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Volumetric determination of progression in autosomal dominant polycystic kidney disease by computed tomography

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Background. Autosomal dominant polycystic kidney disease (ADPKD) is characterized by progressive renal enlargement and renal failure. We evaluated sequential radiocontrast-enhanced computed tomography (CT) scans to determine the rate of kidney enlargement in patients with ADPKD.

Methods. Ten adult patients with ADPKD (4 men and 6 women) with initial serum creatinine levels ≤1.6 mg/dL had at least two sequential CT scans more than three years apart. The mean patient age at the initial CT study was 33.8 years, and the mean initial serum creatinine concentration was 1.1 mg/dL (range 0.6 to 1.6 mg/dL; range of calculated creatinine clearances 60 to 135 mL/min/1.73 m^2). Total volume (Vt) was determined by manual tracing of renal areas in contiguous 5 to 10 mm thick axial CT slices for each kidney. The area of noncystic parenchyma (Vp) in each slice was determined by differential densitometry segmentation analysis of contrast-enhanced tissue, and total cyst volume (Vc) was the difference between Vt and Vp. The mean diameters of individual cysts were measured sequentially in selected cases.

Results. The mean initial Vt, Vp, and Vc values (± SEM) were 561 ± 66, 243 ± 19, and 317 ± 57 mL per kidney, respectively. In 10 patients, after a mean of 5.7 years (range 3.3 to 11.9), Vt increased 323 ± 79 mL ($P < 0.01$, range −25 to 1182 mL); the rate of volume increase was 53.9 ± 10.4 mL/year/kidney ($P < 0.001$). In eight patients with repeat contrast-enhanced scans, Vt, Vp, and Vc increased 211 ± 58 mL ($P < 0.005$), 26 ± 11 mL ($P > 0.05$), and 185 ± 52 mL ($P < 0.01$), respectively. In 19 individual spherical cysts selected in six patients, the mean initial volume was 15.0 ± 7.2 mL (range 1.1 to 137 mL), and the average rate of volume increase was 0.52 ± 0.21 mL/month ($P < 0.025$, range 0.02 to 4.15 mL/month). In five patients who eventually required dialysis, 11.2 years after the initial CT scan, the initial cyst/kidney volume ratio (combined for both kidneys) exceeded 0.43; four patients with lower cyst/kidney volume ratios had serum creatinine levels <1.5 mg/dL, 8.7 years after the initial CT scan.

Conclusions. On the basis of this preliminary survey of archival material, we conclude that conventional contrast-enhanced CT scans can be used to quantitate volume components of progression in ADPKD. The rates of individual kidney and cyst enlargement are highly variable within and between patients, but overall, the values increase over time. The volume fraction of kidneys comprised of cysts may be a useful indicator of ADPKD progression.

Key words: PKD, fluid secretion, chloride transport, renal cell proliferation, hereditary disease, chronic renal insufficiency, kidney cysts.

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Renal enlargement is a hallmark of autosomal dominant polycystic kidney disease (ADPKD) [1–3]. Recent evidence indicates that the progressive increase in kidney size in patients with ADPKD is primarily due to the proliferation of mural epithelial cells and the accumulation of fluid within innumerable cysts [1, 3, 4]. It is widely believed that this increase in cyst volume (Vc) is responsible for the ultimate decline in glomerular filtration rate that is a feature of ADPKD. Indeed, the appearance of polycystic kidneys on serial ultrasound and computed tomography (CT) studies supports the view that absolute renal size may be a risk factor for hypertension and the progression to end-stage renal failure [1, 5–7]. However, in 19 postmenopausal women with ADPKD and well-maintained renal function, a quantitative CT study of sequential CT scans taken one year apart did not find significant changes in total kidney volume nor changes in creatinine clearance [8]. On the other hand, a recent study of CT scans obtained eight years apart in nine patients showed that the polycystic kidneys enlarged and that the extent of enlargement correlated inversely with the change in iothalamate and creatinine clearances [9]. In view of these preliminary findings, additional studies are needed to determine in ADPKD subjects if absolute kidney size or the rate of kidney enlargement is a marker of the propensity to develop renal insufficiency.

Nineteen years ago, we reported the first study of ADPKD that compared contrast-enhanced CT to ultrasound for the purpose of diagnosis [10]. Since then, we have used CT routinely to establish the diagnosis of

Table 1. Description of patient cohort

Patient #	Sex	Initial age *years*	Initial scan: Initial creatinine *mg/dL*	Initial scan: Initial creatinine clearance[a]	Initial scan: Indication for scan	Initial scan: Slice *mm*	Interval between scans *years*	Interval between initial scan and ESRD or most recent creatinine *years*	Follow-up scan: Indication for scan	Follow-up scan: Follow-up creatinine *mg/dL*	Follow-up scan: Follow-up creatinine clearance[a]	Follow-up scan: Slice *mm*
1	M	41	1.5	60.7	Diagnosis	10	11.9	11.9 (ESRD)	Transplant	>10	Dialysis	10
2	M	34	1.6	62.3	Diagnosis	10	5.0	12.0 (ESRD)	Routine	1.8	52.8	10
3	M	31	1.3	78	Diagnosis	10	4.6	9.0 (ESRD)	Pain	1.8	54.1	5
4	F	32	1.0	80.3	Diagnosis	10	4.7	11.5 (1.0)	Pain	1.0	76.6	10
5	F	42	0.9	94.6	Diagnosis	10	3.3	15 (1.0)	Pain	1.0	91.6	10
6	F	25	0.9	92.9	Diagnosis	5	6.7	8 (1.0)	Pain	1.0	80.5	10
7	F	35	0.9	81.3	Diagnosis	10	6.1	6.1 (0.9)	Routine	0.9	83.5	8
8	F	46	1.2	60	Diagnosis	10	4.6	11.0 (ESRD)	Routine	1.9	38.6	10
9	F	27	0.6	135	Diagnosis	10	5.3	12.0 (ESRD)	Size	1.0	78.4	10
10	M	25	1.0	117	Diagnosis	8	5.0	9 (1.4)	Pain	1.4	78	10

[a] Estimated from Cockroft Gault formula and body surface area, mL/min/1.73 m^2

polycystic kidney disease. In a cohort of ADPKD patients collected since 1969, we found 10 with good to excellent initial renal function who had more than one contrast-enhanced CT study and a follow-up period long enough that a significant portion of the patients developed end-stage renal failure. We used these archival CT scans to determine the extent to which changes in cyst and parenchymal volume components of renal mass might be used as surrogate markers of disease progression. To determine the rates of kidney and cyst enlargement, we measured total kidney volume (Vt), total parenchyma volume (Vp), and total Vc in sequential CT scans. We also analyzed volume changes in carefully selected individual renal cysts. The results support the view that relatively early in the course of the disease the extent of renal cystic change is an indication of future deterioration in renal function.

METHODS

Subjects for this study were drawn from a cohort including 162 females and 126 males with ADPKD who were seen in the PKD Consultation Clinic at the Kansas University Medical Center (Kansas City, KS, USA) since 1969. All patients had a clinical history, physical findings, and family history consistent with the diagnosis of ADPKD. To confirm the diagnosis, CT scans were performed in 173 patients, and of these, 75 were administered intravenous iodinated contrast material to enhance the renal parenchyma. In patients younger than 30 years of age, the diagnosis of ADPKD was confirmed by the demonstration of at least three cysts in each kidney. In older patients, at least four cysts per kidney were required to establish the diagnosis. Ten unrelated subjects (6 females and 4 males) had routine follow-up contrast-enhanced CT scans on at least two occasions separated in time by at least three years. The initial scans were done in the course of the diagnostic evaluation; the second scan was done for pretransplant evaluation, pain, rapid increase in kidney size, or routine follow-up (Table 1). Patients 4 and 5 had four separate contrast-enhanced scans.

GE 8800 and 9800 series (GE Medical Systems, Milwaukee, WI, USA) and Siemens (Siemens Medical Systems, Iselin, NJ, USA) CT scanners were used in the course of the studies. For all but one of the studies (patient 1, second study used a GE HiQ spiral CT scanner, 120 kVp, 280 mA), the images were acquired during a series of breath holds. The patients were coached in a repeat breath hold technique that returned the kidneys to a reasonably consistent position at resting lung volume. Axial cross-sectional images of the entire length of the kidneys were captured on conventional x-ray film together with calibration markers. After informed consent, fasting subjects were administered iodinated contrast material intravenously over a period of several minutes. The scan procedure was repeated, and images were routinely taken two to five minutes after beginning the contrast infusion in order to optimize the difference in density between the renal cysts and the functioning parenchyma.

Volumetric analysis

Total kidney volume, Vp, and Vc were determined by computer-assisted analysis of contrast-enhanced CT images stored on standard x-ray film. A single operator performed all of the analyses (M.K.) and had no knowledge of the clinical status of the individual from whom the scan was derived. Individual contrast-enhanced CT sections were scanned into a file (Power Macintosh), and the images were analyzed using the NIH Image analysis software package. The perimeter of each kidney was carefully outlined in each slice with an electronic cursor and the enclosed total area (At, cm^2) recorded. The coefficient of variation of 10 repeated measurements of At was 1.5% (intraoperator error). The computer displays

of the contrast-enhanced images were adjusted for contrast and brightness such that the intensity of the contrast material within the parenchyma of the circumscribed area of interest gave a sharp distinction between the light parenchyma and the darker cysts, so that cysts as small as 1 cm in diameter or larger could be readily identified. The area of contrast-enhanced parenchyma within the circumscribed area of interest was determined by density segmentation computer thresh-holding, which yielded the total area of high-density tissue within each renal cross section. The total area of the contrast-enhanced components within the slice was taken to reflect the area of parenchyma (Ap). Ap represents tissue capable of increasing the intensity of the contrast above unenhanced tissue density levels and, after contrast infusion, to levels higher than that of liver, spleen, and skeletal muscle. The coefficient of variation of 10 repeated measurements of Ap was 2.5%. It should be noted that the intrarenal collecting system, including the pelvis, which contained contrast material, was included in the Ap measurement. Thus, in this study, Ap is not strictly an indicator of parenchyma in the classic anatomic sense of the term. Total cyst area (Ac) was assumed to equal to At − Ap. Total volumes for each kidney (Vt, Vp, Vc) were determined in individual subjects according to the method of Breiman et al [11], which sums the region of interest areas (per slice) through the anatomical volume (derived from the measurements of area in 0.5 to 1.0 cm thick contiguous CT sections).

A second set of Vt measurements was made in all 10 of the subjects. However, Vp and Vc measurements could not be made in patients 1 and 2 because of the appearance of hyperdense cysts in the unenhanced scan of the second study [12].

Individual cyst volume

We measured the change in Vt in 19 individual cysts in 7 of the subjects in whom sequential CT scans were performed. We selected only spherical-shaped cysts exceeding 1 cm in diameter that could be visualized in more than one contiguous slice and that could be unequivocally tracked over time by virtue of their unique location within the kidney and juxtaposition to other anatomic markers such as calyces and adjacent cysts. An individual spherical cyst in the last CT scan was identified in respect to its location within the kidney. This cyst was then identified in the preceding scan and confirmed in relation to the adjacent markers. The slices in the initial and follow-up scans were identified in which the diameter of the cyst was maximal. At least three diameters were measured at 60° angles with respect to one another and averaged. The volumes were calculated using the formula, $4/3\pi\ r^3$, where r is equal to one half of the average diameter of the cyst.

Serum creatinine was measured in the hospital laboratory by a generally accepted method, and the creatinine clearance was estimated using the formula of Cockcroft and Gault [13].

Mean, standard deviation, standard error, and linear regression were calculated in the usual fashion, and paired and unpaired *t*-tests were used to determine levels of significance where appropriate. Statistical significance was accepted at two-sided P values <0.05.

RESULTS

General features

Ten patients who had sequential contrast-enhanced CT scans at least three years apart were included in the study (Table 1). This group included six women and four men whose mean ages were 32.7 and 34.5 years, respectively, when the initial CT scans were performed. The average initial creatinine level was 1.09 mg/dL. The average duration between the first and second CT scan was 5.7 years. Eight patients (1–3, 5, 7–10) were hypertensive before the initial scan (persistent elevation of blood pressure >140/90 mm Hg), and two had liver cysts (4 and 6). Patient 1 developed end-stage renal failure shortly before the second scan was performed. In the remaining nine patients, the mean serum creatinine level increased from 1.04 to 1.30 mg/dL between the first and second scan. Five patients (1, 2, 3, 8, and 9) eventually developed end-stage renal disease (ESRD) after a mean interval of 11.2 years following the initial CT scan (Table 1).

Representative contrast-enhanced CT scans used in this study are illustrated in Figure 1. In this subject (patient 5), four sequential scans were obtained over a period of 12.7 years. Three of these sequential scans of each kidney obtained in 1985, 1988, and 1994 are shown in Figure 1 to illustrate the CT technique and some obvious changes in kidney and cyst size. (Between 1988 and 1994, an extensive cyst reduction surgical procedure was conducted on the right kidney. Consequently, only the 1985 and 1988 scans are included in the data analysis of the current study. This patient was also excluded from the analysis of kidney function outcome. The follow-up serum creatinine level in Table 1 was drawn after the second scan in 1988.) The degree of parenchymal contrast enhancement varied from scan to scan because a uniform time point was not always used to obtain images after the infusion of contrast was begun. Nonetheless, in each example, the density of the renal parenchyma was higher than that of the liver, skeletal muscle, and intrarenal cysts. These scans also demonstrate the significant change in volume of some of the individual cysts within the kidneys.

Morphometric analysis of area and volume components

We included patients in whom CT studies had been done at least three years apart. This limit was chosen

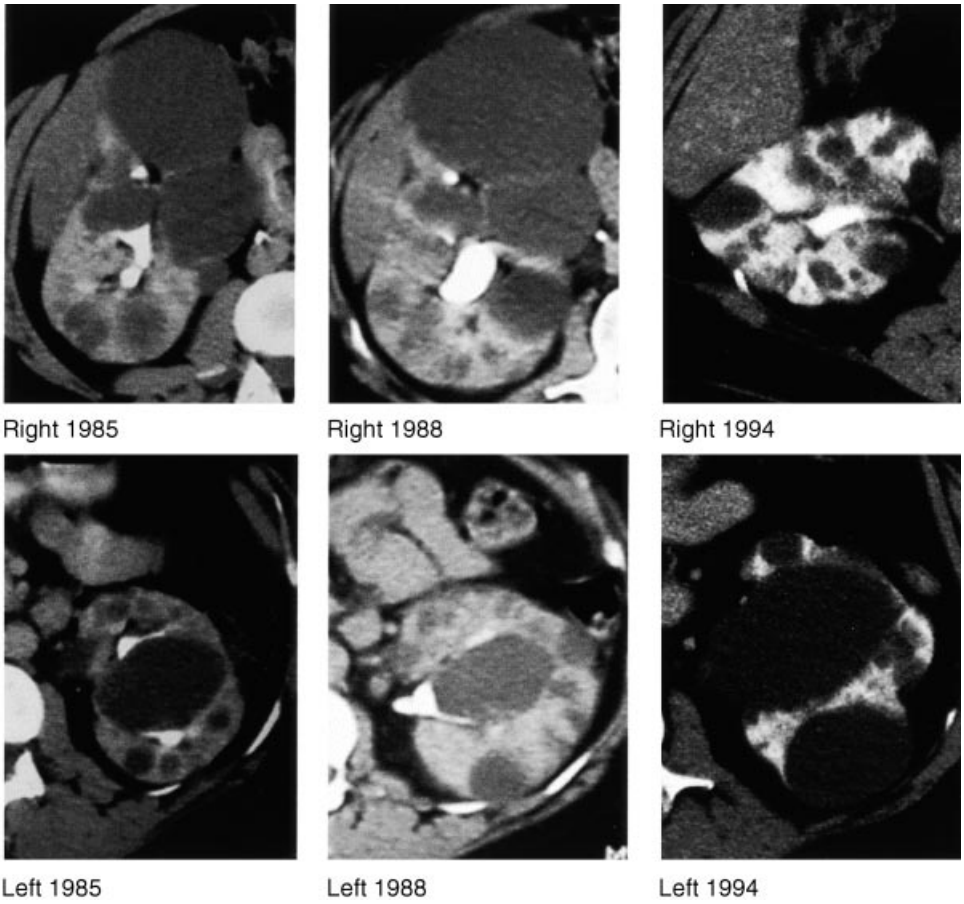

Fig. 1. Sequential contrast-enhanced computed tomography (CT) scans obtained in patient 5. Cross-section slices were obtained at approximately the same locations within individual kidneys. These scans illustrate the accumulation of contrast within the parenchyma to levels exceeding that of liver, skeletal muscle, and intrarenal cysts. Note the enlargement of the large spherical cyst on the anterior surface of the right kidney between 1985 and 1988. In 1992, an operation was performed at the University of Oregon Health Sciences Center on the right kidney to remove cysts and decrease the overall size. Cyst decompression in the right kidney was evident two years later (Right, 1994). In contrast, the unoperated left kidney enlarged progressively from 1985 to 1994.

because preliminary estimations of kidney volume using CT and ultrasound determinations of length, width, and height indicated that renal volume in the larger cohort of patients would enlarge approximately 10 to 50 mL/year (unpublished observations of the authors). We reasoned that errors in renal position introduced by the repeated breath hold technique would be proportionately less significant the larger the change in absolute cyst and kidney volume between the two scans. Assuming a mean kidney volume of 500 mL, the anticipated increase in average size over three years would be expected to fall into a range between 6 and 30%.

We evaluated changes in kidney volume components due to cysts and parenchyma in two ways: Mean cyst to total kidney area ratios were determined in contiguous axial slices, and three-dimensional measurements of total kidney and Vcs were derived from contiguous axial slices along the complete length of the kidney.

Ratio of cyst to total kidney areas. This sampling method determines the ratio of cyst to total kidney areas (Ac/At, fractional cyst area) in selected individual, contiguous kidney slices from a specific region of the kidney. In this instance, the center of the kidney served as the point of reference, and equal numbers [5] of "samples" were selected on either side of center (10 total slices). It was further assumed that the center of the kidney remained relatively constant from year to year. Since this is a sampling method, small changes in renal position, as might occur with multiple breath holds, would not influence the results to the same extent as in the three-dimensional volume method. For this analysis, 10 contiguous CT slices were selected from the central region of each kidney in the first and second CT scans in the eight patients with repeated contrast-enhanced scans (Table 2). Ac/At increased in 13 of 16 kidneys. The average increase in fractional cyst area was 0.098 ± 0.025 ($P < 0.01$).

Three-dimensional volume method. In this method, volume elements determined from all contiguous CT

Table 2. Fraction of mean cross-section kidney area (At) composed of cysts (Ac)

Patient #	Kidney	Initial CT scan Ac/At[a] SE	Follow-up scan Ac/At[a] SE	Change follow-up − initial Ac/At
3	Left	0.561 ± 0.023	0.646 ± 0.040	0.085
	Right	0.429 ± 0.017	0.424 ± 0.018	−0.005
4	Left	0.314 ± 0.032	0.422 ± 0.034	0.108
	Right	0.392 ± 0.015	0.617 ± 0.038	0.225
5	Left	0.642 ± 0.028	0.608 ± 0.036	−0.034
	Right	0.640 ± 0.050	0.671 ± 0.040	0.031
6	Left	0.252 ± 0.019	0.395 ± 0.027	0.143
	Right	0.257 ± 0.017	0.331 ± 0.024	0.074
7	Left	0.387 ± 0.037	0.421 ± 0.055	0.034
	Right	0.169 ± 0.033	0.175 ± 0.025	0.006
8	Left	0.541 ± 0.034	0.538 ± 0.018	−0.003
	Right	0.450 ± 0.026	0.481 ± 0.035	0.031
9	Left	0.484 ± 0.023	0.723 ± 0.038	0.239
	Right	0.409 ± 0.018	0.711 ± 0.020	0.302
10	Left	0.366 ± 0.027	0.538 ± 0.027	0.172
	Right	0.440 ± 0.021	0.594 ± 0.034	0.154
	Mean	0.421	0.518	0.098
	SD	0.135	0.151	0.100
	SE	0.034	0.038	0.025

[a] Mean of 10 axial slices distributed equally (5 each) on either side of center

slices were summed to give the total kidney volume. Vt, measured in all 10 patients on two occasions, increased in 18 of 20 kidneys. The average Vt increased from 561 to 884 mL (323 ± 79 mL, $P < 0.01$, corresponding to an average rate of volume increase of 53.9 ± 10.1 mL/year/kidney, $P < 0.001$; Table 3). In patients 3 through 10 in whom Vc and Vp could be determined in the second scan, mean Vt increased from 458 ± 55 to 669 ± 95 mL (211 ± 58, $P < 0.005$), corresponding to an average rate of volume increase of 45.0 ± 12.3 mL/year/kidney ($P < 0.005$). The major component of this increase was due to the expansion of the Vc from 219 ± 23 to 405 ± 73 mL (185 ± 52, $P < 0.005$), corresponding to an average rate of Vc increase of 38.9 ± 10.4 mL/year/kidney ($P < 0.005$). The increase in Vc accounted for the majority of the increase in kidney volume (185/211 × 100 = 87.6%). Vp increased in 12 and decreased in 4 kidneys. The average Vp increase of 26 ± 11 mL corresponded to an average rate of volume increase of 6.1 ± 2.9 mL/year/kidney; neither value reached statistical significance. We estimate that inclusion of the intrarenal collecting system in the Vp determination may have inflated these measurements by as much as 25 to 75 mL per kidney. We have assumed, based on their appearance in these scans, that the collecting system contributions to Vp in individual patients remained relatively constant between the first and second scans. Vc/Vt was also determined from the data in Table 3. For patients 3 through 10, the mean Vc/Vt determined by the three-dimensional volume method increased from 0.441 ± 0.044 to 0.552 ± 0.044, which is in good agreement with the fractional cyst area changes (Ac/At) determined with the sampling method in Table 2.

Symmetry of kidney enlargement

To determine the extent to which polycystic kidneys enlarge symmetrically, we compared the Vt of left and right kidneys in 10 patients over the interval between the first and second CT scan (Table 3 and Fig. 2). There was considerable variability in kidney size within and among patients, but as illustrated in Figure 2 by the slope of the linear regression plot near unity and the intercept near zero, there was no systematic enlargement of one kidney greater than the other. The average rates of kidney enlargement of 4.3 ± 1.1 mL/month for the left and 4.7 ± 1.5 mL/month for the right were not different.

Relationship between age and kidney volume

Clinical observation suggests that kidney volume increases with age. To quantitate this relationship, we plotted the relationship between Vt and age in all 20 kidneys that were studied on two occasions by CT (Fig. 3). As shown previously in Table 3, kidney volume increased at vastly different rates in different patients. Figure 3 also suggests that the subjects may be separated into two general groups based on the rate of volume increase: those whose kidneys enlarge at a relatively rapid rate and those in whom kidney enlargement is barely perceptible. Although the number of patients analyzed is too small to make any sweeping conclusions, Figure 3 suggests that about one half of the patients had a more aggressive form of the disease than the remainder.

Sequential measurements of individual cyst volumes

The mean diameters (range 1.1 to 8.3 cm) of 19 individual cysts in 7 patients (patients 4 through 10) were measured at least twice over an average time interval of 5.7 years (Fig. 4). The rate of increase in the volumes of individual cysts was highly variable as was the case for total kidney volume. The average rate of cyst enlargement was 0.52 ± 0.21 mL/month ($P < 0.025$, range 0.02 to 4.15 mL/month). In patient 5, three sequential measurements were made in two cysts over an interval of 38 months. In these two cysts, the rate of enlargement appeared to accelerate.

Prognostic indicators of ESRD at first CT scan

We evaluated the potential utility of absolute kidney volume, the rate of increase in kidney volume and the initial fractional Vc (Vc/Vt determined from the three-dimensional volume method) as indicators of future end-stage renal failure (Fig. 5). It should be noted that for the evaluation in Figure 5, the respective Vc and Vt values were combined for the left and right kidneys, and the ratio of these combined volumes was taken to represent the mean Vc/Vt for the individual patient.

Table 3. Changes in total (Vt), parenchymal (Vp), and cyst (Vc) volumes[a] of individual kidneys between initial and follow-up measurements

Patient #	Kidney	Initial CT scan, *mL*			Follow-up CT scan, *mL*			Follow-up − initial, *mL*			Rate of volume change *mL/year/kidney*		
		Vt	Vp	Vc	Vt	Vp	Vc	Vt	Vp	Vc	Vt	Vp	Vc
1	Left	1113	256	857	2179			1066			89.6		
	Right	837	320	517	2019			1182			99.3		
2	Left	807	250	557	1328			521			104.2		
	Right	1126	219	907	1442			316			63.2		
3	Left	790	346	444	920	342	578	130	−4	134	28.3	−0.9	29.1
	Right	472	270	202	447	241	206	−25	−29	4	−5.4	−6.3	0.9
4	Left	293	192	101	397	210	187	104	18	86	22.1	3.8	18.3
	Right	329	193	137	611	225	387	282	32	250	60.0	6.8	53.2
5	Left	518	210	308	717	280	436	199	70	128	60.3	21.2	38.8
	Right	834	234	600	1248	361	887	414	127	287	125.5	38.5	87.0
6	Left	192	141	51	291	164	127	99	23	76	14.8	3.4	11.3
	Right	194	140	54	242	160	82	48	20	28	7.2	3.0	4.2
7	Left	260	145	115	320	160	160	60	15	45	9.8	2.5	7.4
	Right	193	162	30	207	174	33	14	12	3	2.3	2.0	0.5
8	Left	324	141	183	311	144	167	−13	3	−16	−2.8	0.7	−3.5
	Right	531	289	242	535	266	269	4	−23	27	0.9	−5.0	5.9
9	Left	529	279	250	1006	286	721	477	7	471	90.0	1.3	88.9
	Right	452	270	182	1236	350	886	784	80	704	147.9	15.1	132.8
10	Left	639	382	257	1156	467	689	517	85	432	103.4	17.0	86.4
	Right	781	428	353	1066	405	661	285	−23	308	57.0	−4.6	61.6
Mean		561	243	317	884	265	405	323	26	185	53.9	6.2	38.9
SE		65.7	18.6	57	129	25	73	79	11	52	10.1	2.9	10.4

[a] Determined from summation of all CT volume elements between cephlad and caudad poles of kidneys

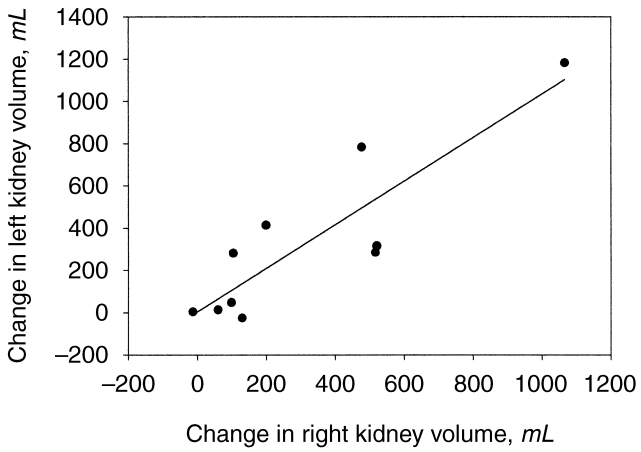

Fig. 2. Relationship between change in total kidney volume (Vt) of right and left kidneys in 10 ADPKD patients studied on two separate occasions. Regression line is as follows: (left kidney, mL) = 4.5 mL + 1.03 × (right kidney, mL); $r^2 = 0.77$, $P < 0.01$.

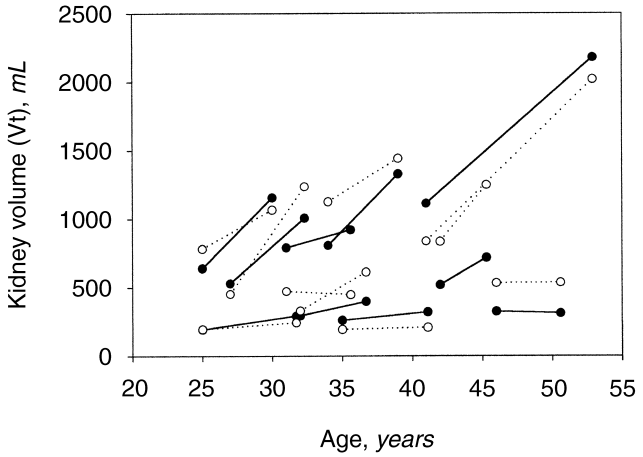

Fig. 3. Relationship between age and kidney volume, Vt, for individual kidneys studied on two occasions. Symbols are: (●) left; (○) right.

Patient 5 was excluded from this analysis because, as illustrated in Figure 1, one of the kidneys was operated on to reduce the Vc and the potential impact on outcome is uncertain.

For each of the indicator measurements, the patients were divided into two groups: those who required dialysis or transplantation by the time of this report and those whose who did not. In the dialysis group (patients 1 through 3, 8, and 9), the mean age at the first CT scan was 35.8 years, and the total follow-up period beyond the initial CT scan study averaged 11.2 years (Table 1). In the four patients that did not require dialysis, the mean age at the initial CT scan was 29.3 years, and the total follow-up averaged 8.7 years. In this latter group, the most recent serum creatinine levels were all <1.5 mg/dL. Initial kidney volume appeared greater in the dialysis-treated group than in the group that did not reach end stage, but the difference between them was not statistically significant. The rate of kidney enlargement was also greater in the dialysis-treated group than in the group that did not reach end stage, but the difference between them was not statistically significant either. On the other hand, the initial fractional Vc, Vc/Vt, was

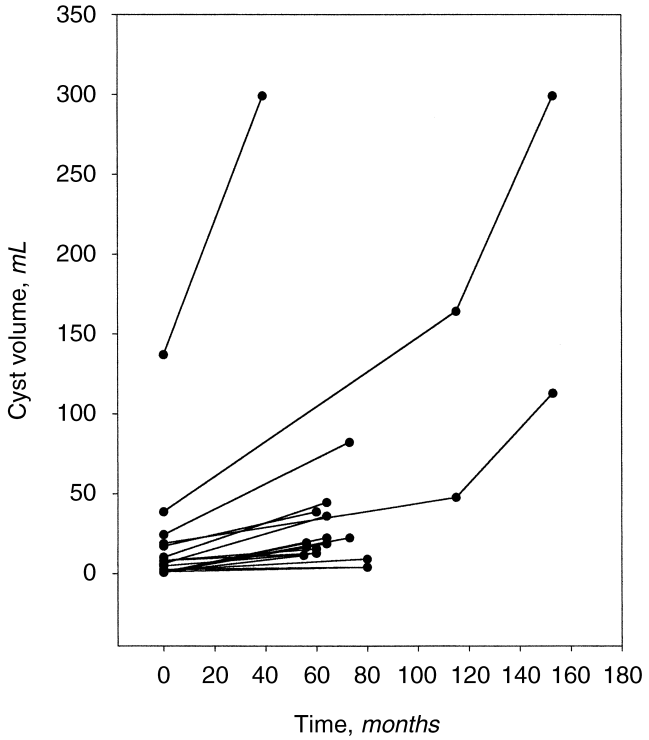

Fig. 4. Sequential determinations of volume in individual cysts (discussed in the main body of the text).

consistently higher in the dialysis-treated than in the untreated group, and this difference was statistically significant ($P < 0.02$). Based on this preliminary analysis of a small group of subjects, it would appear that Vc/Vt values greater than about 0.43 (Fig. 5) may portend an adverse functional outcome. It should be noted that determination of Ac/At in kidney samples as discussed in the **Methods** section (Table 2) gave similar results to those for Vc/Vt displayed in Figure 5.

DISCUSSION

This retrospective study confirms in quantitative terms the long-held views that among individuals with ADPKD, the kidneys enlarge at vastly different rates and that this increase is due largely to the accumulation of fluid within cysts. Furthermore, the current study demonstrates that CT scans stored on conventional x-ray film are an important resource for the determination of renal volume components and possibly of prognosis. These findings must be weighed, of course, against the fact that the scans examined in this study were performed before the installation of fast CT (spiral) and magnetic resonance scanners, and may have been subject to quantization errors secondary to respiratory motion artifacts and changes in the display of contrast-enhanced parenchyma during repeated breath hold maneuvers [9, 14]. However, because we examined only subjects in whom CT scans had been performed long enough apart to encompass relatively large changes in cyst and kidney volumes, we think we have diminished the likelihood that the observed changes are a consequence of systematic errors related to kidney motion or position.

We had to contend with other potential sources of error in the determination of Vt, Vp, and Vc based on three-dimensional methods. In early generation CT scanners, slice thicknesses of 10 mm were commonly used to decrease the number of breath holds and to reduce radiation exposure. Cysts smaller that 10 mm in diameter are common in ADPKD, and it is likely that some were undetected. The blurring of contrast margins about cysts owing to partial volume effects and signal noise can also contribute to error [9, 14]. However, most of the problems related to the uncertainty of renal or cyst position in archival scans was diminished by using an alternative sampling technique in which the fractional areas of cysts and parenchyma were determined throughout a specified region of the kidneys. To determine a mean Ac/At profile for each kidney, we analyzed 10 contiguous slices distributed equally on either side of center in the longitudinal plane (Table 2). These measurements showed that the fractional area of cysts increased in 13 of 16 kidneys by a mean of 9.8%, confirming the general conclusion derived from the volumetric determinations that the increase in renal size was due to an increase in the volume fraction of cysts.

In the context of the current study, Vp represents the renal mass components that are enhanced by contrast material. While it is reasonable to assume that most of this mass is comprised of functioning renal tubules and vascular components, the renal collecting system and interstitial components, including inflammatory infiltrates and fibrous material, that separate adjacent renal tubules would also be included in this component as well. Hyperdense cysts would be included as parenchyma as well, although in this study, we excluded those cases in which hyperdense cysts were prominently displayed in unenhanced CT scans. Although it may have been slightly overestimated because of the minimum 10 mm slice thickness used in this study, the finding that Vp determined in most of the patients fell within the upper range of normal values for kidney weight (volume) [15, 16] suggests that the three-dimensional method used registers a reasonably close approximation of this volume component (Table 3). Vp remained relatively unchanged over the interval between the two CT scans, with the exception of patient 5, in whom Vp increased significantly in both kidneys with no apparent explanation.

The current assessment in archival material is in general agreement with a recent prospective study in which fast electron beam computerized tomography (EBCT) was used to evaluate the course of kidney enlargement

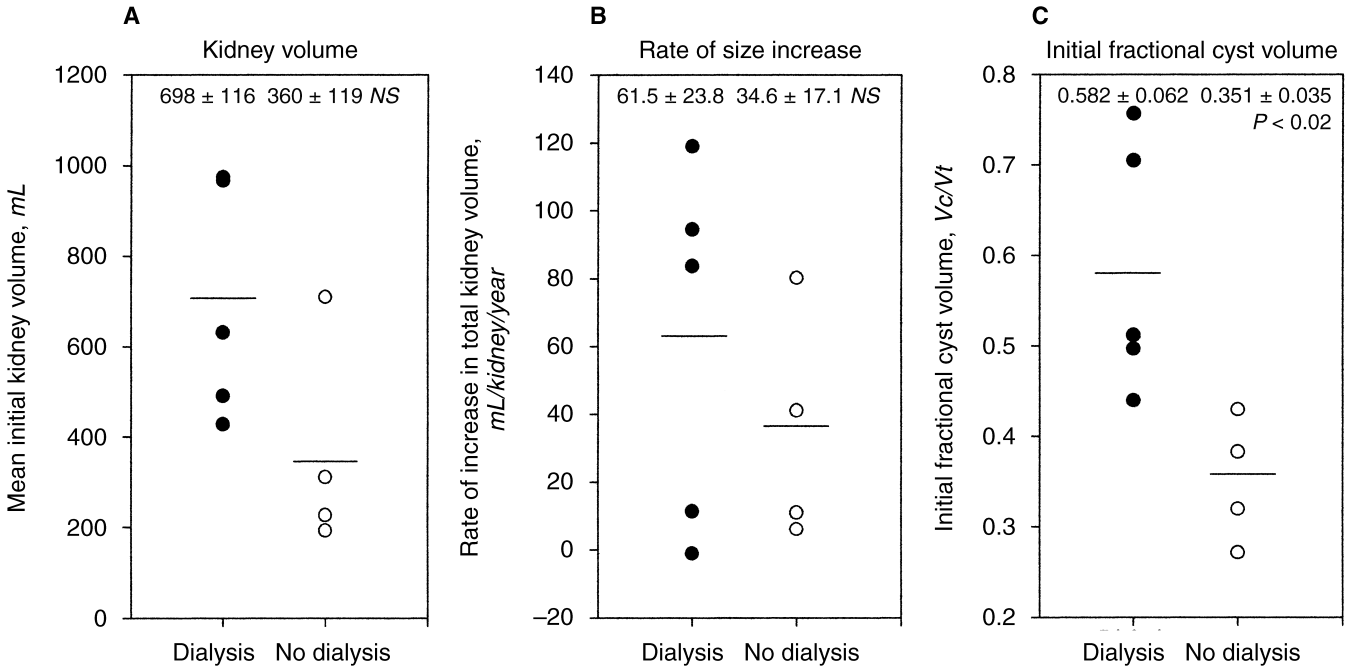

Fig. 5. Relationship between the initial kidney volume (*A*), rate of kidney volume increase and initial fractional cyst volume (*B*), and functional outcome (*C*).

in nine ADPKD subjects who were restudied over an eight-year interval [9]. The superiority of the EBCT method, which enables scanning of entire renal volumes in a single breath hold and direct computer analysis of original digital image data, in comparison to the current study is unquestioned. Nonetheless, the quantitative data determined in the EBCT and in the current study were remarkably similar. In the EBCT study, kidney volume increased in 8 of 9 subjects, and the mean rate of increase was 24 mL/year/kidney. This rate of kidney enlargement is of the same order of magnitude found in the current study in which total kidney volume increased in 9 of 10 patients at a mean rate of 53.9 mL/year/kidney. The higher rate of enlargement in the current study may be related to the fact that in the Mayo Clinic study the cases were studied prospectively without regard to symptoms, whereas in the current report, the patients were often re-examined for clinical evaluation (Table 1). The increase in fractional Vc (Vc/Vt) in the EBCT study was 2.0% per year. In the current study, fractional Vc, determined with both the three-dimensional volume and area sampling methods, increased 1.96% per year. Thus, the archival CT scans appeared to yield volumetric data that agreed rather well with a newer and improved technology.

The major contributor to the increase in renal volume was the accumulation of fluid within the cysts. There was considerable renal size asymmetry within individual patients, although for the group as a whole neither kidney was systematically larger than the other (Fig. 2). This finding suggests that random, localized intrarenal factors may be important in determining the rate at which individual cysts enlarge within polycystic kidneys. Were cyst enlargement dependent entirely on humoral factors, one might expect uniform enlargement to be the rule rather than the relatively uneven process demonstrated for individual kidneys and individual cysts in this study. We think that the asymmetry of cyst development and enlargement is an important clue to the pathogenesis of progression in this disease and a fruitful area for future study.

The cysts in ADPKD are lined by a single layer of cells that derive from renal tubular epithelium [4]. Sustained proliferation of these cells and the accumulation of fluid within the potential space created by this mural expansion are major pathogenetic elements in the enlargement of polycystic kidneys. Thus, the rate of cyst enlargement determined in contrast-enhanced CT scans reflects two apparently coordinated processes: cellular proliferation and fluid accumulation. The rate of overall kidney enlargement varied widely among patients (Tables 2 and 3 and Figures 2–5), a feature that was also reflected in the wide range of volume increases observed in individual cysts (Fig. 4). A unique feature of the current study that bears on the mechanisms of cyst expansion is the sequential measurement of volume in individual renal cysts. Some cysts enlarged relatively rapidly, whereas others appeared dormant. In two of the cysts, we were able to make three sequential measurements of volume. As shown in Figure 4, the rate of cyst growth in these

cysts increased between the second and third measurement of Vc. This finding supports the view that fluid accumulated in those cysts by a nonlinear mechanism that increased as the surface area of the cysts increased. This is the type of volume increase that would be predicted were transepithelial secretion the principal mechanism of fluid accumulation, rather than simple trapping of unreabsorbed glomerular filtrate [17]. Thus, future studies to monitor specifically with slices narrower than 10 mm the size of individual cysts in larger numbers than reported here will be useful for determining the effects on fluid accumulation of pharmacologic agents that inhibit net fluid secretion.

Two additional points can be made based on the increase in individual Vcs noted in Figure 4: (*1*) the rate of increase in cyst wall surface area, a reflection of the rate of proliferation of the mural epithelial cells, is relatively slow in ADPKD (although renal cysts may be regarded as neoplastic [4], they are relatively slow-growing neoplasms for the most part), and (*2*) the rate of transepithelial fluid secretion into the cysts that have no other apparent source of fluid is relatively low. For example, if it is assumed that the cyst with the fastest rate of volume increase in Figure 4 had no afferent tubular connection and, consequently, no source of glomerular filtrate, the transepithelial fluid secretion rate, determined from the increase in volume in relation to surface area, would be approximately 0.045 $\mu L/cm^2$/hour. This rate is much lower than the average rate of fluid secretion (0.38 $\mu L/cm^2$/hour) observed in intact cysts dissected from human polycystic kidneys and maximally stimulated with forskolin (which increases intracellular cAMP) [18–20]. It is conceivable, therefore, that in situ cysts may experience periods of relatively rapid expansion interspersed with periods of more sluggish growth.

The diversity in the rates of in situ cyst enlargement is consistent with studies in renal cell culture and animal models of renal cystic disease that implicate hormones, autocrine, and paracrine factors in determining the rate of cell proliferation and fluid accumulation [4, 21]. It is possible that in patients with relatively rapid rates of cyst and kidney expansion renal enlargement may be driven by extracystic factors that regulate the rates of epithelial proliferation and transepithelial fluid secretion. A recent study suggests, for example, that interleukin-1β, a product of inflammation, may stimulate the secretion of chloride and fluid by renal epithelial cells [22]. Focal or diffuse inflammation in polycystic kidneys could create an environment conducive to an accelerated rate of cyst enlargement.

"Progression" in ADPKD can be viewed in two different contexts: progressive discomfort and cosmetic problems caused by massive renal enlargement and progression to renal insufficiency [1, 4–7, 23–26].

Progressive discomfort and cosmetic problems caused by massive renal enlargement

In some patients, the enlargement of polycystic kidneys is associated with unrelenting pain and a feeling of abdominal fullness. Hypertension and renal hemorrhage are more common in patients with greatly enlarged kidneys, and the cosmetic disfiguration can be upsetting. In this respect, measures to control renal enlargement in those with relatively rapid increases in kidney size could provide important symptomatic relief and possibly diminish other symptoms and signs of the disease. Thus, it might be reasonable to consider patients with rapidly increasing renal size for cyst reduction procedures to allay symptoms and, thereby improve their quality of life. Although surgical reduction of Vc had no appreciable bearing on the course of renal dysfunction in a small prospective study of patients with advanced disease, the comfort level of the patients was greatly improved [27, 28]. Determining the rate of kidney enlargement earlier in the course of the disease might reveal individuals who would benefit from cyst reduction procedures before the volume fraction of cysts exceeded an irreversible limit.

Progression to renal insufficiency

Not all patients with polycystic kidney disease progress to end-stage renal failure [29]. Consequently, there is considerable interest in finding surrogate markers of polycystic kidney disease that will monitor progression and predict future outcome. Kidney volume, on the face of it, would seem to be a reasonable candidate for such a marker. One study that utilized quantitative volumetric CT to evaluate kidney enlargement in postmenopausal women over a one-year interval found that total renal volume and creatinine clearance did not change significantly [8]. On the other hand, the current study and a recent report based on sequential CT volume measurements in both men and women over intervals greater than three years demonstrated increases in total renal volume in most of the subjects, although the rates of enlargement varied widely among individuals [9]. Thus, in patients at higher risk for pronounced kidney enlargement and deterioration in function than postmenopausal women, sequential measurements of total renal volume may uncover at a relatively early stage those patients who are destined to develop massively enlarged kidneys and progress to renal failure.

In the current study of a relatively few patients, we examined three factors that may forecast an unfavorable prognosis for the duration of life-sustaining renal function. The initial volume of the kidneys and the rate of kidney enlargement were not significantly correlated with outcome, possibly because the number of subjects was relatively small. On the other hand, in those patients destined to develop end-stage renal failure the fractional

Vc (Vc/Vt) determined at the initial CT scan was significantly greater in those who eventually developed renal failure than in those who did not progress to renal insufficiency. Patients with initial Vc/Vt values greater than 0.43 developed ESRD, whereas those with values lower than this did not. This finding suggests there may be a threshold above which fractional Vc triggers elements leading to progressive loss of functioning parenchyma.

Obviously, additional studies in larger numbers of age- and gender-matched patients will be needed to verify these preliminary findings. In this regard, the new generation of magnetic resonance imaging scanners would seem to be especially well suited for this type of prospective investigation. If our initial observations are confirmed, it would mean that a nonazotemic ADPKD patient with a Vc/Vt greater than 0.43 has less than approximately 11 years before the kidneys fail, barring intercurrent problems such as renal infection, obstructing stone, or renal infarction, which could accelerate the process. Conversely, patients with lower Vc/Vt values and reasonably normal creatinine clearances may have a more favorable prognosis.

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