Saudi J Kidney Dis Transpl 2016;27(6):1139-1147

Saudi Journal of Kidney Diseases and Transplantation

Original Article

Renal Shear Wave Velocity and Estimated Glomerular Filtration Rate in Children with Chronic Kidney Disease

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ABSTRACT. A shear wave velocity (SWV) value obtained by the acoustic radiation force impulse technique depends on tissue elasticity. We investigated the relationship between SWV values and the estimated glomerular filtration rate (eGFR) in children with chronic kidney disease. A total of 29 patients were enrolled in the study. There were 18 primary and 11 secondary cases of vesico-ureteral reflux. eGFR was calculated using Schwartz's formulas (2012). Partial eGFR for each kidney was assessed by multiplying the eGFR by the percentage of renal function measured by means of renal (99m)Tc-dimercaptosuccinic acid scintigraphy. All ultrasound tests were done by a single qualified technician using a convex probe (frequency 4 MHz) on an S-2000 system. The mean SWV values of the two kidneys were significantly and negatively correlated with eGFR calculated with both univariate (cystatin C [Cys C]) and multivariate (creatinine, Cys C, and nitrogen) equations. Of all the formulae, the strongest correlation was obtained with eGFR (Cys C). SWV of the renal cortex correlates with the eGFR of patients affected by malformative uropathies. Nevertheless, this technique needs standardization and validation.

Introduction

Malformative uropathies are a considerable cause of chronic kidney disease (CKD), renal insufficiency, and transplants, especially in children. Malformative uropathies of the lower urinary tract include vesicoureteral reflux (VUR) and posterior urethral valves (PUVs). The mechanisms for the development of CKD in the presence of VUR and/or PUVs are complex. Reverse flow of urine can affect all of the urinary tract organs including the kidney.[1] The pathogenesis of CKD can be linked to the substitution of the glomeruli with fibrotic, non-functional tissue. Primary high-grade VUR is an established cause of renal scarring.[2] Moreover, long-term renal prognosis in PUVs is worse in children with bilateral VUR and with severe initial presentation.[3]

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Serial serum creatinine (Scr) and cystatin C (Cys C) are routinely measured during follow-up of renal function in children with CKD. In particular, serum Cys C has been proposed as a better marker of glomerular filtration (GFR), even in cases of sub-clinical renal dysfunction.[4] Based on Scr alone, or Cys C alone, or in combination with blood urea nitrogen (BUN), univariate or multivariate equations, respectively, have been formulated to give an estimation of the GFR (eGFR) of patients with CKD.[5]

Acoustic radiation force impulse (ARFI) is a recently established ultrasound (US)-based diagnostic technique that allows physicians to obtain a measure of the elastic properties of an organ.[6] Shear wave velocity (SWV) obtained by the ARFI technique depends on the elasticity of tissues. The speed of the shear waves within a region of interest (ROI) selected by the operator on the conventional US image may be represented either with a qualitative (i.e., a gray-scale map) or with a quantitative (i.e., the precise determination of the SWV) approach.[7] SWV proves accurate in the grading of liver fibrosis in patients with chronic hepatitis or cirrhosis;[6] on the contrary, these results when dealing with kidneys are controversial at present.[8]

In nephrology, most renal elasticity quantification studies are on transplanted kidneys. Recently, SWV values were found to be positively correlated with the grade of allograft fibrosis and inversely correlated with eGFR.[9]

On the contrary, native kidneys have been poorly investigated. We recently reported that the renal SWV values of children affected by high-grade VUR were significantly higher than healthy controls.[7] Since childhood malformative uropathies are associated with CKD and reduced renal function, the aim of the present study was to analyze previous investigation results by assessing the existing relationship between SWV values and eGFR.

Subjects and Methods

High-grade VUR (Grade III or higher) was adopted as the primary inclusion criterion in this study. VUR and grading were assessed by a standard radiological method - voiding cystourethrogram (VCUG) - according to the classification criteria of the International Reflux Study Committee.[10] Based on the above criterion, a total of 29 patients were included in our study. There were 18 primary and 11 secondary (PUVs) VUR; 13 monolateral (7 right) and 16 bilateral VUR. Two children with PUVs had a solitary functional right kidney. One of them had a VUR of Grade I (the left kidney, surgically removed, had a VUR of Grade V). Twenty-seven children enrolled in the present protocol had also participated in one of our previously published studies.[7] This study was approved by the Ethic Committee of our Institution.

At the time of admission, the patients were in good condition. The renal function of each patient was assessed measuring by standard methods, the laboratory parameters namely Scr, CysC, BUN, and urinary protein/creatinine ratio). CysC was measured by immunonephelometry using a latex particle-coated method with specific antibodies.[11]

All children underwent (99m)Tc-dimercaptosuccinic acid (DMSA) scintigraphy, with age- and weight-related dose reduction according to the recommendations of the European Association of Nuclear Medicine[12] to assess the percentage of renal scintigraphic uptake by each kidney.

The eGFR was calculated by means of Schwartz's multivariate or univariate formulas for children with CKD.[5] In particular, the multivariate equation was: eGFRncc = 39.8 × [(ht (m)/Scr)^0.456 × (1.8/cysC)^0.418 × (30/BUN) ^0.079 × 1.076 males × (ht (m)/1.4)] ^0.1 79; the univariate equations were: eGFRcr = 0.413 [ht (cm)/Scr] and $eGFR_{cy}$ = 70.69 (cysC)^ − 0.931. Partial eGFR (peGFR) for the right and left kidneys was calculated by multiplying the eGFR by the percentage of renal function of each kidney, assessed by means of renal DMSA scintigraphy.

USs were performed by a single qualified technician with 15 years of experience in abdominal US using a convex probe (frequency 4.5 MHz) on an ACUSON S2000TM system

(Siemens, Erlanger, Germany). All patients were evaluated soon after micturition, in the supine position with a subcostal approach, during breath-holding. The technician was blinded concerning the scintigraphy and VCUG results, to prevent possible bias. The US system was equipped with a quantitative implementation of the ARFI technology (virtual touch tissue quantification) expressing the SWV value as m/s. The ROI was placed in the renal cortex, parallel to the renal capsule with the main axis lying parallel to the pyramids. A mean of three different measurements obtained at the upper, middle, and lower third of the parenchymal kidney (ROI) resulted in the final SWV value for each kidney.[7] The average of the SWV values obtained for the right and the left kidney was considered as the mean SWV value for the patient under consideration.

All statistical analyses were performed employing the software R, version 3.0.0 [R Development Core Team (2013). R: a language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria]. Descriptive statistics (mean, standard deviation, minimum, and maximum) were calculated for the considered variables. The association between SWV and selected variables was evaluated by means of the Pearson's correlation coefficient (also after adjustment for age and sex). A multiple regression analysis was also done considering the $eGFR_{cys}$ as the dependent variable and SWV of the left and right kidneys as two independent variables.

Results

Table 1 shows the median values, together with the associated interquartile range (IQR) and range (minimum–maximum) of age at examination, physical parameters, serum level of Scr, nitrogen (BUN), Cys C levels and spot urinary protein/creatinine excretion, and the eGFR of the children with high-grade VUR enrolled in the present study. Of children with primary VUR and PVUs, 33% and 36%, respectively, had kidney damage with mild decreased renal function (eGFR = 60–89 mL/min per 1.73 m^2). Body surface area, calculated using the Dubois formula, was 1.434 ± 0.319 m^2.

We performed the correlation analysis between the grade of VUR and SWV (m/s) results. Considering the maximum VUR grade of the two kidneys (or the VUR of the only one single kidney for 2 children), there were one child (with PUVs) with right Grade I, 12 children with Grade III, 10 with grade IV, and six with Grade V. A significant correlation was found between VUR grade and SWV of the right kidney (r = 0.434; P = 0.019) as well as between VUR grade and SWV of the left kidney (r = 0.439; P = 0.017).

Table 2 shows the median values, together with the associated IQR and range (minimum–maximum) of scintigraphic uptake values (%), ARFI determination as quantitative measurement of SWV (m/s) and partial eGFR (peGFR; mL/min per 1.73 m^2) for the right (29 total) and the left (27 total) kidneys. There were two non-

Table 1. Demographic characteristics, serum and urinary laboratory data and eGFR of enrolled childrenwith high-grade VUR.

Demographic and laboratory variables	Median (IQR)	Range (minimum–maximum)
Sex (male/female)	18/11	-
Age (years)	12.0 (5.0)	8–21
Body weight (kg)	45.0 (23.3)	23.4–94.0
Height (cm)	154 (26)	126–184
Creatinine (mg/dL)	0.65 (0.23)	0.47–1.12
Cystatin C (mg/L)	0.74 (0.15)	0.63–1.33
Nitrogen (mg/dL)	15.1 (3.0)	10.7–24.9
U-protein/U-creatinine (mg/mg)	0.096 (0.043)	0.040–0.259
$eGFR_{ncc}$ (mL/min per 1.73 m^2)	95.6 (18.8)	64.2–122.8
$eGFR_{cr}$ (mL/min per 1.73 m^2)	100.0 (25.7)	66.4–131.8
$eGFR_{cy}$ (mL/min per 1.73 m^2)	93.6 (17.6)	54.2–108.7

IQR: Interquartile range, eGFR: Estimated glomerular filtration rate, VUR: Vesicoureteral reflux.

Table 2. Scintigraphic data, US results, and peGFR of the right and left kidney of the enrolled patients with high-grade VUR.

Data on right and left kidneys	Right (n =29)		Left (n = 27[§])	
	Median (IQR)	Range (minimum–maximum)	Median (IQR)	Range (minimum–maximum)
DMSA scintigraphy (%)	48 (24)	15–100	52.0 (19.5)	19–85
SWV (m/s)	5.03 (2.53)	2.70–11.03	4.67 (1.28)	3.20–7.33
$peGFR_{ncc}$ (mL/min per 1.73 m^2)	47.9 (21.4)	12.5–95.9	52.9 (17.4)	16.3–81.3
$peGFR_{cr}$ (mL/min per 1.73 m^2)	47.8 (27.2)	14.4–103.2	49.5 (20.2)	16.7–96.2
$peGFR_{cy}$ (mL/min per 1.73 m^2)	48.9(21.5)	12.2–92.4	50.3 (17.0)	15.3–72.3

[§]Two kidneys were non-functional at DMSA scintigraphic analysis. IQR: Interquartile range, peGFR: Partial estimated glomerular filtration rate, DMSA: (99m)Tc-dimercaptosuccinic acid, US: Ultrasound, VUR: Vesicoureteral reflux.

functional left kidneys at scintigraphic evaluation.

The mean SWV was negatively correlated with eGFR calculated both with univariate - Scr based (eGFRcr) and CysC based ($eGFR_{cys}$) and multivariate - Scr, BUN, and CysC based (eGFRncc) equations. The correlation was significantly different from 0 for both eGFRncc and $eGFR_{cys}$ and approached significance for the eGFRcr. This result was confirmed also after adjustment for age and sex of the patients (Table 3). On the other hand, no significant correlation (both simple and age and sex adjusted) was found with the protein excretion rate (urinary protein/creatinine ratio). The correlations between mean SWV and peGFR were in general not significant (the only exception being when $peGFR_{cys}$ of the right kidney was considered).

Slightly different results were found when the same analysis was repeated on the right and left kidneys separately. The SWV values of the two kidneys separately correlated significantly with both multivariate and univariate peGFR of the same kidney. The strongest correlation was always obtained with $peGFR_{cys}$. This result was confirmed also after adjustment for age and sex of the patients (Table 3). On the other hand, no significant correlation (both simple and age and sex adjusted) was found with the protein excretion rate (urinary protein/creatinine ratio).

Finally, we did a multiple regression analysis on the 27 patients with complete scintigraphic observations, considering the $eGFR_{cys}$ as the dependent variable and SWV of the left and right kidneys as the two independent variables. These two variables were not significantly correlated with each other (r = 0.270; P = 0.17) and separately correlated significantly with $eGFR_{cys}$ (left kidney: r = 0.522, P = 0.005; right kidney: r = 0.554, P = 0.003). When both these variables were included in the regression equation, the percentage of variance explained the significant increase from 30.7% (when only the SWV of the left kidney was included in the regression equation) to 45.7% (t = 2.57; P = 0.017). The regression coefficients of the SWV of the left and right kidneys were not significantly different from each other (t = 1.14; P = 0.27) so that the final regression equation was $eGFR = 127 - 3.40 \times SWV_{left} - 3.40 \times SWV_{right}$; or, combining the SWV of the two kidneys: $eGFR = 127 - 6.80 \times SWV_{mean}$. In other words, when the mean SWV increases 1 m/s, the expected decrease in $eGFR_{cy}$ is about 6.8 mL/min per 1.73 m^2. Figure 1 shows both observed (circles) and predicted (dashed line) values of $eGFR_{cy}$ in relation to the average SWV. Dotted lines show the 95% confidence interval for individual $eGFR_{cy}$ in relation to mean SWV. A residual analysis did not show any evident violation of the regression assumptions.

Discussion

We investigated the existing relationship between SWV values, which give a measure of renal stiffness, and renal function expressed as eGFR calculated with the three Schwartz formulas for

Table 3. Simple (r) and partial (r_{par}) correlation coefficients (sex and age adjusted) between SWV and urinary protein excretion and eGFR derived from multivariate and univariate Schwartz formulas for patients with CKDs.

Renal function	Right kidney (n=29)				Left kidney (n=27)				Mean (n=27)			
	r	P	r_{par}	P	r	P	r_{par}	P	r	P	r_{par}	P
SWV (m/s) versus												
$eGFR_{ncc}$	−0.285	0.150	−0.300	0.145	−0.363	0.063	−0.409	0.043	−0.409	0.034	−0.478	0.016
$eGFR_{cr}$	−0.288	0.146	−0.170	0.418	−0.225	0.259	−0.323	0.115	−0.365	0.062	−0.320	0.118
$eGFR_{cy}$	−0.493	0.009	−0.468	0.018	−0.554	0.003	−0.532	0.006	−0.654	<0.001	−0.661	<0.001
Right $peGFR_{ncc}$	−0.451	0.014	−0.512	0.005	0.208	0.297	0.150	0.476	−0.307	0.119	−0.345	0.091
Right $peGFR_{cr}$	−0.462	0.012	−0.458	0.014	0.243	0.222	0.176	0.399	−0.302	0.125	−0.299	0.147
Right $peGFR_{cy}$	−0.519	0.004	−0.568	0.002	0.111	>0.5	0.077	>0.5	−0.416	0.031	−0.421	0.036
Left $peGFR_{ncc}$	0.259	0.192	0.236	0.256	−0.525	0.005	−0.506	0.010	−0.023	>0.5	−0.051	>0.5
Left $peGFR_{c}$	0.193	0.335	0.271	0.191	−0.462	0.015	−0.465	0.019	−0.048	>0.5	−0.006	>0.5
Left $peGFR_{cy}$	0.140	0.485	0.138	>0.5	−0.622	0.001	−0.582	0.002	−0.159	0.429	−0.158	0.451
U-protein/U-creatinine (mg/mg)	0.021	>0.5	0.296	0.126	0.335	0.087	0.258	0.213	0.140	0.486	0.362	0.076

peGFR: Partial estimated glomerular filtration rate, eGFR: Estimated glomerular filtration rate, CKD: Chronic kidney disease.

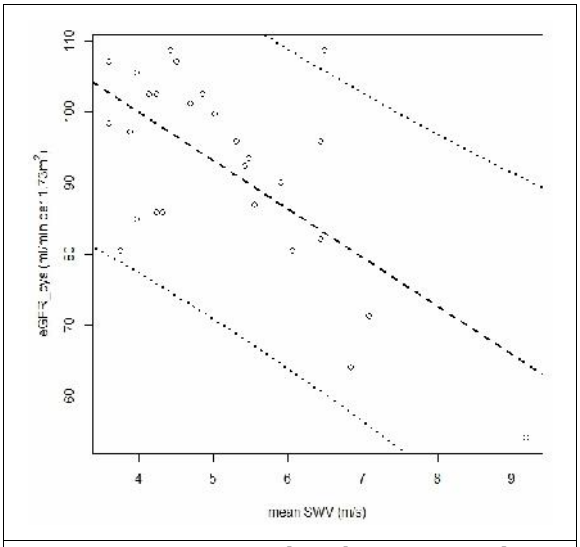

Figure 1. Regression analysis between partial estimated glomerular filtration rate ($peGFR_{cys}$), and mean shear waves velocity (SWV). The circles refer to the observed values, while the dashed line refers to predicted eGFR values on the basis of the regression equation $eGFR_{cy} = 127 - 6.80 \times SWV_{mean}$. Ninety-five percent confidence intervals for estimated values are also shown (dotted lines).

CKD.[5] The results of this study showed a close correlation between mean SWV values of the two kidneys combined and $eGFR_{cy}$. In particular, there was a higher mean SWV value shown in kidneys with lower $eGFR_{cy}$. On the other hand, a significant correlation was found between SWV values for each kidney and the peGFR of the same kidney with all three formulas. Moreover, of the three formulas, the best correlation between the SWV value of each kidney and the corresponding peGFR was found when calculated by means of the serum Cys C-based formula (pe GFR_{cys}).

The liver is the organ most frequently studied with the ARFI technique, particularly to give a measure of fibrosis and cirrhosis.[13] Nanashima et al reported that SWV values of the liver with severe fibrotic stage at biopsy were significantly higher than those of lower severity stages.[14]

To date, there have been only a few studies on the ARFI technique applied to normal kidneys. In 327 healthy adults, the mean SWV value was 2.15 ± 0.51 m/s, changing with both sex and age.[15] In 202 healthy children, at an average age of 8.1 years (±4.7), the mean SWV value was 2.19 m/s for the right kidney and 2.33 m/s for the left kidney.[16]

SWV values may depend on conditions that alter renal stiffness, in particular affections that may change the renal histology. To date, evaluation of renal allograft fibrosis with the ARFI technique has given conflicting results. Syversveen et al reported comparable SWV values in adult renal transplants with or without fibrosis, with a mean decreasing trend from lower (Grades I, II) to higher (Grade III) levels of fibrosis assessed at biopsy.[17] Again, Syversveen et al reported that SWV values in kidney transplants were dependent on the applied transducer force.[18,19] On the contrary, in a prospective study design, Stock et al showed a significant positive but moderate correlation between SWV values and the grade of fibrosis in eight transplanted kidneys.[20] In agreement, Grenier et al reported that supersonic shear imaging gave a measure of renal cortical stiffness that correlated mainly with chronic parenchymal microlesions.[21] For the above reasons, authors have suggested that the measure of renal allograft stiffness can be used as a promising non-invasive tool to evaluate global histological renal deterioration from rejection.

Patients with malformative uropathies of the lower urinary tract often develop reflux nephropathy and CKD.[22] Matsuoka et al reported an association between the decrease in the number of glomeruli, an increase in glomerular hypertrophy and proteinuria, and decreased renal function in 71 children affected by primary VUR.[23] However, Tietjen et al showed that PUVs frequently lead to renal dysplasia and renal failure.[24]

Guo et al reported significantly lower SWV values in the CKD patients (age range 17–87 years) compared to the healthy participants. SWV values correlated significantly with eGFRcr, serum BUN, and Scr, but not with serum cysC concentration.[15]

Recently, we reported that SWV values of the renal parenchyma were higher in children with CKD from malformative uropathies. The mean SWV values followed the sequence: secondary

high-grade VUR (PUVs) > primary high-grade VUR > healthy contralateral kidney of the high-grade VUR > healthy participants.[7]

Göya et al have performed ARFI measurements in children (aged 5.6 ± 3.1 years) with various degree of VUR, with or without renal damage detected by means of DMSA scintigraphy. They showed lower SWV values in DMSA abnormal kidneys (1.83 ± 0.44 m/s) compared to DMSA normal kidneys (2.39 ± 0.23 m/s) and lower SWV values in patients with high-grade VUR compared with those without VUR.[6] Their results showed that more is the renal damage, the slower is the propagation of shear waves[8] and this is in conflict with that previously reported for older children.[6] Thus, it has been hypothesized that there are various degrees of fibrosis depending on the cause of damage and the time since damage.[8] However, there are other renal parameters that must be taken into account. Gennisson et al showed that the anisotropy and the level of vascular and urinary pressure, differently and with various degrees can affect the stiffness of the renal cortex.[25] Besides, high urinary pressure in urinary tract obstructions causes an increase of intrarenal tubular pressure,[26] and consequently, an increase of stiffness. Similarly, in patients affected by high-grade VUR, the intrarenal reflux is a condition that involves backflow of urine into the collecting system of the nephrons,[27] maybe with a modest effect on the renal stiffness. Indeed, children with primary VUR had lower renal SWV values than those with PUVs.[6] Interestingly, our results concerning the relationship between VUR grade and SWV values might support the hypothesis that urinary pressure can also affect the renal stiffness. Accordingly, Sohn et al[28] found in 51 young children with hydronephrosis a median SWV higher in kidneys with high-grade hydronephrosis (2.02 m/s) than of normal kidneys (1.75 m/s). Finally, the effect of the blood perfusion on renal stiffness warrants further investigations.[25]

Some authors found a correlation between the measure of renal stiffness (i.e., SWV) and the eGFR in patients with renal allograft. In particular, they reported that SWV values were negatively correlated with eGFR: increases in SWV values were closely associated with a decrease in eGFRcr.[9,29] In chronic allograft nephropathy, He et al attributed the variations of SWV values to the role of urinary pressure and renal perfusion, interstitial edema, and interstitial fibrosis.[9]

The SWV obtained in our study was higher than others.[7,16] We feel that the difference is due to many factors, related both to technical and anatomical aspects: strength of compression,[18] orientation of the ROI and anisotropy.[30] Anatomical factors also play an important role because the kidney is a highly anisotropic organ with important differences when considering the cortex and the medulla. Physical factors include the frequency of the probe, compression, and distance from source to target.[31] An examination protocol, including the patient's position (prone or supine), which is able to standardize both compression (the same way was done with the liver, with the intercostal approach to the right lobe), to minimize the effects of anisotropy and the source to target distance, is necessary to get comparable results.

Conclusion

We found that SWV of the renal cortex correlates with the eGFR of patients affected by malformative uropathy. Nevertheless, given conflicting results in the literature, this technique needs standardization and validation.

Conflict of interest: None declared.

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