Computed Tomography Evaluation of Autosomal Dominant Polycystic Kidney Disease Progression: A Progress Report

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At the moment, there are no effective therapies to prevent or slow the progression of autosomal dominant polycystic kidney disease (ADPKD). Radiologic evaluations are used to monitor volume of renal cysts and parenchyma during disease evolution. Volumetric quantifications based on computed tomography were used to investigate the relation between structural and functional changes in patients with advanced-stage ADPKD. By use of image-processing techniques, volume of kidneys, renal cysts, fully enhanced parenchyma, and faintly contrast-enhanced parenchyma, referred to as intermediate, was estimated. GFR measurements and computed tomography evaluations were repeated 6 mo later. No statistically significant correlations were found between volumes of cysts and parenchyma and intermediate volume and GFR. However, the ratio of intermediate over parenchymal volume strongly correlated with GFR ($r = -0.81$, $P < 0.001$). In addition, there were significant correlations between percentage changes in intermediate volume (absolute or relative to parenchyma) and GFR changes during the observation period ($r = -0.70$ and $r = -0.75$, $P < 0.01$). These data support the hypothesis of a significant relation between radiologic appearance of renal structure and functional changes and suggest new ways that renal dysfunction in ADPKD may be predicted. Further work is necessary to determine the nature of faintly contrast-enhanced parenchyma and its role in renal functional loss.

Clin J Am Soc Nephrol 1: 754–760, 2006. doi: 10.2215/CJN.02251205

Eight to 10% of patients with ESRD are affected by autosomal dominant polycystic kidney disease (ADPKD), a hereditary disease whose progression is largely related to the development and growth of cysts and the concomitant disruption of normal renal tissue (1,2). Patients who have ADPKD present faster decline in GFR compared with those who have other renal diseases, and current therapies are inefficient at arresting or even slowing the progressive loss of renal function. As a result, approximately 50% of patients who have ADPKD need renal replacement therapy by 60 yr of age (1).

Besides monitoring renal function by standard measurements, follow-up of patients with ADPKD is based largely on radiologic investigations that are performed with ultrasounds, computerized tomography (CT), or magnetic resonance imaging, with the aim of evaluating renal cyst morphology and volume and estimating the amount of residual renal parenchyma. Investigation of the three-dimensional structures in kidneys that are affected by ADPKD usually takes place on bidimensional images that are analyzed by conventional radiologic procedures, which do not allow quantification of the real volume extension of renal cysts and parenchyma in the entire organs. Characterization of the progression of the disease in terms of kidney structural changes at the single-patient level therefore is not feasible; neither is the evaluation of the effect of therapeutic interventions that aim to interfere with the process of epithelial cell fluid secretion and/or reabsorption.

The use of three-dimensional imaging and advanced image-processing techniques recently allowed us to investigate the relations between structure and function in the polycystic kidney. Among other observations, data reported in the context of the Consortium for Radiologic Imaging Studies of Polycystic Kidney Disease (CRISP) study (3) showed a significant correlation between renal and cyst volume and GFR. The study was performed using magnetic resonance imaging evaluations on a large group of patients and showed an inverse relation between percentage volume of the organ occupied by cysts and GFR. However, although significant, the correlations presented in that context were not strong ($r = -0.44$), suggesting that patients with a given cyst volume may have high or low values of GFR. Regarding disease progression, King *et al.* (4) showed, in a previous longitudinal study based on CT, a significant relation between changes in cyst volume and changes in GFR over time. Once again, although of primary importance, this correlation was weakened by the high degree of variability affecting the observed parameters. In an attempt to characterize disease progression and find predictors of renal failure, Size *et al.* (5) retrospectively compared longitudinal CT acquisitions that

Received December 23, 2005. Accepted April 26, 2006.

Published online ahead of print. Publication date available at www.cjasn.org.

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ISSN: 1555-9041/104-0754

were performed on a group of 10 patients during a period that ranged from 3 to 12 yr and estimated total kidney and cyst volume from each CT sequence. The authors found no significant difference between initial kidney volume or rate of kidney volume change in patients who developed end-stage renal failure compared with the rest. Instead, the initial relative volume of cysts over total kidney volume was significantly different between the two groups, suggesting a possible predictor of renal failure.

Different from total kidney volume, measurements of cyst and parenchyma volumes from medical images can only be determined empirically. Cyst volume probably is underestimated because of the inability to discern small cysts, and parenchyma may be overestimated because of inclusion of small cysts that contain contrast and volume averaging errors that are inherent in using finite imaging resolutions. In this study, we evaluate contrast-enhanced and contrast-unenhanced regions of polycystic kidneys from CT acquisitions in addition to the selective measurements of kidney volume and cyst volume in an effort to find correlations with changes in renal function. For this purpose, we take advantage of the data collected during a recently published study that aimed to evaluate the effect of somatostatin treatment on patients with advanced-stage ADPKD (6). In that study, multislice CT imaging and state-of-the-art image-processing techniques were used to determine reliably kidney tissue volumes in patients with ADPKD. In this work, we focus on the results that were obtained during the placebo phase of that study, with the aim of investigating the predictive power of structural quantification with respect to the deterioration of renal function.

Materials and Methods

This report focuses on renal function and kidney volume data that were measured before and after the placebo phase of a recently published study (6). Briefly, 13 patients with advanced-stage ADPKD were imaged twice 6 mo apart by means of a multislice CT scanner (Picker CT-Twin; Picker International Inc., Highland Heights, OH). Patients who were enrolled in the study were 18 yr or older, had clinical and echographic diagnosis of ADPKD, and presented serum creatinine levels <3.0 but >1.2 mg/dl (>1.0 mg/dl if female). Exclusion criteria for the study were concomitant systemic disease, urinary tract disease, diabetes, abnormal urine analysis suggestive of concomitant glomerular disease, urinary tract lithiasis, infection or obstruction, and presence of hemorrhagic or complicated cysts. Patients who were affected by conditions that could prevent completion of follow-up, interfere with data collection or interpretation, or interfere with comprehension of the purpose and risk of the study were not considered eligible for participation. The reader is referred to Ruggenenti *et al.* (6) for further details on the study design.

For CT evaluations, a single breathhold scan (120 kV; 230 mAs; field of view 43 cm; matrix 512×512; collimation 5 mm; pitch 1; increment 3 mm, overlap $>50\%$) was performed 90 s after injection of 170 ml of nonionic contrast agent (IOPAMIRO; Bracco, Milan, Italy) at a rate of 2.5 ml/s. No episodes of contrast-induced nephropathy were observed. GFR was measured in each patient before scanning by means of Iohexol plasma clearance technique, as described previously (7). Once acquired, images were transferred in DICOM 16-bit format from the clinical scanner onto PC workstations for subsequent processing. Except where explicitly stated, all image-processing steps were performed with in-house software based on the Insight Toolkit version 2.0 (8) and developed in the C++ programming language.

Image Processing

Initially, kidneys were outlined manually on all acquired digital images by a trained radiologist (G.F.) using an interactive image editing software (GIMP; GNU Image Manipulation Software, www.gimp.org). The operator was not required to identify kidney boundaries precisely; instead, he was allowed to place the outline within the region of fat normally surrounding the kidney, which appears as a low-intensity region on CT images. Only in cases in which fat was absent and the kidney was adjacent to other organs that presented higher image intensity (*e.g.*, the liver) was the operator required to identify kidney boundaries carefully. From the outlined images, binary masks were generated and were used to define regions of interest on the original DICOM images.

An image enhancement step was performed to reduce the effect of noise on the acquired images. In particular, we used anisotropic diffusion filtering to smooth high-frequency noise while preserving relevant features, such as the boundary between cysts and parenchyma. For this purpose, we used the approach presented by Whitaker and Xue (9) already implemented within the Insight Toolkit.

Binary masks that were generated from the outlines were applied to the enhanced images, and image segmentation was applied to the resulting kidney regions. Toward this end, we used a histogram-based statistical approach known as Otsu's thresholding (10). In this method, the histogram of image intensities is partitioned in a predetermined number of classes N_c separated by $N_c - 1$ thresholds. Thresholds are set so as to maximize the between-class variance, expressed by

$$\sigma_b^2 = \sum_{i=1}^{N_c} \omega_i(\mu_i - \mu)^2 \quad (1)$$

where ω_i is the voxel probability of belonging to class i, μ_i is the mean intensity of class i, and μ is the overall mean image intensity. Originally available as part of the Insight Toolkit limited to the case $N_c = 2$, the implementation has been generalized to $N_c \geq 2$. The new implementation now is available as part of the Insight Toolkit.

For using Otsu's method on outlined images, the number of tissue classes had to be determined *a priori* on the basis of visual inspection of the images. For this purpose, we identified fat surrounding kidneys as the lowest intensity class; cysts as the second lowest, with an intensity slightly higher of that of water; and renal parenchyma as the highest intensity class, with an intensity corresponding to that of the contrast agent. Careful inspection of CT images, however, also evidenced the consistent presence of large areas of kidney with an intensity higher than that of cysts but lower than that of contrast agent, as shown in Figure 1. These regions, which typically appeared at intensities of approximately 100 HU, were observed throughout the volume of all patients and did not necessarily correspond to the transition between cysts and parenchyma. We therefore defined a separate class for these regions, from now on referred to as the intermediate tissue class.

After the application of Otsu's method with a number classes equal to 4, each voxel in the volume was classified as fat, cyst, intermediate, or parenchyma, as shown in Figure 2. From the segmented images, cyst, intermediate, and parenchymal volumes were computed by multiplying the voxel count of each class by voxel volume, as determined by the acquisition protocol.

Validation of the segmentation procedure was performed in two stages. The first stage had the purpose of assessing the accuracy of cyst volume determinations and was performed similarly to what was reported by King *et al.* (4). Briefly, a phantom was built by placing ping-pong balls filled with physiologic salt solution (mimicking cysts)

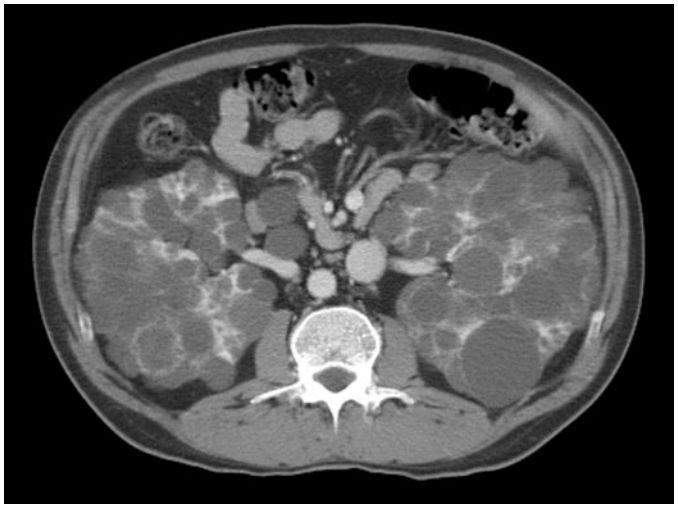

Figure 1. Example of the radiologic appearance of kidneys with advanced autosomal dominant polycystic kidney disease (ADPKD; patient 13). Several hypointense regions are visible along with cysts and fully enhanced parenchyma.

into a glass beaker, filled with a 1.23% solution of contrast agent in water (mimicking renal parenchyma). The phantom was scanned with the same protocol used for patient imaging. The whole volume measurement procedure (region drawing, image enhancement, and pixel classification) then was applied to the acquired CT images, and the resulting volume values were compared with the true values, determined by direct measurements of inner ball diameter. Mean ball value was 31.18 cm^3, and the volume of 10 ping-pong balls as measured on CT images was 305.54 cm^3, yielding a volume quantification error of 0.7%.

The second stage was aimed at testing the capability of our segmentation procedure to discern the intermediate tissue class in addition to cysts and parenchyma. A large cyst was simulated by means of a polyethylene cylinder (12-mm radius, 15-mm thickness). A radio-opaque gel that simulated contrast-enhanced parenchyma was prepared by mixing a 3% agarose solution with 0.75% contrast agent. The amount of contrast agent was chosen so that the difference in intensity between the solution and the polyethylene cylinder reflected that of parenchyma and cysts (approximately 200 HU). The appearance of intermediate volume was simulated by partial volume effect, obtained by mixing 20 ml of agarose gel with an equal volume of small polyethylene discs (1-mm radius, 1-mm thickness) in a 50-ml tube. The large polyethylene cylinder was sunken in a beaker that contained 100 ml of radio-opaque agarose gel solution. The phantom was acquired with the same acquisition parameters as in the study, and one acquired image was analyzed with the image-processing technique presented above, as shown in Figure 3. As expected, the intensity of the simulated intermediate volume was intermediate (HU = 5 ± 22) between that of simulated parenchyma (HU = 164 ± 20) and cysts (HU = −75 ± 7.4). Our segmentation method successfully discerned among the three simulated tissue classes. Only one of 716 pixels that belonged to the intermediate component was classified as cyst (0.1% misclassification ratio), whereas 32 of 659 pixels that belonged to the cyst component were classified as intermediate (4.8% misclassification ratio). These latter pixels belonged to the boundary between simulated cyst and parenchyma, and their intermediate intensity was due to partial vol-

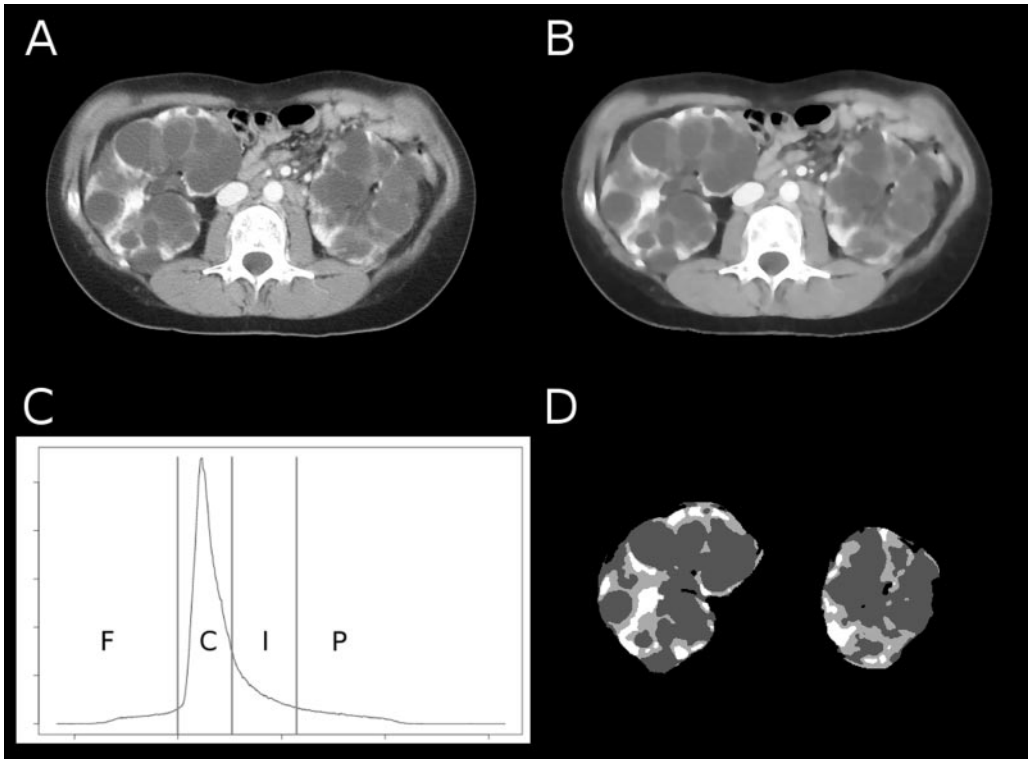

Figure 2. Representative computed tomography (CT) image before (A) and after (B) the application of anisotropic diffusion. (C) Image volume histogram and segmentation thresholds (F, fat; C, cysts; I, intermediate; P, parenchyma). (D) Segmented kidney tissue components.

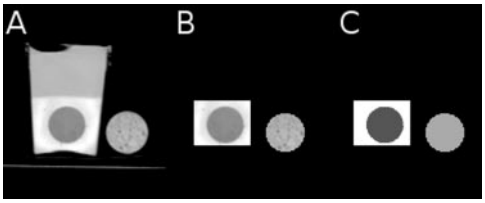

Figure 3. (A) Acquired CT image of the phantom: On the left, the beaker with the radio-opaque agarose gel and the polyethylene disk; on the right, the Corning tube filled with the 50% mixture of agarose gel and small polyethylene disks. (B) CT image cropped before classification. (C) Correctly classified image.

ume effects. It therefore is expected that a fraction of the pixels that sit on the boundary between large cysts and parenchyma contribute to the intermediate volume fraction *in vivo*. However, it has to be noted how visual inspection of CT images shows that large portions of intermediate volume are not associated with such boundaries, as shown in Figures 1 and 2.

Statistical Analyses

Statistical analysis was performed with the R statistical software (11). Significance of differences between baseline and 6-mo follow-up was tested by means of paired *t* test. Correlation between GFR and volumetric measurements was assessed using Pearson correlation test. Tests were considered significant at $P < 0.05$.

Results

The results of kidney function and volume quantifications that were performed at baseline and 6 mo later are shown in Table 1. Both functional and volumetric data were markedly heterogeneous among the patient population. Total kidney volume was highly variable, with values up to 4.5 L, whereas parenchymal volume was more evenly distributed. Total kidney volume increased significantly during the 6-mo period ($P < 0.01$) as a result of a significant increase in cyst volume ($P < 0.01$). Intermediate and parenchymal volumes only numerically increased with time, but the differences were not statistically significant and the increase in parenchymal volume was close to the limits of accuracy of the measurement method. Mean GFR averaged 56.4 ml/min at baseline evaluation, with values ranging from normal to severely low. Data show a nonstatistically significant trend toward decrease in mean GFR during the 6-mo follow-up period.

Volumes of kidney tissue plotted against GFR values are shown in Figure 4. For each patient, baseline and 6-mo values were averaged to yield a representative value for the follow-up period. No significant correlations were found between GFR and any of the measured tissue volumes. In particular, three of four patients who presented high cyst volumes ($V_{Cys} > 2$ L) had good renal function (GFR $>$ 60 ml/min), whereas five of nine patients who had cyst volumes $\leq$1.5 L had GFR $<$50 ml/min. As for parenchyma, a direct relationship between parenchymal volume and GFR was hinted at by the plot, but no statistical significance was found. These relationships did not change when baseline and follow-up data were considered separately. On the contrary, a statistically significant inverse correlation was found between the ratio of intermediate volume over parenchymal volume (V_{Int}/V_{Par} %) and GFR, both at baseline ($r = -0.81$, $P < 0.001$) and after the 6-mo observation period ($r = -0.80$, $P < 0.005$), as shown in Figure 5.

The relation between percentage change in total, cyst, inter-

Table 1. Renal function and kidney volume in patients with late-stage ADPKD at baseline and after 6-mo follow-up[a]

Patient	Age	GFR (ml/min)			V_{Tot} (ml)			V_{Cys} (ml)			V_{Int} (ml)			V_{Par} (ml)		
		Baseline	6 Mo	Δ%	Baseline	6 Mo	Δ%	Baseline	6 Mo	Δ%	Baseline	6 Mo	Δ%	Baseline	6 Mo	Δ%
1	41	48.7	45.9	−5.7	2269	2457	8.3	1347	1438	6.8	644	727	12.8	278	292	5.3
2	49	34.9	30.9	−11.5	2181	2201	0.9	1561	1583	1.4	464	461	−0.6	156	157	0.7
3	48	32.1	25.3	−21.2	1716	1960	14.2	894	981	9.7	600	731	21.8	222	249	12.0
4	58	36.8	32.0	−13.0	1469	1570	6.9	958	1032	7.7	374	417	11.5	137	120	−11.8
5	53	86.7	77.7	−10.4	3402	3607	6.0	2774	2942	6.1	348	384	10.2	280	281	0.4
6	38	45.0	42.6	−5.3	1722	1992	15.6	1211	1400	15.6	356	426	19.6	155	165	6.4
7	48	100.8	101.8	1.0	3596	3872	7.7	3099	3400	9.7	229	211	−7.8	267	260	−2.6
8	41	86.8	90.8	4.6	1832	1890	3.2	820	868	5.8	642	640	−0.3	370	383	3.5
9	35	69.9	73.9	5.7	1756	1931	10.0	966	1056	9.2	502	542	7.9	287	334	16.4
10	39	71.9	76.7	6.7	1457	1354	−7.1	797	736	−7.6	437	403	−7.8	223	215	−3.6
11	38	67.1	79.3	18.2	3384	3593	6.2	2094	2350	12.2	976	949	−2.8	314	294	−6.2
12	54	28.5	23.4	−17.9	4295	4548	5.9	2805	2792	−0.5	1207	1425	18.0	282	331	17.2
13	33	87.8	94.1	7.2	2282	2385	4.5	1371	1440	5.0	611	631	3.3	299	314	5.0
Mean	44.2	61.3	61.1	−3.2	2412	2566	6.3	1592	1694	6.2	569	611	6.6	252	261	3.3
SD	7.9	24.9	28.4	11.5	935	999	5.7	825	880	5.9	269	311	10.1	69	78	8.5
P		0.8574 (NS)			<0.01			<0.05			0.0502 (NS)			0.1267 (NS)		

[a]ADPKD, autosomal dominant polycystic kidney disease; V_{Cys}, cyst volume; V_{Int}, intermediate volume; V_{Par}, parenchymal volume; V_{Tot}, total volume.

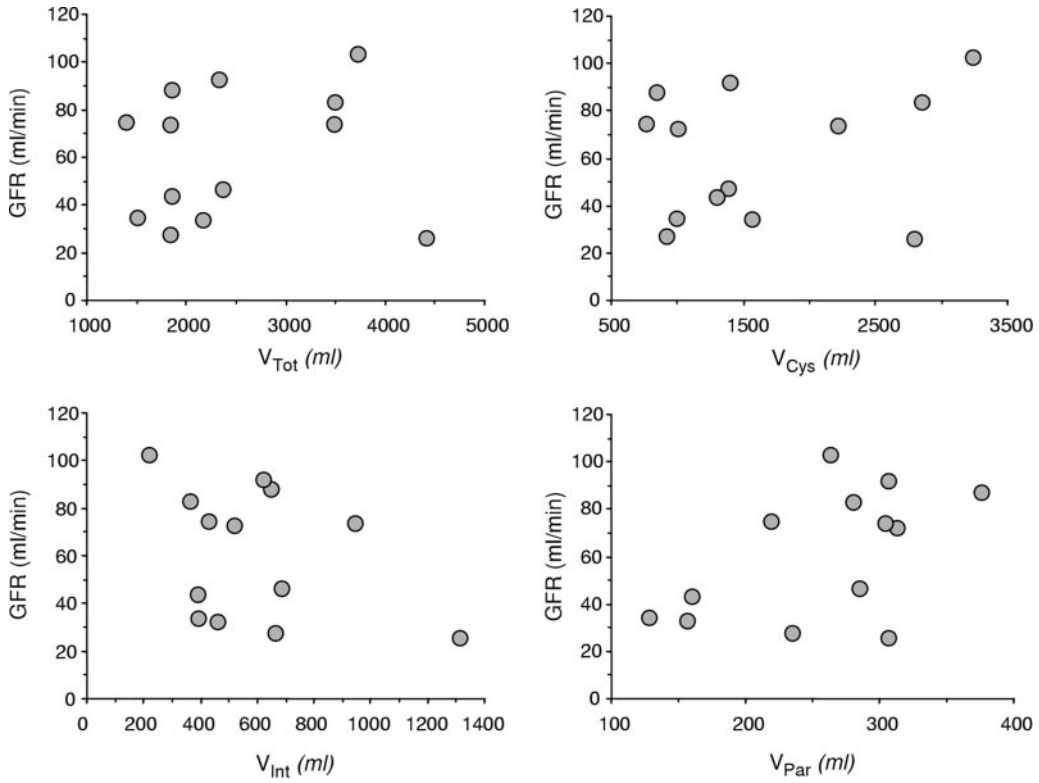

Figure 4. Kidney tissue volumes plotted against GFR. Individual values are obtained by averaging baseline and 6-mo follow-up values.

mediate, and parenchymal volume during the observation period *versus* changes in GFR also was taken into account. No significant correlations were found between percentage change in total, cyst, and parenchymal volume and percentage change in GFR. Percentage change in intermediate volume (ΔV_{Int}%), however, did correlate significantly with percentage changes in GFR ($r = -0.70$, $P < 0.01$), as shown in Figure 6 (top). In addition, as shown in Figure 6 (bottom), changes in intermediate volume relative to the baseline parenchymal volume ($\Delta V_{Int}/V_{Par}$ %) also correlated significantly with percentage changes in GFR ($r = -0.75$, $P < 0.005$).

Discussion

As mentioned previously, several reports in the literature (1,12,13) show that the progression of ADPKD is characterized by enlargement of renal cysts and loss of renal parenchyma. Until now, however, a direct demonstration of the relation between degree of structural alterations and loss of renal function is lacking (2), in that some patients may have very large cyst volume yet normal renal function, or, on the contrary, they may have small cyst volume but very low values of GFR.

In this study, we used CT imaging and state-of-the-art image-processing techniques to estimate renal volumes accurately in 13 patients who had advanced-stage ADPKD. Manual quantification of tissue volumes in patients with ADPKD is challenging because of the complex morphology that results from the development of the disease, which causes a large number of cysts of various sizes to grow at the expense of functional renal parenchyma. For this reason, we developed a semiautomatic method to allow a detailed characterization of kidney tissue volumes. Previous work in this direction has been geared toward the quantification of total kidney and cyst volume.

Three kidney tissue classes were characterized on CT images: Cysts, parenchyma, and intermediate volume. Large cysts appeared mostly uniform in intensity on all images, because the presence of large hemorrhagic cysts, which potentially could lead to nonuniformities, was limited by the exclusion criteria that were adopted in the selection of the patients who participated in the study (6). We cannot exclude, however, that hemorrhagic or protein-rich cysts of smaller size were classified in part as noncystic tissue. Renal parenchyma appeared bright and was assumed to represent functioning tissue. However, this same region also may include dilated tubular structures and small cysts that are still communicating with the tubular lumen. The slight increase in measured parenchymal volume in eight of 13 patients during the follow-up period therefore may be ascribable to this latter effect, as already pointed out in our previous study (6). Intermediate volume was introduced in the classification process to account for the presence of regions in which some enhancement could be noticed but whose intensity was markedly lower than that of typical vascularized tissue that was perfused uniformly with contrast, such as the renal parenchyma.

Our results on kidney tissue volume and GFR measurements allowed us to investigate the relation between morphologic and functional changes. Several patients had good renal function

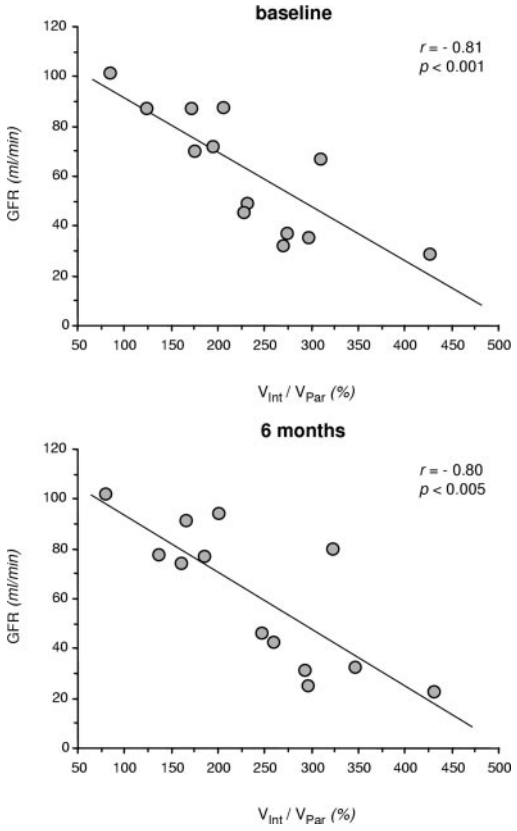

Figure 5. Ratio between intermediate volume over parenchymal volume plotted against GFR at baseline (top; $r = -0.81$, $P < 0.001$) and at the and of the 6-mo follow-up period (bottom; $r = -0.80$, $P < 0.005$).

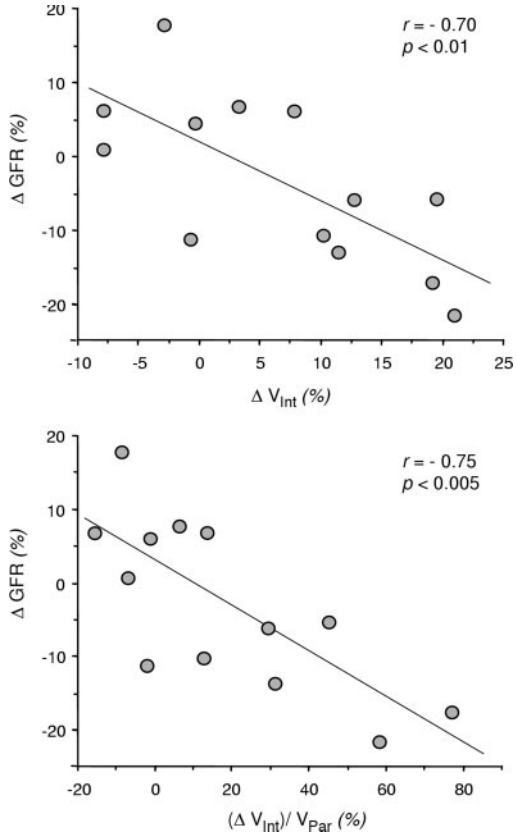

Figure 6. (Top) Percentage changes in intermediate volume plotted against percentage changes in GFR during the 6-mo period. (Bottom) Ratio between changes in intermediate volume over baseline parenchymal volume against percentage changes in GFR during the 6-mo period.

despite high cyst volumes and low residual parenchyma and *vice versa*. Therefore, no statistically significant relationships were observed between renal tissue volumes and renal function, although parenchymal volume showed a trend toward a positive correlation with GFR. It must be pointed out that the lack of an inverse correlation between cyst volume and renal function might be due to the relatively small size of our study and to the more advanced stage of the disease that characterized our patient population, and this could explain the discrepancy with previously reported studies (3,4). On the contrary, we did find a significant inverse correlation between GFR and the ratio between intermediate volume and parenchymal volume (V_{Int}/V_{Par}; see Figure 5). Patients with the highest ratio of intermediate to parenchymal volume showed the lowest GFR values, whereas patients with a low ratio of intermediate to parenchymal volume had high GFR. It is interesting that the largest cyst and parenchymal contiguous regions were found in patient 7, as shown in Figure 7, for which the highest GFR also was measured. Moreover, the patient presented the largest cyst volume and the smallest intermediate volume in the group. Image inspection showed that the morphology of structural alterations in this case followed a different path when compared with the rest of the patients in this study. In fact, in this patient, cysts formed mainly on the cortical side of the kidney and grew outward, so a large contiguous portion of parenchyma was preserved together with renal function, despite the large volume reached by cysts (see Figure 7). These observations potentially lead us to reconsider the role of cyst volume measurement alone in monitoring disease stage or progression or even in testing the effect of new treatments for ADPKD. The latter consideration is strengthened when one takes into account the relative changes in the observed quantities with time. In fact, although we did not find any significant correlation between percentage changes in total and cyst volume and percentage variations in GFR, we found a statistically significant correlation between percentage variations in intermediate volume and GFR. This seems to suggest that the growth of larger cysts is not reflected readily in a loss of renal function but rather that changes on a smaller scale are involved more directly in the process of renal functional loss. Whether a causal relationship exists between intermediate volume change and functional loss is not possible to assess in the context of this study. In particular, intermediate volume could be associated with regions of impaired contrast uptake as a result of low GFR, thereby being an effect rather than a representation of the cause of functional loss. However, at the same time, regions of lower contrast enhancement likely could be the result of the presence of enhanced and nonenhanced tissue within the same voxel. It is well known from the literature that a fraction of noncystic

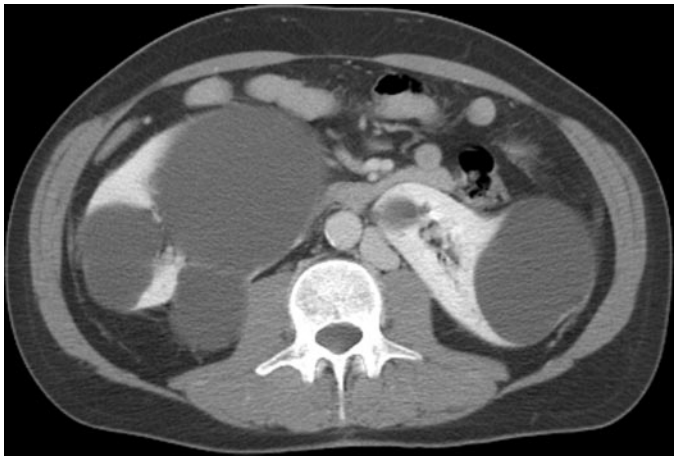

Figure 7. Radiologic appearance of kidneys in patient 7, who presented the largest cyst volume and at the same time the highest GFR in the group. In this patient, large cysts grew, leaving a considerable portion of parenchyma intact. It is interesting that this patient also had the smallest intermediate volume in the group.

renal tissue in ADPKD consists of atrophic or dilated tubuli, submillimetric cysts, and fibrotic lesions (13,14). In this case, intermediate volume could correspond to parenchymal tissue's undergoing structural changes, and this could explain the strong correlations found with renal functional loss, although further work is required before this hypothesis can be accepted.

Conclusion

Our findings further corroborate the need for finer quantification of tissue volume and morphology beyond sole cyst volume measurement and indicate a possible a new predictor of renal functional loss on the basis of renal structure evaluation. Our hypothesis is that the presence of diffuse changes in residual parenchyma as detected by contrast-enhanced CT may be deleterious for renal function. If our hypothesis is confirmed by future work, then this observation may represent an important shift in the follow-up and treatment of ADPKD.

Acknowledgments

Part of the work was presented as a poster at the annual meeting of the American Society of Nephrology, November 8 to 13, 2005, in Philadelphia, PA (*J Am Soc Nephrol* 16: S19A, 2005).

We thank Eng. Alessandra Zanardi for the help in image processing and data management and Dr. Flavio Gaspari for performing Iohexol determinations.

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