

Magnetic Resonance Measurements of Renal Blood Flow and Disease Progression in Autosomal Dominant Polycystic Kidney Disease

Vicente E. Torres,* Bernard F. King,* Arlene B. Chapman,[†] Marijn E. Brummer,[†] Kyongtae T. Bae,** James F. Glockner,* Kraisthith Arya,[†] Dana Risk,[†] Joel P. Felmlee,* Jared J. Grantham,[‡] Lisa M. Guay-Woodford,[§] William M. Bennett,^{||} Saulo Klahr,** Catherine M. Meyers,[¶] Xiaoling Zhang,** Paul A. Thompson,** J. Philip Miller,** and the Consortium for Radiologic Imaging Studies of Polycystic Kidney Disease (CRISP)

*Mayo Clinic College of Medicine, Rochester, Minnesota; [†]Emory University School of Medicine, Atlanta, Georgia;

[‡]University of Kansas Medical Center, Kansas City, Kansas; [§]University of Alabama, Birmingham Alabama; ^{||}Northwest Renal Clinic, Portland, Oregon; [¶]National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases/Division of Kidney, Urologic, and Hematologic Diseases, Bethesda, Maryland; and **Washington University, St. Louis, Missouri

Whether changes in renal blood flow (RBF) are associated with and possibly contribute to cystic disease progression in autosomal dominant polycystic kidney disease (ADPKD) has not been ascertained. The Consortium for Radiologic Imaging Studies of Polycystic Kidney Disease (CRISP) was created to develop imaging techniques and analyses to evaluate progression. A total of 131 participants with early ADPKD had measurements of RBF and total kidney (TKV) and cyst (TCV) volumes by magnetic resonance and of GFR by iothalamate clearance at baseline and 1, 2, and 3 yr. The effects of age, gender, body mass index, hypertension status, mean arterial pressure (MAP), TKV, TCV, RBF, renal vascular resistance (RVR), GFR, serum uric acid, HDL and LDL cholesterol, 24-h urine volume, sodium (UNaE) and albumin (UAE) excretions, and estimated protein intake were examined at baseline on TKV, TCV, and GFR slopes. TKV and TCV increased, RBF decreased, and GFR remained stable. TKV, TCV, RVR, serum uric acid, UAE, UNaE, age, body mass index, MAP, and estimated protein intake were positively and RBF and GFR negatively correlated with TKV and TCV slopes. TKV, RBF, UNaE, and UAE were independent predictors of TKV and TCV slopes (structural disease progression). TKV, TCV, RVR, and MAP were negatively and RBF positively correlated with GFR slopes. Regression to the mean confounded the analysis of GFR slopes. TKV and RBF were independent predictors of GFR decline (functional disease progression). In ADPKD, RBF reduction (1) parallels TKV increase, (2) precedes GFR decline, and (3) predicts structural and functional disease progression.

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Autosomal dominant polycystic kidney disease (ADPKD) is a systemic, inherited disorder that is characterized by development of renal cysts and enlargement and, at a late stage, decline in renal function (1). Hypertension, vasoconstriction, and remodeling of small renal arteries and arterioles occur early, before development of renal insufficiency (2,3). It is possible that these are secondary to the development of renal cysts (4). The expression of polycystin 1 and polycystin 2 in vascular smooth muscle (5–7) and endothelial cells (8) and the functional alterations of vascular smooth muscle (9,10) and endothelial cells (11,12) with *PKD1* or *PKD2* mutations raise the possibility of a direct role of these muta-

tions in their pathogenesis. The extent to which changes in renal blood flow (RBF) and vascular remodeling are associated with and possibly contribute to cystic disease progression and functional decline has not been ascertained, in part because of the lack of noninvasive methods. The National Institutes of Health–sponsored Consortium for Radiologic Imaging Studies of Polycystic Kidney Disease (CRISP) was created to develop imaging techniques and analyses to follow disease progression and evaluate treatments for ADPKD (13–16). Here, we examine the changes in RBF, renal volume, and GFR over time and whether changes in RBF are associated with and possibly contribute to the structural and functional progression of ADPKD.

Materials and Methods

Study Organization

CRISP clinical centers included the Mayo Clinic College of Medicine and University of Alabama at Birmingham, Emory University, and University of Kansas Medical Center. Washington University served as the data coordinating and image analysis center (13–16). The data

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Address correspondence to: Dr. Vicente E. Torres, Division of Nephrology and Hypertension, Mayo Clinic, Rochester, MN 55901. Phone: 507-284-7527; Fax: 507-266-9315; E-mail: torres.vicente@mayo.edu

coordinating and image analysis center collected images that were transferred from the collaborating institutions in Digital Imaging and Communications in Medicine format, segmented and analyzed the images, stored and recorded the results, and performed statistical analysis. Magnetic resonance imaging (MRI) determinations of RBF were performed at the Mayo Clinic College of Medicine on a Signa CV/I 1.5T scanner (GE Medical Systems, Milwaukee, WI) and Emory University on a Gyroscan Intera 1.5T scanner (Philips Medical Systems, Best, The Netherlands).

Study Protocol

Patients with ADPKD were eligible when they were older than 15 and younger than 46 yr and had a measured or estimated creatinine clearance of >70 ml/min (13). Patients were ineligible when they had undergone renal surgery, had cyst drainage procedures, were unable to undergo breath-hold MRI, or had other medical conditions that potentially affected renal function. Hypertension status was defined as a previous diagnosis and current use of antihypertensive medications or systolic and diastolic BP $>140/90$ mmHg on three consecutive visits.

After signing an informed written consent, enrolled patients were scheduled for 2-d evaluations in the General Clinical Research Center at baseline and 1 (YR1), 2 (YR2), and 3 (YR3) yr later. Each time, they were instructed to continue their medications, to discontinue any nonsteroidal anti-inflammatory medications for at least 7 d before evaluation, and not to initiate diuretic therapy within 14 d of evaluation. During the day before admission, patients collected a 24-h urine sample for determination of creatinine, urea nitrogen, sodium (UNaE), and albumin (UAE) excretions. Weight, height, and body mass index (BMI) were measured at admission. BP were measured in the morning, before antihypertensive medication intake, in the left and right arms after being seated for at least 5 min on three occasions 3 min apart using an oscillometric measuring device. Blood was obtained before GFR studies for the determination of blood hemoglobin, serum electrolytes, liver enzymes, and lipid profiles using standard laboratory techniques. GFR was measured by a nonradiolabeled iothalamate clearance technique with sonographic monitoring of bladder emptying (15). The mean coefficient of variation was 4.9%. GFR also was estimated using the Modification of Diet in Renal Disease (MDRD) equation: $186.3 \times \text{serum creatinine}^{-1.154} \times \text{age}^{-0.203} \times 0.742$ (if female) $\times 1.212$ (if black) (17). Protein intake (g/d) was estimated using the equation $6.25 \times [\text{urine urea nitrogen in g/d} + (0.03 \times \text{weight in kg})]$ (18).

Measurements of Total Kidney Volume and Total Cyst Volume

Magnetic resonance imaging studies were performed in the morning before medication intake and breakfast (13–16). Coronal T2-weighted images (single-shot fast spin-echo/half-Fourier acquired single-shot turbo spin-echo) and gadolinium-enhanced three-dimensional volume-interpolated spoiled-gradient echo coronal T1-weighted images were obtained (3-mm slice thickness). The volumes of individual kidneys were measured in T1-weighted images with a stereology method and calculated from the set of contiguous images by summing the products of the area measurements and slice thickness. A region-based threshold method was used to calculate cyst volumes (19). Reliability coefficients were 0.998 for total kidney volume (TKV) and 0.961 for total cyst volume (TCV) in repeatedly acquired images on individual patients. The average coefficients of variation of the TKV and TCV measurements in the repeated analysis of 99 images were 0.01 and 0.26%, respectively.

Measurements of RBF

Thick-section, oblique-axial, two-dimensional, phase-contrast, breath-hold MR angiograms were obtained along the course of each renal artery and acted as reference images (14). The MR flow measurements were obtained perpendicular to the oblique-axial, two-dimensional reference images of the renal arteries using a cardiac-gated, two-dimensional, fast gradient-echo, phase-contrast pulse sequence. MR blood flow pulse sequence parameters were reported previously (14). The velocity encoding value was 100 cm/s, and flow acquisition was obtained in the slice direction. Flow analysis was performed using FLOW software Version 4 (Medis, Leiden, The Netherlands). Semiautomated or manual techniques were used for definition of the vessel borders in the flow images depending on image quality. Vessel area estimations were made in images at all phases of the cardiac cycle. RBF measurements at Emory University in YR3 of the study were not comparable to those in the previous years because of software upgrades. Therefore, these values were not used in the analysis. Renal vascular resistance (RVR) was calculated as mean arterial pressure (MAP)/RBF $\times 80,000$ (20). Renal plasma flow and filtration fraction (FF) were calculated using accepted formulas. The average interviewer coefficient of variation of RBF measurements using the same image acquisitions is 2.5% with a reliability coefficient of 0.983 (14). The average coefficient of variation for repeated RBF measurements using independent acquisitions is 2.9 or 6.0%, depending on whether the acquisitions included the same or a different scouting process (21).

Statistical Analyses

The data were examined using SAS system software (SAS Institute, Cary, NC). Mixed model ANOVA (PROC MIXED; SAS) was used to detect the statistical significance of changes over time. Correlations between baseline values and slopes estimated by individual regressions within each participant were computed as Pearson r values. For ensuring that outlier cases did not distort the correlations, Spearman values also were checked (these did not differ greatly and are not presented).

Results

Baseline Characteristics and Longitudinal Changes

A total of 131 patients participated in this study (58 at the Mayo Clinic and 73 at Emory University). Forty-nine were male, and 82 were female. The mean age at entry into the study was 31.5 yr (range 15 to 46). Table 1 summarizes the relevant clinical, radiologic, and laboratory parameters at baseline, YR1, YR2, and YR3. BMI tended to increase and reached statistical significance at YR3. MAP decreased significantly from baseline to YR1 and remained stable during YR2 and YR3. Baseline TKV and TCV were 891 and 316 ml, respectively. TKV and TCV increased significantly and RBF decreased significantly from year to year. Despite the lower RBF, RVR at YR1 remained stable as a result of the reduction in MAP. Significant increases in RVR were detected at YR2 and YR3. GFR (measured by the iothalamate clearance or estimated by the MDRD equation) was stable at baseline, YR1, and YR2. Compared with baseline, mean measured and estimated GFR (eGFR) values were 2.8 and 5.3 ml/min per 1.73 m² lower in YR3, but only the change in eGFR reached statistical significance. The decreasing RBF and stable GFR resulted in an increase in FF that was statistically significant in YR2 and YR3. The increase in FF in YR3 was accompanied by a significant increase in UAE. Serum HDL cholesterol levels were significantly lower in YR1, YR2, and

Table 1. Clinical, radiologic, and laboratory parameters^a

Parameter	Baseline	Year 1	Year 2	Year 3
BMI	25.67 ± 0.45	25.93 ± 0.44	26.08 ± 0.45	26.41 ± 0.48 ^{c,d}
MAP (mmHg)	96.3 ± 0.9	93.6 ± 0.9 ^c	92.5 ± 0.9 ^c	93.3 ± 1.1 ^c
Log 10 TKV (ml)	2.95 ± 0.02	2.97 ± 0.02 ^c	3.00 ± 0.02 ^{c,d}	3.01 ± 0.02 ^{c,d,e}
Log 10 TCV (ml)	2.50 ± 0.04	2.57 ± 0.04 ^c	2.61 ± 0.04 ^{c,d}	2.66 ± 0.04 ^{c,d,e}
RBF (ml/min per 1.73 m ²) ^b	736.8 ± 20.2	683.6 ± 16.0 ^c	644.4 ± 17.7 ^{c,d}	602.6 ± 23.0 ^{c,d,e}
RVR (dynes s/cm ⁻⁵) ^b	11,552 ± 368	11,788 ± 339	12,606 ± 414 ^{c,d}	13,391 ± 588 ^{c,d}
GFR (ml/min per 1.73 m ²)	98.7 ± 2.0	98.7 ± 2.1	99.2 ± 2.4	95.9 ± 2.4
RPF (ml/min per 1.73 m ²) ^b	446.5 ± 12.0	419.8 ± 9.2 ^c	394.2 ± 11.0 ^{c,d}	359.8 ± 13.4 ^{c,d}
Log 10 FF (%) ^b	-0.648 ± 0.010	-0.633 ± 0.010	-0.598 ± 0.012 ^{c,d}	-0.575 ± 0.012 ^{c,d}
Serum creatinine (mg/dl)	1.00 ± 0.02	0.99 ± 0.02	1.01 ± 0.02	1.04 ± 0.02 ^{c,d,e}
MDRD GFR	85.2 ± 2.24	84.8 ± 2.0	83.4 ± 2.2	79.9 ± 2.0 ^{c,d,e}
Serum uric acid (mg/dl)	5.02 ± 0.12	5.01 ± 0.12	5.19 ± 0.13 ^{c,d}	5.38 ± 0.14 ^{c,d,e}
Serum HDL cholesterol (mg/dl)	47.8 ± 1.1	42.7 ± 1.0 ^c	42.7 ± 1.0 ^c	42.7 ± 1.1 ^c
Serum LDL cholesterol (mg/dl)	101.2 ± 2.8	100.1 ± 2.1	100.0 ± 2.5	100.0 ± 2.6
Urine volume (ml/d)	2427 ± 96	2797 ± 90 ^c	2730 ± 95 ^c	2768 ± 99 ^c
UNaE (mEq/d)	182.3 ± 6.9	190.0 ± 6.7	190.2 ± 6.7	181.3 ± 6.3
Log 10 UAE (mg/d)	1.38 ± 0.04	1.34 ± 0.04	1.36 ± 0.04	1.45 ± 0.05 ^{d,e}
Protein intake (g/d)	71.7 ± 2.0	72.9 ± 2.1	75.7 ± 2.0 ^c	75.6 ± 2.1 ^c

^aData are means ± SEM. BMI, body mass index; FF, filtration fraction; MAP, mean arterial pressure; MDRD, Modification of Diet in Renal Disease; RBF, renal blood flow; RPF, renal plasma flow; RVR, renal vascular resistance; TKC, total cyst volume; TKV, total kidney volume; UAE, urinary albumin excretion; UNaE, urinary sodium excretion.

^bYear 3 RBF, RPF, FF, and RVR values and statistical comparisons with baseline, year 1, and year 2 include only patients who were studied at the Mayo Clinic.

^c*P* < 0.05 versus ^abaseline, ^dyear 1, and ^eyear 2 values.

YR3 compared with baseline values. No significant changes were detected in serum LDL cholesterol or uric acid. Twenty-four-hour urine output was significantly higher in YR1, YR2, and YR3, whereas UNaE remained unchanged. Estimated protein intake was significantly higher in YR2 and YR3 compared with baseline.

Correlations between Baseline Parameters and Indices of Disease Progression

Table 2 shows the correlations between relevant baseline clinical, radiologic, and laboratory parameters and the slopes in TKV (or TCV) and in measured GFR or eGFR. TKV, TCV, RVR, serum uric acid, UAE, and UNaE were positively correlated with TKV slopes during the 3 yr of follow-up (Figure 1). Weak positive correlations with age, BMI, MAP, and estimated protein intake also were detected. RBF, eGFR, and measured GFR were negatively correlated with TKV slopes (Figure 1). A weak negative correlation with HDL cholesterol also was detected. Similar correlations were observed with TCV slopes. TKV, TCV, RVR, and MAP were negatively and RBF positively correlated with measured GFR slopes (Figure 2) but not with eGFR slopes. Measured GFR at baseline was negatively correlated with the measured GFR slope (Figure 2) but not with the eGFR slope. Similarly, the eGFR at baseline was negatively correlated with the eGFR slope but not with the measured GFR slope. This suggests that these correlations are due to regression to the mean, rather than disease progression (see Discussion).

Regression Analysis for Structural Disease Progression

Multiple regression models were used to determine which baseline variables were independently predictive of structural progression reflected by TKV (Table 3) or TCV slopes (data not shown). For the model of TKV slope with baseline TKV in the model (Table 3, columns 1 through 3), three baseline variables contributed independently (TKV and UNaE positive, RBF negative). For the model of TKV slope with baseline TKV excluded from the model (Table 3, columns 4 through 6), three variables contributed independently (UAE and UNaE positive, RBF negative). Similar results were obtained when TCV slope was used to examine structural progression, with the same variables showing similar results in these models (data not shown). Replacing RVR for RBF showed that RVR also was a strong independent positive predictor of TKV (found significant with baseline TKV excluded or included in the model) and TCV (found significant with baseline TCV excluded or included in the model) slopes (data not shown).

Regression Analysis for Functional Disease Progression

Multiple regression models were used to determine which baseline variables are independently predictive of functional progression (estimated by GFR slope), including either TKV (Table 4) or TCV (data not shown) as predictors. For the model of GFR slope with baseline GFR in the model (Table 3, columns 1 through 3), four baseline variables contributed independently (RBF and UAE positive, TKV and GFR nega-

Table 2. Pearson correlation coefficients among baseline clinical, radiologic, or laboratory parameters and the slopes of log 10 TKV, log 10 TCV, measured GFR or estimated MDRD GFR

Parameter	Log 10 TKV Slope		Log 10 TCV Slope		GFR Slope		MDRD GFR Slope	
	<i>r</i>	<i>P</i>	<i>r</i>	<i>P</i>	<i>r</i>	<i>P</i>	<i>r</i>	<i>P</i>
Age	0.22	0.018	0.25	0.006	−0.08	NS	0.14	NS
BMI	0.19	0.042	0.17	NS	−0.05	NS	0.30	0.001
MAP	0.18	0.053	0.21	0.021	−0.24	0.010	−0.08	NS
Log 10 TKV	0.69	<0.001	0.73	<0.001	−0.40	<0.001	−0.05	NS
Log 10 TCV	0.64	<0.001	0.65	<0.001	−0.38	<0.001	−0.06	NS
GFR	−0.18	0.052	−0.17	NS	−0.28	0.002	−0.08	NS
RBF	−0.30	<0.001	−0.33	<0.001	0.24	0.009	0.15	NS
RVR	0.37	<0.001	0.41	<0.001	−0.30	0.001	−0.13	NS
MDRD GFR	−0.26	0.004	−0.25	0.006	0.06	NS	−0.39	<0.001
Serum uric acid	0.34	<0.001	0.33	<0.001	−0.07	NS	0.13	NS
Serum HDL cholesterol	−0.18	0.051	−0.14	NS	−0.06	NS	−0.20	0.028
Serum LDL cholesterol	0.09	NS	0.04	NS	−0.09	NS	0.12	NS
Urine volume	0.17	NS	0.14	NS	−0.04	NS	0.07	NS
UNaE	0.30	0.001	0.26	0.005	−0.05	NS	0.08	NS
UAE	0.33	<0.001	0.31	0.001	−0.01	NS	−0.10	NS
Protein intake	0.16	NS	0.14	NS	−0.01	NS	0.20	0.027

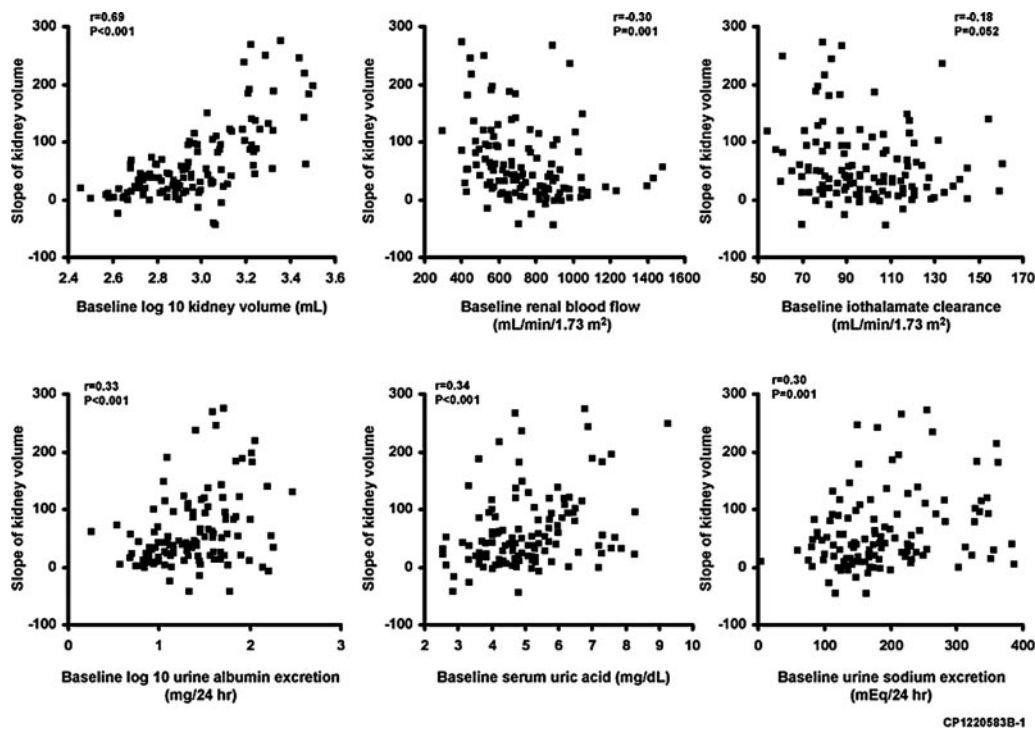


Figure 1. Relationship among total kidney volume slopes and baseline log 10 kidney volumes, renal blood flows, iothalamate clearances, log 10 urine albumin excretions, serum uric acid levels, and urine sodium excretions.

tive). The negative relationship between baseline GFR and GFR slopes is consistent with regression to the mean (see the Discussion section). The baseline RBF result (significant in the model with baseline GFR, NS when baseline GFR is excluded) is interesting. The baseline RBF-GFR slope correlation is significant but not strong ($r = 0.233, P = 0.010$).

When the effect of baseline GFR is statistically partialled out (as is done in a multiple regression), the baseline RBF-GFR slope correlation is much stronger and more significant ($r = 0.512, P < 0.001$). For the model of GFR slope with baseline GFR excluded from the model (Table 4, columns 4 through 6), three baseline variables contributed independently (age

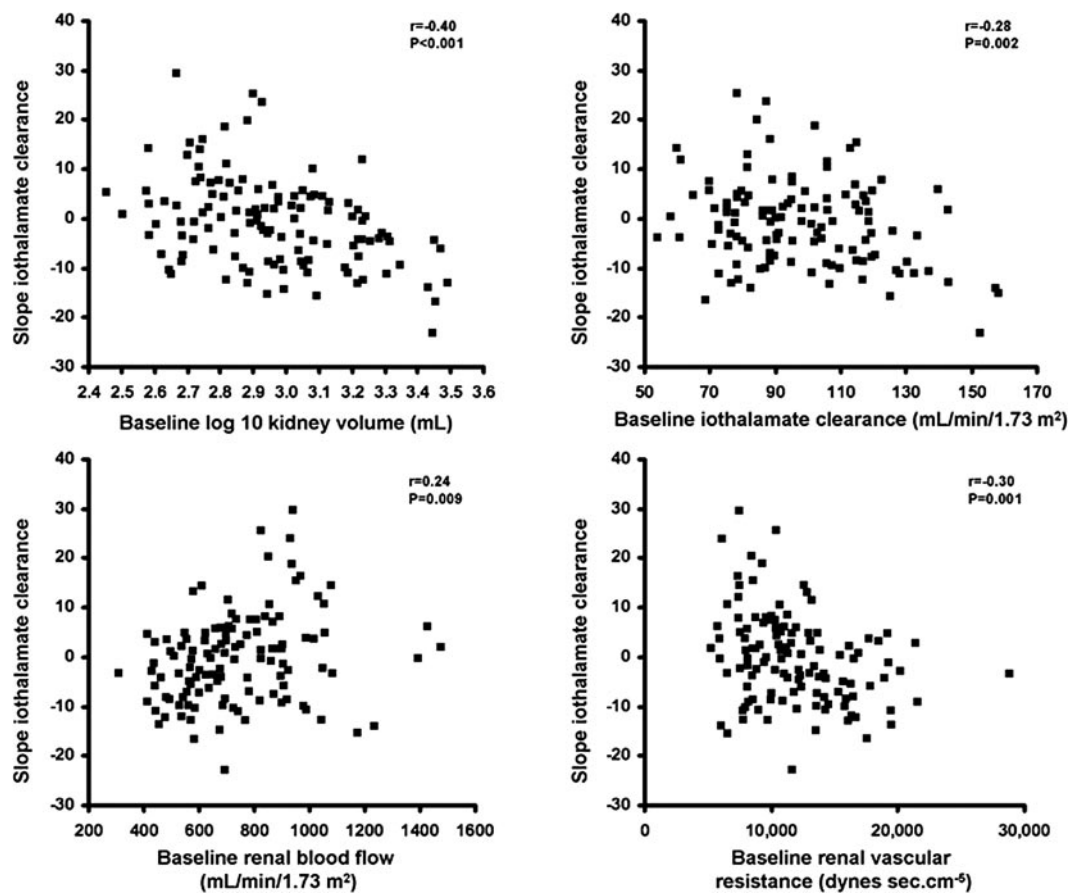


Figure 2. Relationship among iothalamate clearance slopes and baseline log 10 kidney volumes, iothalamate clearances, renal blood flows, and renal vascular resistances.

Table 3. Regression model predicting structural disease progression (TKV) from baseline parameters

Parameter	TKV Slope (R^2 ; ml/yr)					
	0.58			0.40		
	b^a	SE	P	b^a	SE	P
Male gender	1.0	14.3	NS	-8.0	17.0	NS
Age (yr)	-0.58	0.68	NS	0.69	0.78	NS
BMI	0.14	1.04	NS	0.41	1.23	NS
Hypertension	2.8	10.9	NS	22.1	12.5	NS
MAP (mmHg)	-0.59	0.46	NS	-0.28	0.54	NS
Log 10 TKV (ml)	168	25	<0.001	—	—	—
GFR (ml/min per 1.73 m ²)	0.35	0.25	NS	0.35	0.29	NS
RBF (ml/min per 1.73 m ²)	-0.06	0.03	0.038	-0.09	0.03	0.004
Serum uric acid (mg/dl)	4.56	5.49	NS	7.97	6.51	NS
Serum HDL cholesterol (mg/dl)	-0.51	0.47	NS	-0.67	0.56	NS
Serum LDL cholesterol (mg/dl)	0.12	0.14	NS	0.11	0.17	NS
Urine volume (L)	2.40	4.74	NS	0.6	5.6	NS
UNaE (mEq/24 h)	0.18	0.08	0.023	0.26	0.09	0.005
Log 10 UAE (mg/24 h)	12.2	11.9	NS	46.7	12.8	<0.001
Protein intake (g/24 h)	-0.22	0.29	NS	-0.07	0.34	NS

^aSlopes per unit change in baseline parameters. For example, a lower baseline RBF by 100 ml/min per 1.73 m² predicts a steeper increase in the slope of TKV by 6 (with TKV included as a regressor) or 9 ml/yr (without TKV included as a regressor).

Table 4. Regression models predicting functional disease progression (GFR) from baseline parameters

Parameter	GFR Slope (R^2 ; ml/min per 1.73 m ² per yr)					
	0.55			0.28		
	b ^a	SE	P	b ^a	SE	P
Male gender	0.80	2.17	NS	0.86	2.71	NS
Age (yr)	0.09	0.10	NS	0.29	0.12	0.021
BMI	0.18	0.16	NS	0.12	0.20	NS
Hypertension	−0.62	1.65	NS	−0.83	2.06	NS
MAP (mmHg)	−0.07	0.07	NS	−0.12	0.09	NS
Log 10 TKV (mL)	−20.8	3.9	<0.001	−20.8	4.8	<0.001
GFR (ml/min per 1.73 m ²)	−0.28	0.04	<0.001	—	—	—
RBF (ml/min per 1.73 m ²)	0.02	0.00	<0.001	0.01	0.00	NS
Serum uric acid (mg/dl)	−0.67	0.83	NS	0.38	1.02	NS
Serum HDL cholesterol (mg/dl)	−0.05	0.07	NS	−0.08	0.09	NS
Serum LDL cholesterol (mg/dl)	−0.03	0.02	NS	−0.04	0.03	NS
Urine volume (L)	−0.35	0.72	NS	0.17	0.89	NS
UNaE (mEq/24 h)	−0.00	0.01	NS	−0.01	0.01	NS
Log 10 UAE (mg/24 h)	5.07	1.81	0.006	5.84	2.25	0.011
Protein intake (g/24 h)	0.03	0.04	NS	0.02	0.05	NS

^aSlopes per unit change in baseline parameters.

and UAE positive, TKV negative). Similar results were obtained when TKV was replaced by TCV or when RBF was replaced by RVR in the model (data not shown).

Determinants of RBF Decline

To identify factors that are responsible for the decline in RBF, we performed a regression analysis using potentially relevant independent baseline variables or variables averaged during the whole period of observation (Table 5). These models accounted for only a small fraction of the variability in the rate of decline in RBF (R^2 shown in Table 5). The presence of hypertension and lower levels of serum HDL cholesterol were independently associated with a faster decline of RBF. Conversely, the serum uric acid concentration was a negative predictor of RBF decline.

Discussion

In ADPKD, renal growth is characterized by slowly enlarging cystic disease throughout the cortex and the medulla (22). These cysts are clonal outpouchings from single cells along a limited number of collecting ducts and nephrons. The events that initiate the clonal transformation include loss of heterozygosity or a somatic mutation of the allele that is unaffected by the germline mutation or possibly somatic mutations of other related genes. When the cysts reach approximately 2 mm in diameter, the majority become disconnected from the tubules, whereupon their growth requires chloride-driven fluid secretion into the lumen. Compression of the renal arteries and parenchyma by expanding cysts may lead to renal ischemia, activation of the renin-angiotensin system, interstitial inflammation and fibrosis, apoptosis of tubular epithelial cells, vascular sclerosis, and eventually renal failure. Alternatively, mu-

tations in the *PKD* genes may cause directly cyst development, apoptosis of tubular epithelial cells, and remodeling of the renal vasculature, together leading to renal failure. Irrespective of the underlying mechanism, renal hemodynamic changes occur early in ADPKD and may contribute to the development of hypertension and renal insufficiency.

Although all patients with *PKD1* or *PKD2* mutations develop cysts, progression to renal failure varies widely between and within families (23). The disease is more severe in patients with *PKD1* mutations. Among those with *PKD2* mutations, it is more severe in male individuals (24). Modifier genes and environmental factors contribute to this variability. Factors that predict the risk for renal failure have been identified (25). In addition to kidney size, presence of hypertension or proteinuria, hyperlipidemia, low HDL cholesterol levels, and smoking are associated with an increased risk. Whether they increase the risk for cyst growth or simply promote nonspecific vascular, glomerular, or tubulointerstitial mechanisms is not known.

The lack of appropriate noninvasive methods has been an impediment to the study of renal hemodynamics and microvasculature in ADPKD. The few studies in this area have used measurements of RBF that rely on determinations of renal clearance of para-aminohippurate (26–28). These measurements assume normal renal extraction of para-aminohippurate, which is not likely in ADPKD, particularly in the presence of renal insufficiency. CRISP was created to develop imaging techniques and analyses to follow disease progression in ADPKD (13–16). Goals of CRISP included determining whether MR can reliably measure RBF, whether changes can be detected over a short period of time and be used as a surrogate marker of progression, and whether reductions in RBF predict struc-

Table 5. Regression model predicting RBF slopes from parameters at baseline or averaged during the whole period of observation (baseline through year 3)

Parameter	RBF Slope (R^2 ; ml/min per 1.73 m ² per yr)					
	0.22			0.20		
	b ^a	SE	<i>P</i>	b ^b	SE	<i>P</i>
Male gender	−22.2	24.2	NS	−28.7	24.9	NS
Age (yr)	1.39	1.14	NS	1.56	1.21	NS
BMI	1.38	1.75	NS	0.05	1.88	NS
Hypertension	−40.3	18.3	0.030	−34.3	18.3	NS
MAP (mmHg)	1.12	0.77	NS	1.18	1.00	NS
Log 10 TKV (ml)	−27.9	42.3	NS	−68.0	52.3	NS
GFR (ml/min per 1.73 m ²)	−0.056	0.38	NS	−0.62	0.47	NS
Serum uric acid (mg/dl)	20.3	9.1	0.027	17.5	9.4	NS
Serum HDL cholesterol (mg/dl)	1.64	0.75	0.031	2.11	0.85	0.015
Serum LDL cholesterol (mg/dl)	−0.39	0.24	NS	−0.28	0.31	NS
Urine volume (L)	−7.3	8.0	NS	−12.8	8.7	NS
UNaE (mEq/24 h)	−0.15	0.13	NS	−0.10	0.19	NS
Log 10 UAE (mg/24 h)	38.0	20.2	NS	46.3	29.4	NS
Protein intake (g/24 h)	0.41	0.47	NS	0.81	0.69	NS

^aSlopes per unit change in baseline parameters.

^bSlopes per unit change averaged during the whole period of observation.

tural and/or functional progression. We have published validation studies demonstrating the absolute requirement for precise MR blood flow pulse sequence parameters and the accuracy of the measurements in phantoms and their reproducibility in volunteers with ADPKD (14).

The results of our study provide insight to the chronology of RBF changes in relation to changes in kidney volume and GFR. Consistent with previous cross-sectional studies, reductions in RBF occur in parallel with the increases in TKV and precede the decline in GFR. GFR is maintained at least in part by an increase in FF, which is accompanied by an increase in UAE. Reductions in RBF may be secondary to changes in kidney volume, neurohumoral or local mediators, and intrinsic vascular factors. The early reduction in RBF that independently predicts TKV and TCV increases supports previous studies suggesting that renal ischemia or related factors, such as activation of the renin-angiotensin system, promote renal cystogenesis (29–31). Among the remaining baseline parameters that are correlated significantly with TKV or TCV slopes in the univariate analysis (age, BMI, serum uric acid, UAE, and UNaE), only UAE and UNaE were significant independent predictors. Whether increased UAE contributes to cystogenesis is not known, but albumin has mitogenic and apoptotic effects on proximal (OK and LLCPK cells) and collecting/distal (MDCK cells) tubular epithelial cells (32–35). The association of high UNaE with a greater increase in TKV and TCV may be consistent with a cystogenic effect of a high sodium diet, as observed in an animal model of polycystic kidney disease (29). Of note, the daily sodium intakes in motivated study participants (reflected by mean UNaE between 181 and 190 mEq during baseline through YR3) were higher than the recommended 90 mEq,

despite good BP control. These observations suggest that control of dietary sodium may be important for the control not only of BP but also of cystic disease progression.

The relatively small changes in GFR that were observed during the study limited the ability to detect significant baseline predictors of GFR decline. Nevertheless, baseline TKV and TCV, RVR, MAP, and LDL cholesterol were negatively and baseline RBF positively correlated with GFR slopes in the univariate analysis. Only TKV and TCV were strong independent predictors of renal functional decline in the regression analysis when baseline GFR was not included in the model. Low baseline RBF also were predictive of renal functional decline when baseline GFR was used in the model. The failure to detect an effect of baseline RBF on GFR slopes in the model without baseline GFR may be explained by the strong inverse correlation between baseline GFR and the slope of GFR, either measured by iothalamate clearance or estimated by the MDRD equation. This inverse correlation is likely explained by regression to the mean. This is particularly relevant in a population with preserved renal function, because of the wider physiologic variability of GFR and lower precision of GFR measurements within the normal range. Other factors, such as hyperfiltration, that are known to occur in early ADPKD (36) and possibly pharmacologic interventions are less likely to play a role. Because regression to the mean may be more obvious in the participants with milder ADPKD and lower UAE, it also may explain the unexpected positive predictive value of UAE on GFR slopes that was noted in the regression analysis. Overall, the analysis of the effects of baseline parameters on renal functional decline point to the importance of renal cystic disease

and vascular changes as determinants of functional progression in ADPKD.

In a previous cross-sectional analysis of baseline parameters in the CRISP study, RBF (or RVR) but not TKV (or TCV) was found to be a strong independent predictor of GFR. The failure to identify TKV as an independent predictor of baseline GFR may in part be explained by the inclusion criteria requiring a measured or estimated creatinine clearance of >70 ml/min. The strong effect of RBF likely is explained by the physiologic relationship between RBF and GFR. In this longitudinal study, baseline TKV is a stronger predictor of GFR decline than baseline RBF. Nevertheless, both studies identify renal hemodynamic parameters (RBF and RVR) as significant predictors of GFR or GFR decline independent from TKV and TCV. The study cannot determine whether the changes in RBF are secondary to increases in intrarenal pressure related to cyst growth or to other alterations that directly cause arterial constriction and remodeling.

Whereas TKV and RBF are significant predictors of structural progression (increase in TKV) and functional progression (GFR decline), the factors that predict RBF decline are less clear. The results of the study suggest that the presence of hypertension or factors related to hypertension and reduced levels of HDL cholesterol likely play a role. In essential hypertension, a decreased renal vasodilatory response to L-arginine has been associated with decreased serum levels of HDL cholesterol (37). The study unexpectedly detected a positive, rather than a negative, effect of serum uric acid, a factor that has been proposed to play a role in the development of renal microvascular disease (38), on the RBF slopes. This result is difficult to interpret because a number of patients in the study were treated with allopurinol. Importantly, the parameters that were measured in this study accounted for a very small fraction of the variability of the decline in RBF, pointing to the limitations of the current understanding of renal hemodynamics and vascular remodeling in ADPKD.

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Disclosures

None.

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