Quantification and Longitudinal Trends of Kidney, Renal Cyst, and Renal Parenchyma Volumes in Autosomal Dominant Polycystic Kidney Disease

BERNARD F. KING, JUDD E. REED, ERIK J. BERGSTRALH, PATRICK F. SHEEDY II, and VICENTE E. TORRES
Mayo Clinic/Mayo Foundation, Rochester, Minnesota.

Abstract. The aims of this study were to assess the accuracy and reproducibility of volumetric determinations of total kidney, renal cyst, and renal parenchymal volumes, using fast electron-beam computerized tomography scanning, and to determine the rate of change of these volumes. Nine patients with autosomal dominant polycystic kidney disease (ADPKD) and serum creatinine ≤ 1.3 mg/dl and/or an initial iothalamate clearance ≥ to 60 ml/min per 1.73 m^2 were imaged weekly over a 3-wk period (total of 3 times). Approximately 8 yr later, they returned for follow-up studies. The kidney volume estimation technique involved a manual segmentation (perimeter drawing) of the kidneys and a semiautomatic threshold approach, using a histogram analysis of the peak densities of renal parenchyma and renal cysts. At entry, total kidney and renal cyst volumes correlated positively with age, while renal parenchymal volumes and GFR correlated negatively with age. The average coefficient of variation values for the three initial consecutive measurements of total kidney, renal cyst (actual and as a percent of total volume), and renal parenchymal volume were 3.4, 7.2, 5.3, and 5.6%, respectively. During the 8 yr of follow-up, total kidney and renal cyst volumes increased, while renal parenchymal volumes and GFR declined. The rate of increase in total kidney and renal cyst volumes varied markedly from patient to patient. There was a significant correlation between rate of increase in renal cyst volume and the rate of decline in GFR. The patients with an initial urine protein/osmolality ratio >0.13 mg/L per mosmol per kg had a significantly higher increase in renal volume and decline in GFR than those with a lower ratio. In summary, the results of this pilot study suggest that: (*1*) electron-beam computerized tomography is capable of measuring total kidney, renal cyst, and renal parenchymal volumes reproducibly; (*2*) total kidney and renal cyst volumes increase, while parenchymal volumes decrease with time; (*3*) the increase in cyst volume correlates best with the decline in renal function; and (*4*) renal volumes appear to be good surrogate markers for disease progression in ADPKD.

Autosomal dominant polycystic kidney disease (ADPKD) affects approximately 1 in 400 to 1 in 1000 individuals and is the most common single cause of end-stage renal failure after diabetes mellitus and hypertension in the United States (1,2). Recent studies in animal models suggest that the progression of ADPKD may be affected by treatment (reviewed in reference (3). Obstacles to the design of clinical trials are the protracted course, the late occurrence of the decline in GFR, and the lack of a satisfactory understanding of the mechanisms of progression of ADPKD before the development of renal insufficiency (3). Recent studies suggest that interstitial inflammation and fibrosis, renal microvascular disease, and apoptosis of tubular epithelial cells contribute significantly to the progression of this disease (4–9). Whether these processes occur as a result of, in parallel to, or independently from cyst expansion is unknown.

With the improvement of current imaging techniques (computerized tomography [CT], ultrasonography [US], and magnetic resonance [MR]), accurate volume determinations of cystic and noncystic tissue within the kidney have become possible (10–14). Technical difficulties caused by respiratory motion can now be avoided by the rapid acquisition of the necessary transaxial sections in a single breathhold. This study was conducted to assess the accuracy and reproducibility of volumetric determinations of total kidney, renal cyst, and renal parenchymal volumes, using fast electron-beam CT (EBCT) scanning, and to determine the rate of change of these volumes.

Materials and Methods

Patient Population and Study Design

This study was performed in nine patients with ADPKD and an initial serum creatinine ≤ 1.3 mg/dl and/or an initial iothalamate clearance ≥ 60 ml/min per 1.73 m^2. Four of the patients were men and five were women. The patients were imaged weekly over a 3-wk period (total of 3 times) using the same breathhold EBCT technique each time. Approximately 8 yr after these initial studies, they returned for a follow-up EBCT scan using the same technique, measurement of renal volumes, and reevaluation of renal function. In one of the

Received October 29, 1999. Accepted January 18, 2000.
Correspondence to Dr. Vicente E. Torres, Internal Medicine and Nephrology Research, Mayo Clinic, Eisenberg S-24, 200 Frist Street SW, Rochester, MN 55905. Phone:507-284-3588; Fax: 507-284-0944; E-mail: torres.vicente@mayo.edu
1046-6673/1108-1505
Journal of the American Society of Nephrology

patients, only measurements of total kidney volume were possible at follow-up because he declined the administration of intravenous contrast. The study was approved by the Mayo Institutional Review Board, and the patients gave informed written consent.

EBCT Scanning Technique

Single breathhold EBCT scanning (electron-beam CT, Picker Corp., Cleveland, OH) was used to eliminate the problems created by respiratory or other patient motion (10–13). EBCT examinations of the patients began 90 s after starting an intravenous injection of contrast material at a rate of 2 cc/s (Conray 60; 282 mg I/ml, 200 ml). The scans were obtained during one breathhold while the patient suspended respiration at resting lung volume. All scanning was performed at 130 kilovolt peak, 598 milliamperes, 600 ms, 40 cm field of view, 512 × 512, slice thickness 6 mm at a table increment of 6 mm, and at an acquisition time of 0.4 s per slice. Reconstructed transaxial slices were stored on magnetic tape and analyzed on an off-line work station. Volumes were determined from image data, using an off-line Sun system and software developed by one of the authors (J.E.R., see below).

Volumetric Analysis

Individual (right and left) and total kidney, renal cyst, and renal parenchymal volumes were measured and percent cyst volumes were calculated. The renal volumes presented are the sum of the volumes in the two kidneys. The kidney volume estimation technique used a manual segmentation (perimeter drawing) of the kidneys with exclusion of the collecting system and a computer-generated summation of voxel volumes in each kidney. Estimations of renal cyst volumes were obtained by a semiautomatic threshold approach, using histogram analysis of the peak densities of renal parenchyma and renal cysts. Voxels at the margins of the cyst wall were automatically assigned to the cyst volume or parenchymal volume according to their proximity to the nearest peak (cyst or parenchyma) on the histogram. This method allows for a consistent and accurate method for defining cyst/parenchyma interfaces and minimized variation due to partial volume effects and image noise. Renal parenchymal volumes were estimated by subtracting the renal cyst volumes from the total kidney volumes. To assess the accuracy and reproducibility of the measurements before studying the patients, we used a phantom consisting of ping-pong balls filled with saline immersed in a beaker of saline mixed with contrast media. Scans using the same imaging parameters were performed with the beaker placed directly on the patient couch and with the beaker immersed in a large water phantom to more closely simulate patient attenuation. The actual simulated kidney and cyst volumes were 938 and 158 ml, respectively. The actual fraction of simulated cyst volume (ping-pong balls) was 20.3%. Areas were determined by analysis of the histogram of fixed intensities. The measured values by the EBCT technique differed from the actual values by only 2%.

Evaluation of Renal Function

A measurement of serum creatinine and a urinalysis of a first-voided morning specimen, including a determination of osmolality and protein concentration with pyrogallol red molybdate reagent (15), were obtained on all of the patients at the start and completion of the study. GFR values at the start and completion of the study were determined by the clearance of iothalamate in six patients and estimated from the serum creatinine levels using the Cockcroft and Gault formula in three patients (16).

Statistical Analyses

Reproducibility in renal volumes was assessed by calculating the within-patient coefficients of variation ([SD/mean] × 100) based on the three initial CT images. Within-patient annual rates of change in renal volume and GFR were estimated based on slopes from the initial and 8-yr measurements. Associations between continuous factors (GFR, renal volume, age, rates of change in GFR, and renal volume) were assessed using Spearman rank correlation coefficient. All tests were two-sided with P values ≤ 0.05 considered statistically significant.

Results

Patient Characteristics at Entry

The gender, age, body surface area, renal volume measurements, GFR, and proteinuria values at entry and at the end of the study are summarized in Table 1. No significant difference was detected between right and left renal volumes. The ratio of right to left renal volumes in these patients ranged from 0.47 to 1.28 (mean ± SD, 0.94 ± 0.28). Total kidney and renal cyst volumes correlated positively with age, while renal parenchymal volume and GFR correlated negatively with age (Table 2). Correction of renal volume measurements for body surface area did not affect these correlations.

Reproducibility of the Initial CT Volume Measurements

The average (of nine patients) coefficients of variation for the three initial consecutive measurements of total kidney, renal cyst, and renal parenchymal volumes, as well as of the relative cyst volumes (as percent of total kidney volume) over a 3-wk period were 3.4, 7.2, 5.6, and 5.3%, respectively.

Changes in Renal Volumes over Time

Volume measurements 8 yr after the initial studies revealed that the total kidney volumes (Figure 1), as well as the absolute and relative (percent of total) cyst volumes, were consistently higher, whereas the parenchymal volumes were lower (Table 3). Nevertheless, the rates of change of renal cyst and renal parenchymal volumes were not significantly correlated ($r = -0.21$, not significant). The average annual rates of change in total renal volume, cyst volume, parenchymal volume, and in

Table 1. Characteristics of nine ADPKD patients at initial visit[a]

Characteristic	Mean	SD	Range
Male/female	4/5		
Age (yr)	36.6	9.2	21 to 50
BSA (m^2)	1.96	0.34	1.60 to 2.60
Kidney volume (ml)	1193	453	569 to 1985
Cyst volume (ml)	706	487	114 to 1756
Parenchymal volume (ml)	491	190	228 to 886
Cyst/kidney volume × 100	54	21	20 to 88
GFR (ml/min per 1.73 m^2)	91.4	16.1	62 to 113
Proteinuria (yes/no)	3/6		

[a] ADPKD, autosomal dominant polycystic kidney disease; BSA, body surface area.

Table 2. Correlations of renal volumes and GFR with age in nine ADPKD patients at initial visit[a]

Parameter	Value
Renal volume (ml)	0.77 (0.015)
Cyst volume (ml)	0.91 (<0.001)
Cyst percent (%)	0.83 (0.006)
Parenchymal volume (ml)	−0.48 (0.18)
GFR (ml/min per 1.73 m^2)	−0.73 (0.027)

[a] Tabled values are Spearman rank correlation coefficients (*P* value for test of correlation significantly different from zero).

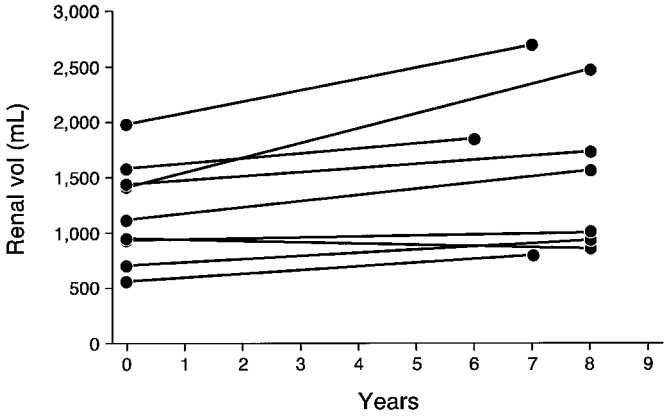

Figure 1. Change in total kidney volume in nine patients with autosomal dominant polycystic kidney disease (ADPKD) throughout the study period.

Table 3. Yearly rate of changes in renal volumes and GFR

Parameter	Mean	SD	Range
Kidney volume (ml)	48.0	44.5	−11.2 to 132.2
Cyst volume (ml)	51.0	47.6	−9.7 to 128.6
Parenchymal volume (ml)	−10.4	26.8	−66.1 to 21.4
Cyst/kidney volume × 100	2.0	2.1	−0.1 to 5.0
GFR (ml/min per 1.73 m^2)	−2.79	2.80	−9.40 to 0

cyst volume as a percent of total renal volume were 48.0, 51.0, −10.4, and 2.0%, respectively (Table 3). The rate of increase in renal size varied markedly from patient to patient, ranging from −11.2 to 132.2 ml/yr. There was a good correlation (r = 0.80, P = 0.0096) within patients between the rate of change of the right and left kidneys (Figure 2). Figure 3 shows the initial and final CT studies in one of the patients, illustrating the increase in total kidney and renal cyst volume and the reduction in renal parenchymal volume.

Correlation with Renal Function and Proteinuria

At entry, GFR values correlated negatively with total renal or cyst volumes and positively with renal parenchymal volume (Table 4). During the 8 yr of the study, the GFR remained stable in one patient and declined in eight patients. The yearly

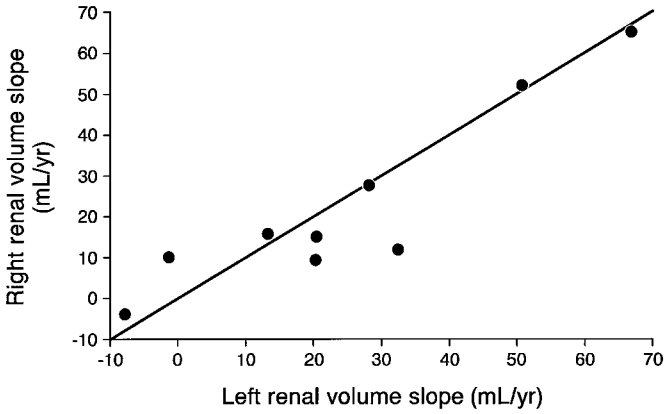

Figure 2. Within-patient correlation of the rate of change in right and left kidney volumes.

rate of decline ranged from 0.3 to 9.4 (mean decline ± SD for the nine patients, 2.8 ± 2.8) ml/min per 1.73 m^2. There was a significant correlation between the rate of decline in GFR and the rate of increase in renal cyst volume (Table 5, Figure 4). In six patients, the urine protein/osmolality ratio (mg/L per mosmol per kg) at the initial evaluation was ≤0.13. In the other three patients, urine protein osmolality ratios were 0.24, 0.35, and 0.45. The patients with proteinuria had a yearly increase in renal volume of 90 ± 49 ml/yr and a yearly decline in GFR of 5.4 ± 3.5 ml/min per 1.73 m^2, compared with 27 ± 22 (P = 0.07) and 1.5 ± 1.2 (P = 0.03), respectively, in the patients without proteinuria.

Discussion

The results of the present study demonstrate that current cross-sectional imaging techniques (in this study, EBCT was used) can provide reproducible measurements of total kidney, renal parenchyma, and cyst volumes. Although we cannot establish the accuracy of these *in vivo* measurements, the methodology used was very accurate in the estimation of simulated renal cyst and parenchymal volumes using a phantom. A potential problem in the estimation of the residual renal parenchyma is the inability of CT to accurately define cysts measuring <2 mm in diameter because of spatial resolution limitations, partial volume effects, and image noise. We believe that these technical problems account for the fact that the initial renal parenchymal volumes in many of our ADPKD patients with normal renal function exceeded the reported normal total kidney volume in healthy individuals (approximately 300 ml/1.73 m^2) (12). However, we cannot completely rule out the possibility that renal hypertrophy or hyperplasia occurring at an early phase of ADPKD might also have contributed to the high renal parenchymal volumes at study entry in these patients.

The longitudinal data indicate that patients with ADPKD experience over time an overall increase in total kidney and renal cyst volumes and a reduction in renal parenchymal volume, but that there is a high degree of variability from patient to patient. Furthermore, the significant negative correlation between the rate of change in renal cyst volume and the rate of

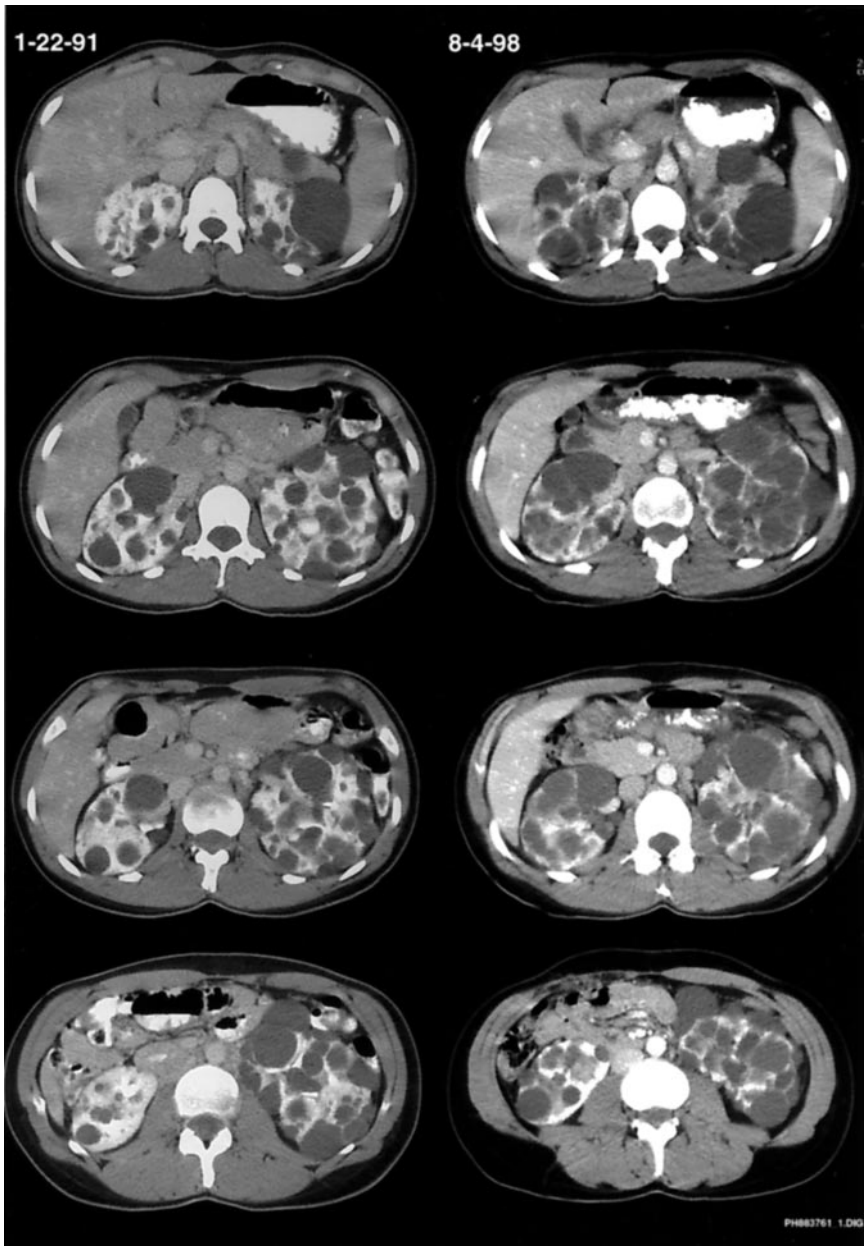

Figure 3. Initial and final fast electron-beam computerized tomography (EBCT) studies in an ADPKD patient illustrating the increase in total kidney and renal cyst volume and the reduction in renal parenchymal volume. The liver was used as an external landmark to approximate the same levels.

decline in GFR confirms previous cross-sectional data (17,18), which relate the degree of impairment of renal function to the increase in renal volume. Therefore, these observations provide further rationale for using the measurements for total kidney, renal cyst, and renal parenchymal volumes as surrogate markers of disease progression in ADPKD.

Previous studies of renal volumes in healthy volunteers and in ADPKD depended on two-dimensional ultrasound (2D US) estimations of total kidney volumes, using a variety of formulas (17–21). This technique depends on certain assumptions of the shape of the kidneys, which may not always be true. It has considerable interobserver and intraobserver error (30 to 40%) because of the difficulty in accurately reproducing renal lengths and diameters due to variability of adequate acoustic windows and areas selected for measurements (22–24). In addition, 2D US cannot provide reliable measurements of renal cyst and renal parenchymal volumes.

A new ultrasound technique, three-dimensional ultrasound (3D US), uses a specialized transducer that contains four matrix arrays arranged in four separate quadrants on the face of the transducer. A 3D volume data set, acquired during a single breathhold, allows the viewing of reconstructed slices of the kidney from any perspective. *In vitro* testing of phantoms and excised organs has shown its accuracy for volume measurements (25–27). Although no published study has documented the accuracy of 3D US to measure the volume of renal cysts, it

Table 4. Correlations of renal volumes with GFR in nine ADPKD patients at initial visit[a]

Parameter	Value
Kidney volume (ml)	−0.40 (0.28)
Cyst volume (ml)	−0.64 (0.06)
Parenchymal volume (ml)	+0.59 (0.09)
Cyst/kidney volume × 100	−0.59 (0.09)

[a] Tabled values are Spearman rank correlation coefficients (*P* value for test of correlation significantly different from zero). GFR (ml/min per 1.73 m^2).

Table 5. Correlation of renal volumes slopes with initial age and GFR slopes in nine ADPKD patients[a]

Parameter	Initial Age (yr)	GFR Slope[b]
Renal volume (cc/yr)	0.43 (0.25)	−0.48 (0.19)
Cyst volume (cc/yr)	0.42 (0.30)	−0.71 (0.046)
Cyst percent (%/yr)	0.18 (0.67)	−0.21 (0.61)
Parenchymal volume (cc/yr)	−0.18 (0.67)	0.33 (0.42)

[a] Tabled values are Spearman rank correlation coefficients (*P* value for test of correlation significantly different from zero).
[b] Annual slope in iothalamate clearance (ml/min per 1.73 m^2 BSA).

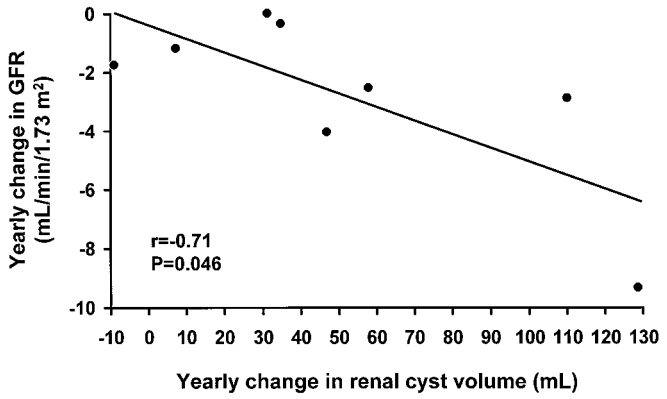

Figure 4. Correlation between the yearly rates of change in renal cyst volume and GFR.

has been shown to be accurate in volume determination of gestational sacks (28). Although still experimental, it holds promise in evaluating renal volumes in young children because of relatively good acoustic windows in children and the quick real time nature of examination. It may be limited in adults because of inadequate acoustic windows (ribs, bowel, fat).

In the current study, we have used CT, a technique frequently used to estimate the volume of abdominal organs (29–32). Earlier applications of CT volumetric analysis of the kidneys, using 10-mm slices acquired during different breathholds, were hampered by respiratory misregistration and partial volume effects (33,34). Recent studies using fast breathhold CT techniques (electron-beam or spiral CT) have had a much higher level of accuracy (10,11,13,14). The current study demonstrates that contrast-enhanced EBCT can provide accurate measurements not only of total kidney volume, but also of renal cyst and renal parenchymal volume with high reproducibility. CT, however, has two significant limitations. The first is the radiation exposure, which ranges from 2.5 to about 4.0 cGy (skin entry dose) after a single study and can be significant in longitudinal studies, particularly in young patients (35). The second is the requirement of the administration of intravenous contrast, which can be nephrotoxic in patients with impaired renal function and can result in rare life-threatening reactions (36).

Because of these limitations and the development of newer and faster breathhold magnetic resonance (MR) techniques, MR has recently received attention in the evaluation of ADPKD (37–45). Two specific new advances in MR imaging have allowed for fast breathhold imaging of the kidneys, half Fourier transform single-shot fast-spin echo (SSFSE), and 3D spoiled gradient echo (3D SPGR) imaging. SSFSE is a 2D acquisition that can acquire multiple high quality images of the abdomen in a single breathhold. This technique has a higher lesion-to-organ tissue contrast, particularly in the cystic regions, that does conventional CT and eliminates motion artifacts and respiratory misregistration error, as well as chemical shift and susceptibility artifacts. One potential limitation of SSFSE breathhold MR imaging in kidney volume estimation is the requirement of a slice thickness of at least 5 mm. The 3D SPGR sequence is a 3D acquisition commonly used in MR angiography of the aorta and renal arteries (46–48). This technique allows a 3D acquisition in a single breathhold during the administration of intravenous gadolinium MR contrast media. Because 3D SGR acquisition can be reconstructed into 1.5- to 3.0-mm slices, it offers the potential for very accurate estimates of renal cyst and renal parenchymal volumes. Although this technique requires the administration of intravenous gadolinium chelate, this has an extremely safe profile and, contrary to contrast agents for CT, is not nephrotoxic (49,50). It seems likely that SSFSE breathhold imaging of the kidneys could be obtained in the future in a 3D acquisition. This would allow reconstructed thin (1.5 to 3.0 mm) slices with inherent bright tissue contrast without need for intravenous gadolinium administration.

ADPKD is characterized by the development and growth of cysts that gradually replace the renal parenchyma and cause renal enlargement. For many years, renal function remains normal, but when the GFR begins to decrease, the rate of decline accelerates with time (51,52). In the Modification of Diet in Renal Disease (MDRD) trial, the decline of renal function occurred more rapidly and more consistently in the patients with ADPKD than in those without (53). It has been proposed that the rate of the decline is related to the rate of growth of the cysts (52). According to a hypothetical model, the radius of the cysts increases at a constant rate that results in an accelerated increase in cyst volume. Initially, the enlargement of the cysts results in displacement rather than in atrophy of the functioning parenchyma, but at later stages, when further displacement of the parenchyma is limited by distention of the

fibrous capsule and increasing amount of interstitial fibrous tissue, compression atrophy ensues. According to this model, the accelerated decline of renal function would parallel the accelerated decrease in the volume of residual functioning tissue.

The observations in the current study are partially consistent with this hypothetical model. Given the slopes of total kidney and renal cyst volume in our patients, it is obvious that the increase in renal volume since birth accelerates over time. The positive correlation between the slopes of total kidney and cyst volumes and patient ages is consistent with this interpretation, although this correlation did not reach statistical significance possibly due to the small number of patients in this study. The rate of increase in cyst volume correlated better with the decline in GFR than with the rate of increase in total kidney volume and the rate of decrease of parenchymal volume, but this observation should be interpreted cautiously because of the small number of patients in the study. Nevertheless, it may indicate, together with the weak correlation between the rate of change in renal cyst and parenchymal volumes, that, in addition to compression atrophy, other factors related to cystogenesis are important in the decline of renal function in ADPKD. Recent studies have shown that the cysts produce a number of factors, such as growth factors, cytokines and chemokines, vasoactive peptides, bioactive lipids, matrix metalloproteinases and their inhibitors, lysosomal enzymes, and reactive oxygen species, capable of affecting, in a paracrine manner, the development of neighboring cysts and causing interstitial inflammation and fibrosis and microvascular disease (reviewed in reference (3). These factors, in addition to an increased rate of tubular epithelial cell apoptosis and compression atrophy, are likely to be important in the progression of renal insufficiency in ADPKD. Regardless of the mechanism(s) by which the development and growth of the cysts results in the progression of renal insufficiency, the results of the current study suggest that renal volumes, particularly renal cyst volumes, can be used as surrogate markers of disease progression in ADPKD.

In summary, the results of this pilot study suggest that current imaging techniques are capable of measuring total kidney, renal cyst, and renal parenchymal volumes reproducibly; that total kidney and renal cyst volumes increase, while parenchymal volumes decrease with time; that the increase in cyst volume correlates best with the decline in renal function; and that renal volumes appear to be good surrogate markers for disease progression in ADPKD.

Acknowledgment

This study was supported by a grant from the Mayo Foundation.

References

1. Iglesias C, Torres V, Offord K, Holley K, Beard C, Kurland L: Epidemiology of adult polycystic kidney disease, Olmsted County, Minnesota: 1935–1980. *Am J Kidney Dis* 2: 630–639, 1983
2. U.S. Renal Data System: *USRDS 1997 Annual Data Report*, 1997
3. Torres V: New insights into polycystic kidney disease and its treatment. *Curr Opin Nephrol Hypertens* 7: 159–169, 1998
4. Van Adelsberg J, Chamberlain S, D'Agati V: Polycystin expression is temporally and spatially regulated during renal development. *Am J Physiol* 272: F602–F609, 1997
5. Wilson P: Pathogenesis of polycystic kidney disease: Altered cellular function. In: *Polycystic Kidney Disease*, edited by Watson M, Torres V, Oxford, Oxford University Press, 1996, pp 125–163
6. Gardner K Jr, Burnside J, Elzinga L, Locksley R: Cytokines in fluids from polycystic kidneys. *Kidney Int* 39: 718–724, 1991
7. Zeier M, Fehrenbach P, Geberth S, Mohring K, Waldherr R, Ritz E: Renal histology in polycystic kidney disease with incipient and advanced renal failure. *Kidney Int* 42: 1259–1265, 1992
8. Woo D: Apoptosis and loss of renal tissue in polycystic kidney diseases [see Comments]. *N Engl J Med* 333: 18–25, 1995
9. Lanoix J, D'Agati V, Szabolcs M, Trudel M: Dysregulation of cellular proliferation and apoptosis mediates human autosomal dominant polycystic kidney disease (ADPKD). *Oncogene* 13: 1153–1160, 1996
10. Lerman L, Bentley M, Bell M, Rumberger J, Romer J: Quantitation of the in vivo kidney volume with cine computed tomography. *Invest Radiol* 25: 1206–1211, 1990
11. Kotre C, Owen J: Method for the evaluation of renal parenchymal volume by x-ray computed tomography. *Med Biol Eng Comput* 32: 338–341, 1994
12. Gremigni D, Todescan G, Giannardi G, Villary N, Boddi V, Brizzi E: Renal volume and human somatic type. *Bull Ital Soc Exp Biol* 60: 887–893, 1984
13. Lerman L, Flickinger A, Sheedy P II, Turner S: Reproducibility of human kidney perfusion and volume determinations with electron beam computed tomography. *Invest Radiol* 31: 204–210, 1996
14. Nawaratne S, Fabiny R, Brien J, Zalcberg J, Cosolo W, Whan A, Morgan DJ: Accuracy of volume measurement using helical CT. *J Comput Assist Tomogr* 21: 481–486, 1997
15. Yoshimoto M, Tsukahara H, Saito M, Hayashi S, Haruki S, Fujisawa S, Sudo M: Evaluation of variability of proteinuria indices. *Pediatr Nephrol* 4: 136–139, 1990
16. Cockcroft D, Gault M: Prediction of creatinine clearance from serum creatinine. *Nephron* 16: 31–41, 1976
17. Gabow P, Chapman A, Johnson A, Tangel D, Duley I, Kaehny W, Manco-Johnson M, Schrier R: Renal structure and hypertension in autosomal dominant polycystic kidney disease. *Kidney Int* 38: 1177–1180, 1990
18. Gabow P, Johnson A, Kaehny W, Kimberling W, Lezotte D, Duley I, Jones R: Factors affecting the progression of renal disease in autosomal-dominant polycystic kidney disease. *Kidney Int* 41: 1311–1319, 1992
19. Sargent M, Gupta S: Sonographic measurement of relative renal volume in children: Comparison with scintigraphic determination of relative renal function. *Am J Roentgenol* 161: 157–160, 1993
20. Emamian S, Nielsen M, Pedersen J, Ytte L: Kidney dimensions at sonography: Correlation with age, sex, and habitus in 665 adult volunteers. *Am J Roentgenol* 160: 83–86, 1993
21. Fick G, Duley I, AM J, Strain J, Manco-Johnson M, Gabow P: The spectrum of autosomal dominant polycystic kidney disease in children. *J Am Soc Nephrol* 4: 1654–1660, 1994
22. Sargent M, Long G, Karmali M, Cheng S: Interobserver variation in the sonographic estimation of renal volume in children. *Pediatr Radiol* 27: 663–666, 1997

23. Zerin J, Blane C: Sonographic assessment of renal length in children: A reappraisal. *Pediatr Radiol* 24: 101–106, 1994
24. Emamian S, Nielsen M, Pedersen J: Intraobserver and interobserver variations in sonographic measurements of kidney size in adult volunteers. *Acta Radiologica* 36: 399–401, 1995
25. Wong J, Gerscovich E, Cronan M, Seibert J: Accuracy and precision of in vitro volumetric measurements by three-dimensional sonography. *Invest Radiol* 31: 26–29, 1996
26. Barry C, Allott C, John N, Mellor P, Arundel P, Thomson D, Waterton J: Three-dimensional freehand ultrasound: image reconstruction and volume analysis. *Ultrasound in Med & Biol* 23: 1209–1224, 1997
27. Gilja O, Thune N, Matre K, Hausken T, Odegaard S, Berstad A: In vitro evaluation of three-dimensional ultrasonography in volume estimation of abdominal organs. *Ultrasound in Med & Biol* 20: 157–165, 1994
28. Steiner H, Gregg A, Bogner G, Graf A, Weiner C, Staudach A: First trimester three-dimensional ultrasound volumetry of the gestational sac. *Arch Gynecol Obstet* 225: 165–170, 1994
29. Thomsen H, Madsen J, Thaysen J, Damgaard-Petersen K: Volume of polycystic kidneys during reduction of renal function. *Urol Radiol* 3: 85–89, 1981
30. Thaysen J, Thomsen H: Involution of polycystic kidneys during replacement therapy of terminal renal failure. *Acta Med Scand* 212: 389–394, 1982
31. Thaysen J, Thomsen H, Sass A, Kristensen J: Volume changes in polycystic kidneys during chronic dialysis and after renal transplantation. *Acta Med Scand* 217: 197–204, 1985
32. Ishikawa I, Saito Y: Volume changes in autosomal dominant polycystic kidneys after the initiation of hemodialysis. *Nephron* 65: 649–650, 1993
33. Schwartz L, Richaud J, Buffat L, Touboul E, Schlienger M: Kidney mobility during respiration. *Radiother Oncol* 32: 84–86, 1994
34. Chuang K, Udupa J: Boundary detection in grey level scenes Proceedings of the Tenth Annual Conference and Exposition of the National Computer Graphics Association, Fairfax, VA, 1989
35. Edwards M: Risks of Medical Imaging. *In* Diagnostic Imaging. Edited by C Putman and C Ravin. Vol 1: Philadelphia, WB Saunders Company, 1994, pp 83–97
36. Katayama H, Yamaguchi K, Kozuka T, Takashima T, Seez P, Matsuura K: Adverse reactions to ionic and nonionic contrast media: a report from the Japanese Committee on the Safety of Contrast Media. *Radiology* 175: 621–628, 1990
37. Luft A, Skalej M, Welte D, Kolb R, Klose U: Reliability and exactness of MRI-based volumetry: a phantom study. *JMRI* 6: 700–704, 1996
38. King B, Reed J, Riederer S, Jack CJ, Sheedy P, Torres V: Reproducibility and longitudinal study of renal parenchyma and cyst volumes using CT and MR imaging in autosomal dominant polycystic kidney disease (ADPKD). *JASN*, 1999
39. Huppert B, Brandt K, Ramin K, King B: SSFSE MR Imaging of the Fetus. *RadioGraphics* 19: S215–S227, 1999
40. Semelka R, Shoenut J, Kroeker M, MacMahon R, Greenberg H: Renal lesions: controlled comparison between CT and 1.5-T MR imaging with nonenhanced and gadolinium-enhanced fat-suppressed spin-echo and breath-hold FLASH techniques. *Radiology* 182: 425–430, 1992
41. Tang Y, Yamashita Y, Namimoto T, Abe Y, Takahashi M: Liver T2-weighted MR imaging: comparison of fast and conventional half-Fourier single-shot turbo spin-echo, breath-hold turbo spin-echo, and respiratory-triggered turbo spin-echo sequences. *Radiology* 203: 766–772, 1997
42. Semelka R, Kelekis N, Thomasson D, Brown M, Laub G: Haste MR imaging: description of technique and preliminary results in the abdomen. *JMRI* 6: 698–699, 1996
43. Reinig J: Breath-hold fast spin-echo MR imaging of the liver: a technique for high-quality T2-weighted images. *Radiology* 194: 303–304, 1995
44. Rydberg J, Lomas D, Coakley K, Hough D, Ehman R, Riederer S: Comparison of breath-hold fast spin-echo and conventional spin-echo pulse sequences for T2-weighted MR imaging of liver lesions. *Radiology* 194: 431–437, 1995
45. Van Hoe L, Bosmans H, Aerts P, Baert A, Fevery J, Kiefer B, Marchal G: Focal liver lesions: fast T2 weighted MR imaging with half-Fourier rapid acquisition with relaxation enhancement. *Radiology* 201: 817, 1996
46. Choyke P, McClellan M, Wagner J, Rayford W, Lyne J, Linehan W: Renal cancer: preoperative evaluation with dual-phase three-dimensional MR angiography. *Radiology* 205: 767–771, 1997
47. Prince M, Schoenberg S, Ward J, Londy F, Wakefield T, Stanley J: Hemodynamically significant atherosclerotic renal artery stenosis: MR angiographic features. *Radiology* 205: 128–136, 1997
48. Wilman A, Riederer S, King B, Debbins J, Rossman P, Ehman R: Fluoroscopically triggered contrast-enhanced three-dimensional MR angiography with elliptical centric view order: application to the renal arteries. *Radiology* 205: 137–146, 1997
49. Goldstein H, Kashaniau F, Blumetti R, Lolyoak W, Hugo F, Blumenfield D: Safety assessment of gadopentate dimeglumine in U.S. clinical trials. *Radiology* 174: 17–23, 1990
50. Arsenault T, King B, Marsh J, Goodman J, Weaver A, Wood C, Ehman R: Systemic gadolinium toxicity in patients with renal insufficiency and renal failure: retrospective analysis of an initial experience. *Mayo Clin Proc* 71: 1150–1154, 1996
51. Gabow P: Definition and natural history of autosomal dominant polycystic kidney disease. *In* Polycystic Kidney Disease. Edited by M Watson and V Torres. Vol 1: Oxford, Oxford University Press, 1996, pp 333–355
52. Reubi F: Pathophysiology of renal failure. *In* Problems in Diagnosis and Management of Polycystic Kidney Disease. Edited by J Grantham and K Gardner. Kansas City, PKR Foundation, 1985: pp81–86
53. Klahr S, Breyer J, Beck G, Dennis V, Hartman J, Roth D, Steinman T, Wang S, Yamamoto M: Dietary protein restriction, blood pressure control, and the progression of polycystic kidney disease. *J Am Soc Nephrol* 5: 2037–2047, 1995