]
Block design	35.4 ± 12.4	39.2 ± 11.9	3.9 ± 4.1	40.1 ± 11.8	44.4 ± 12.0	4.3 ± 10.1	0.63
Stroop interference	36.6 ± 10.2	40 ± 12.2	3.4 ± 7.8	42.1 ± 7.1	41.9 ± 5.1	−0.1 ± 5.6	0.37
Free recall	11.0 ± 1.8	12.1 ± 2.5	1.0 ± 2.3	10.9 ± 2.4	11.2 ± 2.4	0.4 ± 1.7	0.13

The *P* values were calculated using ANCOVA.
[a]$P < 0.05$.
MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment.

associated with lower cognitive function.[33] Aging, stroke, and dementia are all associated with low CVR. Aortic augmented pressure is an indicator of arterial compliance and is associated with age-related cerebral microvascular disease,[34,35] low cerebrovascular reserves,[36] and cognitive impairment.[37]

Greater improvements were observed in several neuropsychological test scores in the intervention arm including trail making A and B. The change in neuropsychological test scores is consistent with subjective improvement in cognition observed clinically in patients when transitioned to LCP tacrolimus. Cognitive impairment is common in KT recipients.[15,38] We assessed cognitive function 12 wk after changing IR tacrolimus to LCP tacrolimus. Change in cognitive function can take time. It is possible that with chronic use, we may see a bigger difference in cognitive function between the 2 groups. Together these data indicated that changing the tacrolimus formulation may favorably affect CBF, cerebrovascular kinetics, and cognitive function. These data are clinically relevant as they suggest that switching IR tacrolimus to LCP tacrolimus may improve CBF and cognitive impairment associated with CNIs. To our knowledge, this is the first study assessing the effect of tacrolimus formulation on CBF. This being a pilot study, we cannot confirm the changes in CBF, CVR, and cognitive function with the change in tacrolimus formulation. However, the findings can be used to design a bigger well-powered study to assess the effect of CNIs on CBF and cognitive function.

Underlying mechanisms associated with cognitive impairment in KT differ from the mechanisms underlying cognitive impairment in other populations. A better understanding of the risks of cognitive impairment in KT recipients and interventions to prevent and manage cognitive impairment are needed. Although some risk factors for cognitive impairment such as age and history of stroke are not modifiable, drug side effects such as those of tacrolimus can be mitigated. Previous studies have assessed ways to reduce tacrolimus exposure through CNI-sparing regiments[39-41] with limited success. Thus, tacrolimus remains part of maintenance immunosuppression in KT. If vasoconstrictive effects of tacrolimus reduce CBF and cause downstream effects, it is important to identify new strategies to minimize these neurotoxic side effects of tacrolimus.

A major limitation of the study was its small size. This was, however, designed as a proof-of-concept pilot study to determine if a larger study should be conducted to assess the effect of CNIs on CBF. Because of the small sample size, despite randomization, we noted small differences in baseline characteristics in the participants. The control arm was younger, had more females, was more educated, and had more patients with coronary artery disease and atrial fibrillation. Despite this, we noted an increase in CBF in the intervention arm. Another limitation was the relatively short follow-up of 12 wk. Although it is possible that conversion to LCP tacrolimus can result in acute improvement in cognitive function, it is also likely that LCP tacrolimus is associated with a lower rate of decline in cognition than IR tacrolimus. Longer studies are needed to assess that effect. The strengths of the study include the study design with randomization of stable KT recipients and blinding of study personnel measuring and analyzing study data. Using ANCOVA instead of the commonly used paired T-test is another strength as paired T-test does not adjust for baseline values. In addition, we used 2 different modalities (MRI and TCD) to assess CBF, and a comprehensive battery of neuropsychological tests to assess different domains of cognition (instead of a screening test alone as used in several transplant studies). Also, the battery was performed in optimal environment by trained personnel in private surroundings.

In summary, this is the first study to indicate that CBF, cerebrovascular kinetics, and cognitive function may be influenced by CNIs. Larger studies are needed to confirm and replicate these findings.

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