Original Paper

High Resolution Ultrasonography for Assessment of Renal Cysts in the PCK Rat Model of Autosomal Recessive Polycystic Kidney Disease

Sarika Kapoor[a,b]   Daniel Rodriguez[a,c]   Katharyn Mitchell[d]   Rudolf P. Wüthrich[a,b]

[a]Division of Nephrology, University Hospital, [b]Institute of Physiology, [c]Molecular and Translational Biomedicine, Competence Center for Personalized Medicine, [d]Clinic for Equine Internal Medicine, Vetsuisse Faculty, University of Zürich, Zürich, Switzerland

Abstract

Background/Aims: The PCK rat model of polycystic kidney disease is characterized by the progressive development of renal medullary cysts. Here, we evaluated the suitability of high resolution ultrasonography (HRU) to assess the kidney and cyst volume in PCK rats, testing three different ultrasound image analysis methods, and correlating them with kidneys weights and histological examinations. ***Methods:*** After inducing anesthesia, PCK rats (n=18) were subjected to HRU to visualize the kidneys, to perform numeric and volumetric measurements of the kidney and any cysts observed, and to generate 3-dimensional images of the cysts within the kidney parenchyma. ***Results:*** HRU provided superior information in comparison to microscopic analysis of stained kidney sections. HRU-based kidney volumes correlated strongly with kidney weights ($R^2=0.809$; P<0.0001). ***Conclusion:*** HRU represents a useful diagnostic tool for kidney and cyst volume measurements in PCK rats. Sequential HRU examinations may be useful to study the effect of drugs on cyst growth without the need to euthanize experimental animals.

© 2016 The Author(s)
Published by S. Karger AG, Basel

Introduction

Autosomal recessive polycystic kidney disease (ARPKD) has been estimated to have an incidence of 1:20,000 people and typically presents *in utero* or during the neonatal period with greatly enlarged, echogenic kidneys [1]. The disease is due to mutations in the gene

Rudolf P. Wüthrich, MD, FACP, FASN

Division of Nephrology, University Hospital, Rämistrasse 100, 8091 Zürich (Switzerland)
Tel. +41 44 255 33 84, Fax +41 44 255 45 93, E-Mail rudolf.wuethrich@usz.ch

KARGER

Pkhd1 which encodes for fibrocystin, a ciliary protein. The major histological manifestation is a fusiform dilatation of the collecting ducts where cysts are attached and do not separate from the parental tubules [2].

The PCK rat model is a well-known orthologous model of ARPKD that has been widely used to assess the therapeutic effect of drugs which retard cyst development in preclinical studies [3]. PCK rats develop multiple cysts in the renal medulla but not in the cortex. As the cysts grow the renal function deteriorates progressively, reducing the life span of the rats which generally die of renal failure.

A non-invasive imaging technique that is capable of high throughput, is relatively inexpensive and provides sufficient resolution to quantify the variables of interest with high accuracy may reduce the number of experimental animals [4]. High-frequency ultrasound technology recently became more accessible, which enables high-quality imaging of anatomical structures in mice and rats, and provides excellent temporal and spatial resolution [5].

Here, we explored for the first time if high resolution ultrasonography (HRU) is a suitable method to assess the cyst burden in anesthetized PCK rats. Ultrasonography was used to image PCK rat kidneys to determine total kidney volume (TKV), total cyst volume (TCV) and total cyst number (TCN). We compared 3 different methods for HRU-based TKV assessments, namely an HRU-stereological (HRUs), an HRU-automated (HRUa) and an HRU-ellipsoid (HRUe) method and correlated the findings with total kidney weight (TKW) and histological examination (HE).

Materials and Methods

Experimental design

All animal experiments were conducted in an ethical and humane fashion, and were approved by the district veterinary office of the Canton Zurich (permit number 175-2012) that is our institutional animal care and use committee (IACUC). PCK rats (an orthologous model of autosomal recessive PKD) were obtained from Charles River Laboratories (Sulzfeld, Germany). Heterozygous Cy/+ Han:SPRD rats (a non-orthologous model of autosomal dominant PKD) and homozygous wild type +/+ rats were obtained from the Rat Resource and Research Center (Columbia, MO, USA). All animals were bred in our animal facility. Only male rats were used since cysts develop more rapidly in male than in female rats. PCK rats were examined at the age of 7 weeks (n=6) and 12 weeks (n=12) by HRU to determine their TKV, TCV and TCN. After HRU examination, the rats were euthanized and both kidneys were excised, decapsulated and weighed. Kidney slices of approximately 2 mm were then fixed in 10% buffered formalin and embedded in paraffin for histological examination. Cy/+ Han:SPRD and wild type +/+ rats were examined at the age of 10 and 12 weeks respectively to compare their renal HRU images with those of the PCK rats.

High Resolution Ultrasonography (HRU)

Animal preparation. Isoflurane (5% induction, then 1.5-2% maintenance) in oxygen (1 L/min) was used to induce and maintain anaesthesia. Physiological variables (heart rate, respiratory rate, rectal temperature) were continuously monitored during the procedure, using a physiological monitoring unit (VisualSonics, Toronto, Canada). As shown in Fig. 1A and 1B, rats were placed in dorsal recumbency and were fixed on a dedicated handling table for rats (VisualSonics) using adhesive tape. The abdomen of the rats was clipped and all hair was removed using hair removal cream (Veet).

Image acquisition

HRU images were acquired using the Vevo 2100 high resolution ultrasound system (VisualSonics) equipped with the 18-38 MHz probe (MS400) and 3-dimensional (3-D) image motor. Acoustic coupling was ensured using ultrasound coupling gel. Following image optimisation, kidneys were imaged in a ventro-dorsal plane to acquire sequential transverse 2-dimensional (2-D) and power Doppler images of each kidney, using an automated 3-D motor head and the respiratory gating feature to avoid artefacts
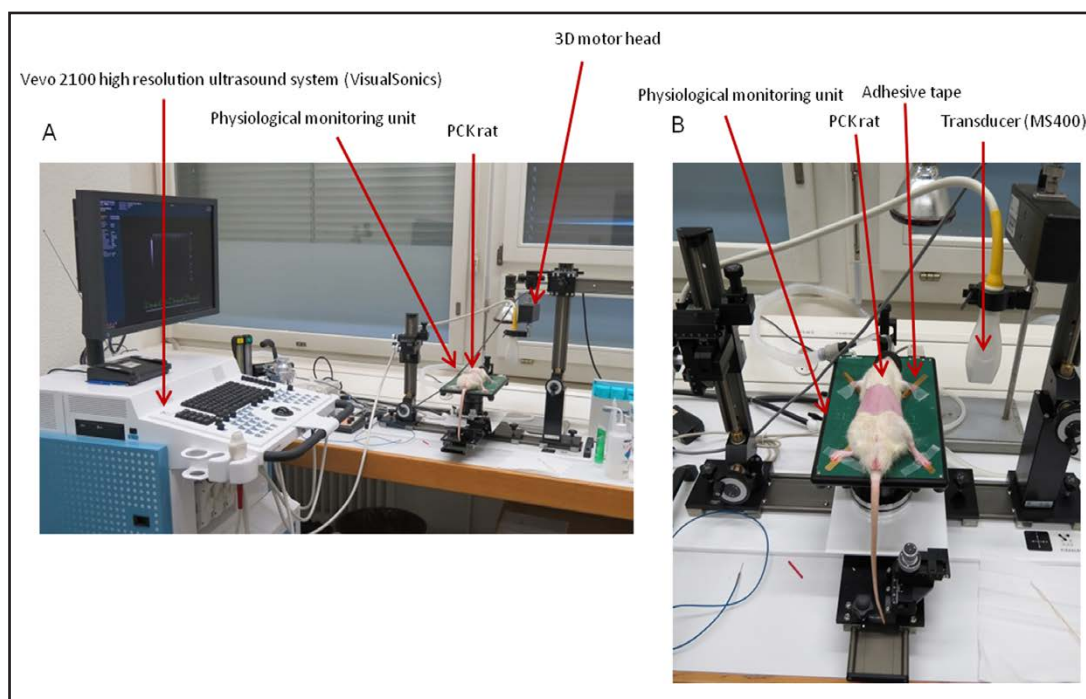
188

Fig. 1. Experimental set-up using high resolution ultrasonography (HRU) for the analysis of kidney and cyst volumes in anaesthetized PCK rats.

associated with respiratory motion. Care was taken to include the cranial and caudal poles of the kidney where possible (maximum scan distance 28 mm). The slice thickness between scanning planes was 0.05 mm with a maximum of 500 frames. The images were captured in digital raw format as 500 frame cineloops. Following imaging, the rats were euthanized with embutramide (T61®) via injection into the liver. All raw data files from HRU were copied to a work station and inspected to confirm complete coverage of both kidneys and image quality.

Image analysis
Stereological method. The 2-D transverse sequential cineloops were reconstructed into a rectangular 3-D model, using the VevoLab v1.6.0 software (VisualSonics). Tracing of the outer kidney surface and the outer wall of each cyst was performed manually in the 3-D reconstruction, using the volume measurement tools present in the VevoLab software as per the manufacturer's instructions. The resulting 3-D model was used to determine the stereological TKV (TKVs). Identification and measuring of all cystic structures allowed the determination of the TCV and the TCN. Finally, cystic index (CI) was calculated in percent as TCVs/TKVs*100.

Automated method. The 2-D transverse cineloops were exported from the VevoLab software and transferred to Analyze 12.0 software (AnalyzeDirect, Inc., Overland Park, KS, USA). Here, tracing of the kidney and cyst surface was performed in the 3-D reconstruction by semi-automatic tools present in the Analyze 12.0 software as per the manufacturer's instructions. The resulting 3-D model was used to determine automated TKV (TKVa) and automated TCV (TCVa). The CI was again calculated in percent as TCVa/TKVa*100.

Ellipsoid method. The 2-D and 3-D cineloops were used to determine the 3 renal dimensions (length, lateral diameter [width], anterior-posterior diameter [depth]). Renal length was determined from axial slices by multiplying the slice thickness by the number of slices between the cranial and caudal poles of the kidneys. Lateral diameter was measured from the lateral extent of the kidney to the renal sinus and

KARGER

Kidney
& Blood Pressure
Research

Kidney Blood Press Res 2016;41:186-196

10.1159/000443420
Published online: March 17, 2016

© 2016 The Author(s). Published by S. Karger AG, Basel
www.karger.com/kbr

189

Kapoor/Rodriguez/Mitchell/Wüthrich: Ultrasonography and Polycystic Kidney Disease

Fig. 2. Representative transverse 2-dimensional (2-D) B-mode images of the right kidney, overlaid with power Doppler (red areas) to identify blood flow within the renal parenchyma in 7-week old PCK rat (A), 12-week old PCK rat (B), 10-week old Cy/+ (Han:SPRD) rat (C) and 12-week old wild-type (+/+) rat (the latter is a 2-D B-mode image without power Doppler) (D).
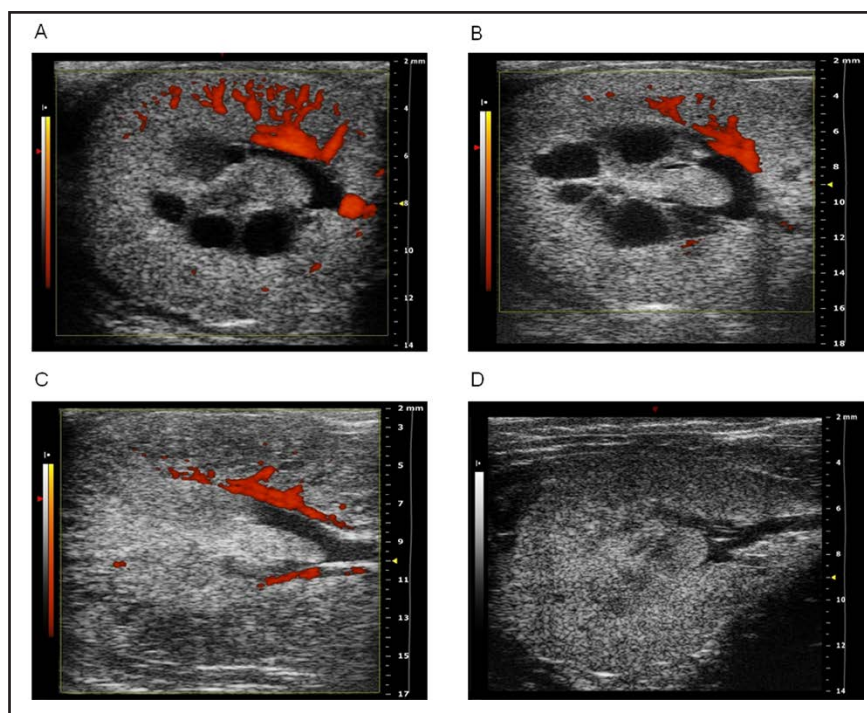
anterior-posterior diameter was measured perpendicular to the lateral diameter. The ellipsoid TKV (TKVe) was calculated using the ellipsoid formula (length × lateral diameter × anterior-posterior diameter × π/6).

Histological analysis (HA)

One of the kidneys from each rat was used for the histological analysis and was sliced perpendicularly to the long axis at approximately 2 mm intervals. Slices from the mid-portion of the kidneys were fixed in 10% buffered formalin overnight, and tissues were then embedded in paraffin. Three μm sections were stained with Periodic acid–Schiff (PAS) staining following a routine protocol. The stained sections were subjected to CI analysis, using the HistoQuest image analysis software (TissueGnostics, Vienna, Austria). We calculated the total cystic and total kidney area in six full cross sections of each kidney and averaged the total cystic area (TCA) and total kidney area (TKA) in each PCK rat. The CI was calculated in percent as TCA/TKA*100.

Statistical analysis

Data are expressed as means ± SD. Different age groups were compared with two-tailed Student's t-test for unpaired data by using the GraphPad Prism version 5.0 software (GraphPad, San Diego, CA, USA). Bland–Altman plot and Pearson correlation test were used to show the differences in TKVs vs TKVa, TKVs vs TKVe, TKW vs TKVs and TKW vs TKVa. P values of <0.05 were considered statistically significant.

Results

TKV, TCV and TCN determination by stereological method

We performed HRU on 7- and 12-week old PCK rats (Fig. 2A and 2B), 10-week old heterozygous Cy/+ Han:SPRD rats (Fig. 2C) and 12-week old wild type +/+ rats (Fig. 2D). The kidney cysts were readily visible in 7- and 12-week old PCK rats. In Cy/+ Han:SPRD rats, the kidneys appeared to be enlarged compared with +/+ wild-type rats. Furthermore, the renal cortex showed an increased echogenicity in Cy/+ compared with +/+. Contrasting with PCK, individual cysts could however not be identified in Cy/+ kidneys, which is in line with the

Table 1. HRU-based stereological analysis of kidney and cyst volume in 7- and 12-week old PCK rat kidneys

	Volume of kidney (mm³)			Volume of all cysts (mm³)			Number of cysts			Cyst index (%)		
	Left	Right	Total	Left	Right	Total	Left	Right	Total	Left	Right	Mean
7-week old PCK rats												
1	1462	1366	2828	116	85	201	27	34	61	7.9	6.2	7.1
2	1439	1557	2996	57	68	125	26	37	63	4.0	4.4	4.2
3	1607	1636	3243	57	68	126	19	37	56	3.5	4.2	3.9
4	1587	1808	3394	77	70	147	24	34	58	4.9	3.9	4.4
5	1842	1812	3654	101	128	230	22	33	55	5.5	7.1	6.3
6	1973	1843	3815	93	160	253	30	38	68	4.7	8.7	6.7
Mean	1652	1670	3322	84	97	180	25	36	60	5.1	5.7	5.4
SD	194	171	345	22	35	50	4	2	4	1.4	1.8	1.3
12-week old PCK rats												
1	1767	2029	3796	50	110	160	22	29	51	2.8	5.4	4.1
2	1906	1902	3808	89	75	163	33	27	60	4.7	3.9	4.3
3	1963	1961	3924	96	102	198	26	25	51	4.9	5.2	5.0
4	1813	2205	4018	60	96	156	23	32	55	3.3	4.3	3.8
5	2078	2052	4130	156	73	229	41	36	77	7.5	3.6	5.5
6	2021	2427	4448	114	151	265	54	39	93	5.6	6.2	5.9
7	2365	2141	4506	119	70	189	21	27	48	5.0	3.3	4.2
8	2001	2543	4544	95	157	252	43	40	83	4.7	6.2	5.5
9	2620	2440	5060	61	94	155	28	25	53	2.3	3.9	3.1
10	2487	2588	5075	56	75	130	29	27	56	2.2	2.9	2.6
11	3106	2366	5472	141	84	225	20	29	49	4.6	3.5	4.1
12	2947	2923	5870	153	98	251	42	50	92	5.2	3.4	4.3
Mean	2256	2298	4554	99	99	198	32	32	64	4.4	4.3	4.4
SD	428	291	653	37	28	44	10	7	16	1.5	1.1	1.0

known histological observations. Thus, the PCK model appeared suitable for determining the TCV and TCN in addition to TKV by HRU, whereas in the Cy/+ only the TKV could be determined.

Thus, we then focused on PCK rats to determine TKV, TVC and TCN in 7- and 12-week old rats by the stereological image analysis method (Table 1). As expected, there was a significant increase in TKVs with age from 3322 ± 345 mm³ at 7 weeks to 4554 ± 653 mm³ at 12 weeks (P=0.0009), whereas the TCVs (180 ± 50 vs 198 ± 44 mm³; P=0.4861), the TCNs (60 ± 4 vs 64 ± 16; P=0.6048) and the CI (5.4 ± 1.3 vs 4.4 ± 1.0%; P=0.0786) did not change between 7- and 12- weeks of age.

Altogether our findings demonstrate that TKVs, TCVs and TCNs can easily be measured by HRU in the PCK rat model, whereas HRU only allows to determine TKVs in the Cy/+ rat model because the cysts are too small to be detected by HRU.

TKV determination by automated and ellipsoid methods

We then determined the TKV by the automated (TKVa) and the ellipsoid (TKVe) method in 7- and 12-week old PCK rats, as well as in 10-week old Cy/+ Han:SPRD rats, and compared the values to the stereologically determined TKVs. These volumes were then correlated with the TKW which was obtained after euthanizing the animals. The time needed to measure TKVs was 20-30 minutes per animal, compared with 15-20 minutes for TKVa and 10-12 minutes for TKVe. Table 2 shows that the TKV analyzed by these three methods showed similar values, but with highest value for TKVs followed by TKVa and TKVe in 7-weeks old (3322 >3141>2937 mm³) and in 12-weeks old (4554 >4308>3871 mm³) PCK rats as well as in 10-weeks old (6610>6442>6035 mm³) Cy/+ rats. The TKV detected by these three methods (TKVs, TKVa, and TKVe) were also in good agreement with the TKW (Table 2).

KARGER

Fig. 3A and 3C show that there was a strong correlation of TKVs with TKVa (R^2=0.991, P<0.0001) and TKVe (R^2=0.966, P<0.0001) in PCK rats (n=18). The corresponding Bland-Altman plots (Fig. 3B and 3D) show that the TKVs exceeds the TKVa by 5.6 ± 2.1% (95% confidence interval, 1.5% to 9.9%) and the TKVe by 15.0 ± 3.8% (95% confidence interval, 7.6% to 22.4%). In Cy/+ rats (n=5) we also found a strong correlation of TKVs with TKVa (R^2=0.973, P=0.0019) and TKVe (R^2=0.999, P<0.0001) (graphs not shown).

TKV correlation with TKW

We then correlated TKVs and TKVa with TKW (Fig. 4A and 4B). TKW correlated well with TKVs (R^2=0.809, P<0.0001) and TKVa (R^2=0.782, P<0.0001) in PCK rats (n=18). The TKW (in mg) exceeded TKVs and TKVa (in mm³) which is consistent with the specific weight of kidney tissue that is higher than water. In Cy/+ rats (n=5) the TKW also correlated well with TKVs (R^2=0.961, P=0.0033) and TKVa (R^2=0.940, P=0.0176) (graphs not shown).

Comparison of HRU with histological analysis (HA)

Using HA, the cyst burden in the PCK model can be estimated by CI determination which is calculated by dividing TCA with TKA and multiplying by 100. We were interested to determine the correlation of this area-based CI by HA with the volume-based CI which is obtained by HRUs and HRUa by dividing the TCV with TKV, multiplied by 100. The CI was significantly higher by HA in comparison to HRUs- and HRUa-based CI in 7- and 12- week old PCK rats (Table 3). Fig. 5A and 5B illustrate the histological view in a 7- and a 12-week old PCK rat and demonstrate the cyst growth between 7- and 12- weeks. Fig. 5C shows that the correlation between the area-based CI and the volume-based CI was weak (R^2=0.026, P=0.5247) (n=18).

3-D reconstruction from HRU

We finally generated 3-D reconstructions of HRU images which were acquired from PCK rat kidneys. Fig. 6A shows the tracings of the outer kidney and cyst wall used for the final reconstruction of the kidney and all cysts. Fig. 6B illustrates the types of 3-D images that can be obtained, revealing excellent spatial resolution of the cysts within the renal parenchyma in PCK rats (see also video clip of 3-D reconstructed kidney with cysts in a 12-week old PCK rat shown at the right QR-Code).

Table 2. Comparison of total kidney volumes as determined by stereological (TKVs), automated (TKVa) and ellipsoid (TKVe) methods with total kidney weight (TKW) in 7- and 12-week old PCK rats and in 10 weeks old Cy/+ Han:SPRD rats

	TKVs (mm³)	TKVa (mm³)	TKVe (mm³)	TKW (mg)
7-week old PCK rats				
1	2828	2695	2513	3470
2	2996	2678	2526	3400
3	3243	3111	2883	4080
4	3394	3215	3073	3430
5	3654	3501	3233	3700
6	3815	3645	3395	4210
Mean	3322	3141	2937	3715
SD	345	366	334	321
12-week old PCK rats				
1	3796	3544	3268	4190
2	3808	3701	3347	3920
3	3924	3592	3147	4140
4	4018	3856	3424	3700
5	4130	3859	3345	3900
6	4448	4212	4056	4500
7	4506	4121	3642	5440
8	4544	4389	3846	4200
9	5060	4834	4455	5630
10	5075	4777	4304	5010
11	5472	5195	4664	6090
12	5870	5610	4950	5900
Mean	4554	4308	3871	4718
SD	653	639	581	816
10-week old Han:SPRD rats				
1	4470	4529	4098	3900
2	6488	6297	5951	6300
3	6973	6515	6321	7600
4	7053	6761	6438	7100
5	8067	8106	7366	8100
Mean	6610	6442	6035	6600
SD	1187	1145	1075	1475

Video clip. Video clip of 3-D reconstructed kidney with cysts in a 12-week old PCK rat.

Fig. 3. Correlation of stereological total kidney volume (TKVs) with automated total kidney volume (TKVa) (A and B) and with ellipsoid total kidney volume (TKVe) (C and D) in 7- and 12-week old PCK rats (n=18).
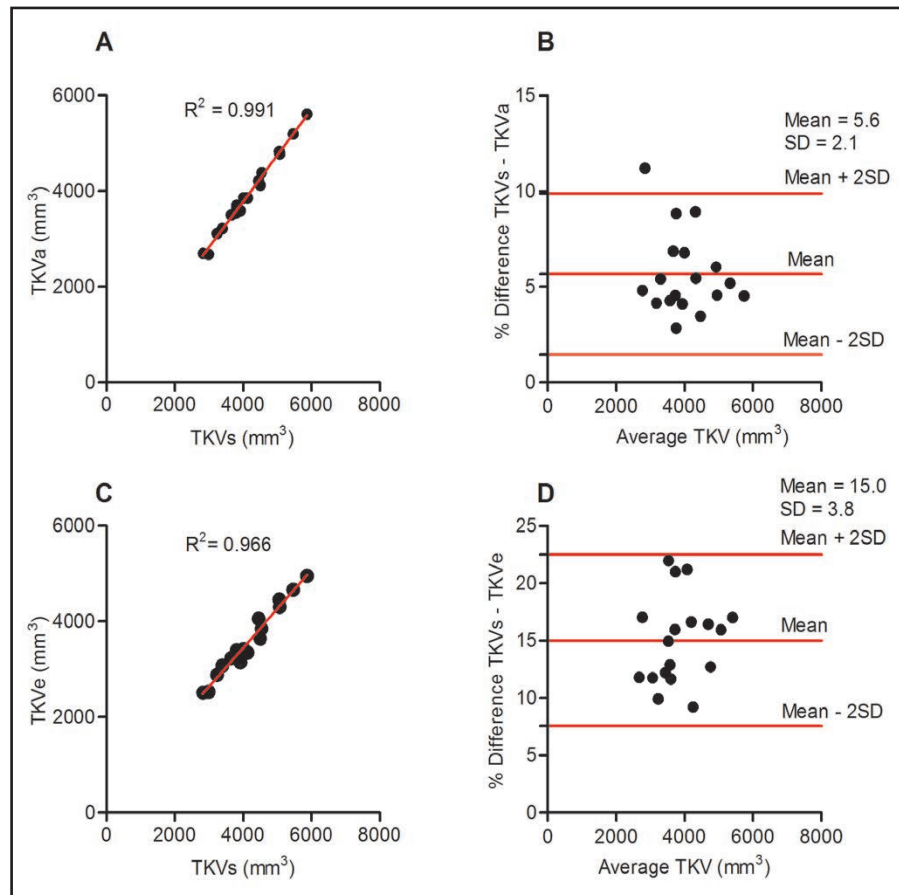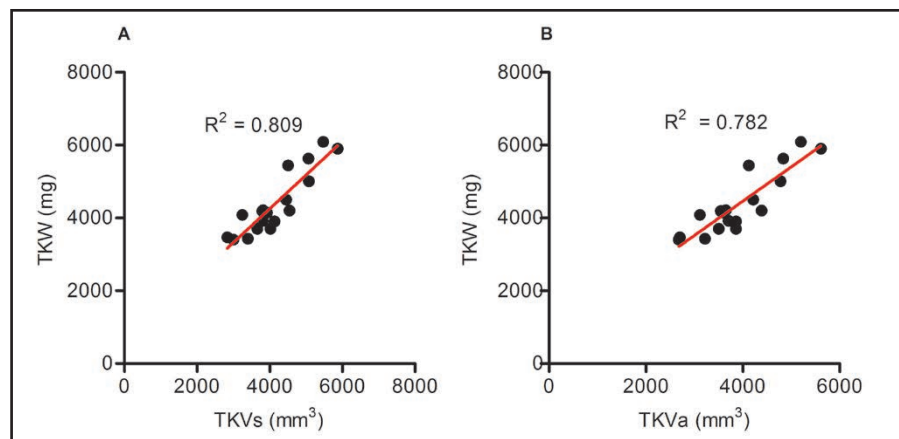

Fig. 4. Correlation of total kidney weight (TKW) with stereological total kidney volume (TKVs) (A) and with automated total kidney volume (TKVa) (B) in 7- and 12-week old PCK rats (n=18).

Discussion

In this study, we tested the utility of HRU in two different rat models of PKD, the PCK and the Han:SPRD rats. HRU allowed to visualize renal cysts and to determine the kidney and cyst volume and the number of cysts in PCK rats, whereas HRU did not allow to visualize the cysts in the Han:SPRD rat model of PKD since the cysts are too small to be visualized with the 18-38 MHz ultrasound probe. Nevertheless, the kidney volumes could be determined by HRU in Han:SPRD rat. Thus, the method could therefore be useful to follow kidney volume changes over time as well as in response to experimental therapies.

KARGER

Kidney Blood Press Res 2016;41:186-196

10.1159/000443420
Published online: March 17, 2016

© 2016 The Author(s). Published by S. Karger AG, Basel
www.karger.com/kbr

193

Kapoor/Rodriguez/Mitchell/Wüthrich: Ultrasonography and Polycystic Kidney Disease

Among the three different types of HRU-based volumetric measurements (stereological, automated and ellipsoid) the stereological method was the most time consuming. Assuming that TKVs might provide the most precise volume measurements, the TKVa and the TKVe appeared to systematically underestimate the "true" TKV. All three methods correlated well with each other, and also with kidney weights. HRU also allowed accurate quantification of the number of cysts in each kidney, a parameter that cannot be obtained with the 2-D histological analysis that is unable to represent the entire kidney.

The HRU-based cyst volume determinations yielded cystic indices (CI) which did not correlate with the indices obtained by histological analysis. Assuming a more precise estimation of the cyst burden by determining the CI with the volumetric method, we believe that HRU improves precision over the histological method. This may be particularly relevant for experimental research which tests novel drugs to retard PKD disease progression.

PKD research has increased exponentially in the last three decades and has led to the development of several candidate drugs to prevent disease progression (i.e. cyst growth). Recent clinical trials with some of these drugs provided modest but encouraging results. However the management of most patients with ADPKD continues to be restricted to the detection and treatment of renal and extra-renal complications, and timely initiation of renal

Table 3. HRU-based cystic index (CI) determination using stereological (HRUs) and automated (HRUa) method, and comparison with histological analysis (HA)-based CI in 7- and 12- week old PCK rats

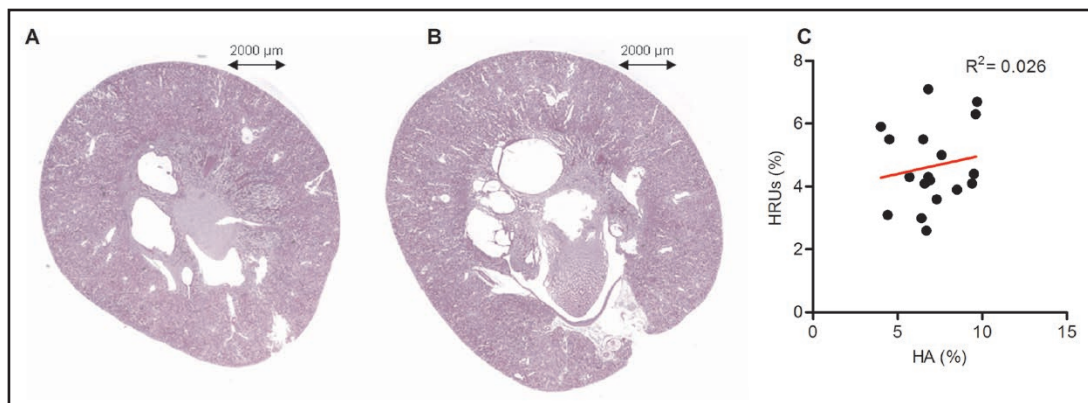|	HRUs (%)	HRUa (%)	HA (%)
7-week old PCK rats			
1	3.9	3.6	8.5
2	4.1	3.9	9.4
3	4.4	4.1	9.5
4	6.3	5.9	9.6
5	6.7	6.4	9.7
6	7.1	6.8	6.8
Mean	5.4	5.1	8.9
SD	1.3	1.3	1.1
12-week old PCK rats			
1	2.6	2.5	6.7
2	3.1	2.9	4.4
3	4.1	3.7	6.6
4	4.1	3.3	7.3
5	4.2	3.9	6.9
6	4.3	4.1	5.7
7	5.0	4.8	7.6
Mean	3.9	3.6	6.5
SD	0.8	0.7	1.0

Fig. 5. Detection of cysts in male PCK rats by histology using Periodic acid–Schiff (PAS) staining in 7-week old (A) and 12-week old (B) PCK rats. Correlation of areal cystic index (%) obtained from histological analysis (HA) with volumetric cystic index (%) obtained from high resolution ultrasonography (HRU) using stereological method (HRUs) in PCK rats (C) (n=18).

replacement therapy which includes dialysis and transplantation [6]. The PCK rat represents a reliable experimental model of PKD that has been widely used to evaluate the efficacy of pharmacological interventions designed to ameliorate PKD. Thus, several drugs have been tested in PCK rats, including vasopressin V_2 receptor antagonists which were shown to be
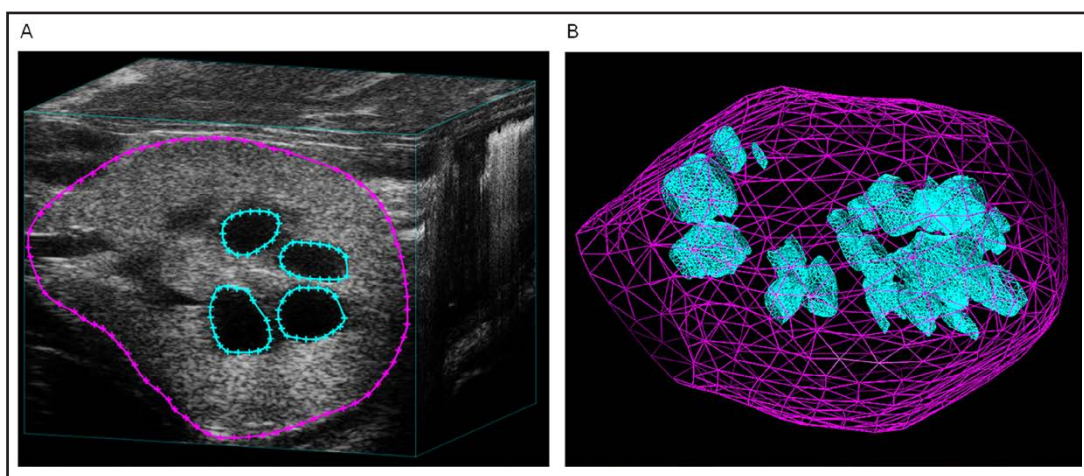
Fig. 6. A 3-dimensional (3-D) reconstruction from a PCK rat kidney showing the tracings of the outer cyst wall used for the final reconstruction (A), allowing visualisation of the kidney and the intra-parenchymal cysts and their spatial orientation (B).

effective in reducing cyst growth and slowing the decline of kidney function [7-9]. Other examples include chronic water loading which also ameliorated the renal pathology by an inhibition of vasopressin secretion [10] and the somatostatin agonists octreotide and pasireotide [11, 12]. In all these studies disease progression was monitored by histological analysis and not by ultrasound imaging. HRU offers the advantage over histological analyses to be more accurate and to be used repetitively without the need to euthanize the experimental animals. In previous studies, we examined the effect of dapagliflozin, an inhibitor of the renal sodium-glucose cotransporter 2 (SGLT2), in Han:SPRD [13] and in PCK rats [14] and found quite surprisingly that the drug had opposing effects. In PCK rats we evaluated the utility of HRU and found that HRU was very robust in evaluating the effect of the drug. Based on our results, we therefore recommend HRU in the PCK rat strain to precisely monitor cyst progression and to study the effect of novel drug therapies.

Our study is extending data from another study where it was shown that volume changes in the rat kidney can be measured *in vivo* with 3-D ultrasound using a position sensor [15, 16]. Furthermore, ultrasonography examination was shown to be useful and reliable for diagnosing PKD in cats with polycystic kidney [17-19]. It has also been shown that the resistive index which measures the arterial resistance in the peripheral vessels by Duplex-ultrasound is a valuable diagnostic tool to detect renal diseases in cats [20]. It is only by the HRU method however that intrarenal cysts can be visualized in rats. HRU therefore opens new possibilities for measurements of the volumes of organs in small animals such as rats.

As there is a great need to reduce the number of experimental animals, HRU might contribute to using a lower number of rats when examining cyst progression in PCK rats, since HRU offers sequential visualization of the cystic disease process in these rats over time. Thus, PCK rat kidneys can be examined at various intervals along a given treatment time, allowing dose adaptations and treatment prolongations without the need to sacrifice the experimental animals. In addition, since PCK also suffer liver disease, the HRU technique could also be used for sequential liver volume measurements. Thus, additional information can be gained in a single experimental animal with the advantage of a potentially lower number of rats.

In summary, we have shown that HRU is a very useful tool for measuring kidney and cyst volume in the PCK rat model of ARPKD, facilitating future pharmacological studies and offering the advantage to use a lower number of experimental animals.

Kidney Blood Press Res 2016;41:186-196

10.1159/000443420
Published online: March 17, 2016

© 2016 The Author(s). Published by S. Karger AG, Basel
www.karger.com/kbr

195

Kapoor/Rodriguez/Mitchell/Wüthrich: Ultrasonography and Polycystic Kidney Disease

Conclusion

HRU was used to determine total kidney and cyst volumes in PCK rats with polycystic kidney disease. HRU allows generating 3-D models from the sequentially obtained 2-D cineloops which scan each kidney from its cranial to caudal pole. This represents an excellent technique for visualizing the spatial orientation of the cysts within the kidney. Moreover, HRU-based TKV showed strong correlation with the respective kidney weights. HRU appears to be a suitable method to assess the progression of disease without euthanizing animals.

Abbreviations

ARPKD- autosomal recessive polycystic kidney disease; CI- cystic index; HA- histological analysis; HRU- high resolution ultrasonography; TCA- total cystic area; TKA- total kidney area; TCN- total cyst number; TCV- total cyst volume; TKV- total kidney volume; TKW- total kidney weight.

Disclosure Statement

The authors declare that they have no competing financial interest in the work presented here.

Acknowledgments

References

1   Harris PC, Torres VE: Polycystic kidney disease. Annu Rev Med 2009;60:321-337.
2   Bergmann C: ARPKD and early manifestations of ADPKD: The original polycystic kidney disease and phenocopies. Pediatr Nephrol 2015;30:15-30.
3   Mason SB, Liang Y, Sinders RM, Miller CA, Eggleston-Gulyas T, Crisler-Roberts R, Harris PC, Gattone VH, 2nd: Disease stage characterization of hepatorenal fibrocystic pathology in the PCK rat model of ARPKD. Anat Rec (Hoboken) 2010;293:1279-1288.
4   Moran CM, Pye SD, Ellis W, Janeczko A, Morris KD, McNeilly AS, Fraser HM: A comparison of the imaging performance of high resolution ultrasound scanners for preclinical imaging. Ultrasound Med Biol 2011;37:493-501.
5   Khankin EV, Hacker MR, Zelop CM, Karumanchi SA, Rana S: Intravital high-frequency ultrasonography to evaluate cardiovascular and uteroplacental blood flow in mouse pregnancy. Pregnancy Hypertens 2012;2:84-92.
6   Chebib FT, Sussman CR, Wang X, Harris PC, Torres VE: Vasopressin and disruption of calcium signalling in polycystic kidney disease. Nat Rev Nephrol 2015;11:451-464.

KARGER

7   Wang X, Gattone V, 2nd, Harris PC, Torres VE: Effectiveness of vasopressin V2 receptor antagonists OPC-31260 and OPC-41061 on polycystic kidney disease development in the PCK rat. J Am Soc Nephrol 2005;16:846-851.

8   Gattone VH, 2nd, Wang X, Harris PC, Torres VE: Inhibition of renal cystic disease development and progression by a vasopressin V_2 receptor antagonist. Nat Med 2003;9:1323-1326.

9   Torres VE, Chapman AB, Devuyst O, Gansevoort RT, Grantham JJ, Higashihara E, Perrone RD, Krasa HB, Ouyang J, Czerwiec FS, Investigators TT: Tolvaptan in patients with autosomal dominant polycystic kidney disease. N Engl J Med 2012;367:2407-2418.

10 Nagao S, Nishii K, Katsuyama M, Kurahashi H, Marunouchi T, Takahashi H, Wallace DP: Increased water intake decreases progression of polycystic kidney disease in the PCK rat. J Am Soc Nephrol 2006;17:2220-2227.

11 Masyuk TV, Radtke BN, Stroope AJ, Banales JM, Gradilone SA, Huang B, Masyuk AI, Hogan MC, Torres VE, Larusso NF: Pasireotide is more effective than octreotide in reducing hepatorenal cystogenesis in rodents with polycystic kidney and liver diseases. Hepatology 2013;58:409-421.

12 Masyuk TV, Masyuk AI, Torres VE, Harris PC, Larusso NF: Octreotide inhibits hepatic cystogenesis in a rodent model of polycystic liver disease by reducing cholangiocyte adenosine 3',5'-cyclic monophosphate. Gastroenterology 2007;132:1104-1116.

13 Rodriguez D, Kapoor S, Riwanto M, Edenhofer I, Segerer S, Mitchell K, Wüthrich RP: Inhibition of sodium-glucose cotransporter 2 with dapagliflozin in Han: SPRD rats with polycystic kidney disease. Kidney Blood Press Res 2015;40:638-647.

14 Kapoor S, Rodriguez D, Riwanto M, Edenhofer I, Segerer S, Mitchell K, Wüthrich RP: Effect of sodium-glucose cotransport inhibition on polycystic kidney disease progression in PCK rats. PLoS One 2015;10:e0125603.

15 Stormark TA, Strommen K, Iversen BM, Matre K: Three-dimensional ultrasonography can detect the modulation of kidney volume in two-kidney, one-clip hypertensive rats. Ultrasound Med Biol 2007;33:1882-1888.

16 Bakker J, Olree M, Kaatee R, de Lange EE, Moons KG, Beutler JJ, Beek FJ: Renal volume measurements: Accuracy and repeatability of US compared with that of MR imaging. Radiology 1999;211:623-628.

17 Biller DS, DiBartola SP, Eaton KA, Pflueger S, Wellman ML, Radin MJ: Inheritance of polycystic kidney disease in Persian cats. J Hered 1996;87:1-5.

18 Bonazzi M, Volta A, Gnudi G, Bottarelli E, Gazzola M, Bertoni G: Prevalence of the polycystic kidney disease and renal and urinary bladder ultrasonographic abnormalities in Persian and Exotic Shorthair cats in Italy. J Feline Med Surg 2007;9:387-391.

19 Lee YJ, Chen HY, Hsu WL, Ou CM, Wong ML: Diagnosis of feline polycystic kidney disease by a combination of ultrasonographic examination and PKD1 gene analysis. Vet Rec 2010;167:614-618.

20 Tipisca V, Murino C, Cortese L, Mennonna G, Auletta L, Vulpe V, Meomartino L: Resistive index for kidney evaluation in normal and diseased cats. J Feline Med Surg 2016, in press.