

# Renal tissue elasticity by acoustic radiation force impulse

## A prospective study of healthy kidney donors

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### Abstract

**Background:** Some studies reported the correlations between renal parenchymal stiffness measured by transient elastography or acoustic radiation force impulse (ARFI) and the extent of interstitial fibrosis. This study was prospectively designed to evaluate the correlation between clinical, histological findings and the kidney shear wave velocity (SWV, m/s) assessed by ARFI elastography to identify factors affecting the kidney SWV in normal patients.

**Methods:** Seventy-three adult living kidney transplantation donors were enrolled in our center between September 2010 and January 2013. Before transplantation, all donors were evaluated by ARFI elastography to identify the range of SWV in kidneys. Time-zero biopsies were performed on all graft kidneys before implantation.

**Results:** Mean age of donors was  $42.0 \pm 11.3$  years. The mean SWV and depth were  $2.21 \pm 0.58$  m/s and  $5.37 \pm 1.06$  cm. All histological findings showed mild degree of the Banff score, only grade I. In univariate analyses, the SWV was not associated with all histological parameters. Age ( $r = -0.274, P = .019$ ) diastolic blood pressure (DBP,  $r = -0.255, P = .030$ ) and depth for SWV measurement ( $r = -0.345, P = .003$ ) were significantly correlated with the SWV. In multivariate linear regression analysis, age, gender, body mass index (BMI), and depth for SWV measurement were significantly correlated with the SWV ( $P = .003, .005, .002, \text{ and } .004$ , respectively).

**Conclusions:** We demonstrated that all histological findings are not correlated with the SWV of donor kidney. Otherwise, factors influencing the kidney SWV assessed by ARFI elastography are age, gender, BMI, and depth for the SWV measurement in donors for kidney transplantation.

**Abbreviations:** ARFI = acoustic radiation force impulse, BP = blood pressure, CI = confidence interval, CKD = chronic kidney disease, IFTA = interstitial fibrosis and tubular atrophy, SWV = shear wave velocity, TE = transient elastography.

**Keywords:** acoustic radiation force impulse, elastography, intestinal fibrosis, living donor kidney transplantation, normal kidney, shear wave velocity

### 1. Introduction

Studies on renal parenchymal stiffness in transplant or chronic kidney disease patients measured by transient elastography or acoustic radiation force impulse (ARFI) were published, on the basis of assessment of liver fibrosis in patients with chronic liver disease.<sup>[1-5]</sup> These studies reported some correlations between

renal parenchymal stiffness measured by transient elastography or ARFI and the extent of interstitial fibrosis.<sup>[1,2,6,7]</sup> In particular, the ARFI technology as a non-invasive tool, using shear wave velocity (SWV) of tissue created by a short-duration high-intensity acoustic pulse, is accurate, reproducible and strongly correlated with the grade of fibrosis.<sup>[5,8]</sup>

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Information about ARFI measurements in normal patients remains insufficient, although many studies that assessed renal parenchymal stiffness by ARFI measurements as a non-invasive tool have been reported. Factors that influence the kidney SWV in normal patients should be studied for precise application of ARFI elastography in kidney transplant patients or chronic kidney disease patients.

We designed this study using ARFI technology as a non-invasive tool for detection of renal parenchymal stiffness. Unlike other studies, this study aims to assess the clinical or histological factors that affect the value of SWV in kidney transplant donors.

## 2. Materials and methods

### 2.1. Study design and patients

Living kidney transplant donors were enrolled in our center between September 2010 and January 2013. Within a week before transplantation, 80 donors were evaluated by ARFI quantification to identify the SWV (m/s) (Fig. 1). Time-zero biopsies were performed on 73 graft kidneys before implantation. Inclusion criteria were adults and living donors for kidney transplantation. Exclusion criteria were allograft from a deceased donor, pediatric transplantation, and multiorgan transplantation. All donors were prospectively enrolled after they provided written informed consent. The study was approved by the Institutional Review Board of Severance Hospital, Yonsei University Health System (1-2010-0011). The primary outcome in our study was the range of SWV in normal kidneys. The secondary outcome was the relationship between clinical or histological findings and SWV.

### 2.2. ARFI elastography

We used an Acuson S2000 ultrasound system with a 4-MHz convex probe (Siemens Medical Solutions, Mountain View, CA) as ARFI technology. A rectangular region of interest (ROI, box with fixed dimensions of 1 cm length and 0.6 cm width) was set adjacent to the lower pole of donors' kidney cortex. Investigators

performed ARFI measurement using a 4-MHz convex probe. Three experienced (more than 5 years) radiologists were randomly assigned, and the SWV values (m/s) were measured 5 times per patient and averaged.

### 2.3. Clinical and histological data

We measured blood pressure (BP), cholesterol, serum creatinine and 24hr urine creatinine clearance on the same day as the ARFI evaluation. Time-zero biopsies were performed on the lower pole of the kidney before reperfusion for kidney transplantation using an 18G needle gun. Biopsy samples were subsequently paraffin-embedded, and permanent sections obtained in this manner were stained with hematoxylin-eosin and Masson's Trichrome and read by a pathologist (experience more than 10 years) specializing in transplantation. Pathological scores were calculated using the Banff 09 scoring system. We defined interstitial fibrosis or tubular atrophy as interstitial fibrosis and tubular atrophy (IFTA).

### 2.4. Statistical analysis

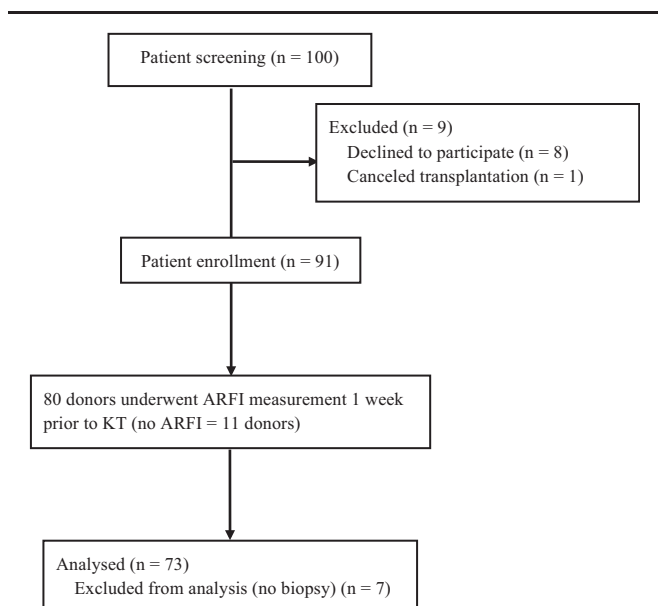
Clinical characteristics and the value of ARFI quantification of donors are expressed as means  $\pm$  standard deviation for continuous variables or frequencies for categorical variables. To examine the associations between SWV and histological findings, Pearson correlation coefficients and independent 2-sample t-tests were used for continuous variables. Differences between groups were analyzed by nonparametric methods (Mann-Whitney tests). Multivariate regression analyses were performed to identify factors influencing the SWV, and  $P < .05$  was considered to be the significance level. For comparison of IFTA and the SWV, we used simple random sampling that considered age and gender. All statistical analyses were performed using SPSS 23 and SAS 9.4.

## 3. Results

### 3.1. SWV measurement, clinical and histological findings

Total 80 kidneys of donors evaluated by ARFI. The intraclass correlations for intraobserver reliability of each investigator were 0.741 (95% confidence interval (CI): 0.635–0.832,  $P < .001$ ), 0.843 (95% CI: 0.724–0.929,  $P < .001$ ), and 0.741 (95% CI: 0.493–0.921,  $P < .001$ ), respectively.

Biopsies were performed on 73 graft kidneys (Fig. 1). Mean age of donors was  $41.97 \pm 11.26$  years (Table 1). Males accounted for 38.4% of total patients. Mean values of serum creatinine and creatinine clearance were  $0.84 \pm 0.19$  mg/dL and  $103.77 \pm 25.20$



**Figure 1.** Schematic diagram of study design. ARFI=acoustic radiation force impulse, KT=kidney transplantation.

**Table 1**

Clinical characteristics and the value of SWV of donors.

Parameters	Mean $\pm$ SD
Age (years)	41.97 $\pm$ 11.26
Gender (male/female)	28/45
Body mass index (kg/m <sup>2</sup> )	23.15 $\pm$ 2.48
Systolic blood pressure (mm Hg)	120.78 $\pm$ 12.15
Diastolic blood pressure (mm Hg)	75.85 $\pm$ 9.60
Serum creatinine (mg/dL)	0.84 $\pm$ 0.19
24hr urine creatinine clearance (mL/min)	103.77 $\pm$ 25.20
Cholesterol (mg/dL)	160.86 $\pm$ 32.97
Shear wave velocity (SWV, m/s)	2.21 $\pm$ 0.58
Depth for SWV measurement (cm)	5.37 $\pm$ 1.06

ARFI=acoustic radiation force impulse, SD=standard deviation, SWV=shear wave velocity.

**Table 2****Univariate analyses of the correlation between the SWV and clinical, histological findings.**

Variables			
<b>Continuous variables</b>		<b>Pearson correlation coefficient (95% CI)</b>	<b>P-value</b>
Age (yr)		-0.274(-0.478, -0.050)	.019
Body mass index (kg/m <sup>2</sup> )		0.160(-.091, 0.392)	.177
Systolic blood pressure (mmHg)		-0.117 (-0.289, 0.061)	.323
Diastolic blood pressure (mm Hg)		-0.255 (-0.475, 0.010)	.030
Serum creatinine (mg/dL)		-0.068 (-0.284, 0.140)	.566
Creatinine clearance (ml/min)		-0.028 (-0.273, 0.258)	.812
Cholesterol (mg/dL)		-0.224 (-0.453, -0.009)	.057
Depth for SWV measurement (cm)		-0.345 (-0.525, -0.135)	.003
<b>Categorical variables</b>	<b>N (%)</b>	<b>Mean ± SD</b>	
Gender			0.065 <sup>a</sup>
male	28 (38.4%)	2.05 ± 0.60	
female	45 (61.6%)	2.31 ± 0.56	
Glomerulosclerosis (gs)			0.605 <sup>a</sup>
0%	50 (68.5%)	2.24 ± 0.58	
>0%	23 (31.5%)	2.16 ± 0.60	
Tubular atrophy (ct)			0.212 <sup>a</sup>
0	46 (63.0%)	2.28 ± 0.59	
1	27 (37.0%)	2.10 ± 0.57	
Interstitial fibrosis (ci)			0.761 <sup>a</sup>
0	60 (82.2%)	2.22 ± 0.53	
1	13 (17.8%)	2.15 ± 0.79	
IFTA (ct + ci)			0.563 <sup>a</sup>
0	46 (63.0%)	2.24 ± 0.58	
1	27 (37.0%)	2.16 ± 0.60	

<sup>a</sup> independent *t*-test, IFTA=interstitial fibrosis and tubular atrophy, SD=standard deviation.

mL/min/1.73m<sup>2</sup>, respectively. The mean SWV and depth were 2.21 ± 0.58 m/s and 5.37 ± 1.06 cm (Table 1). Abnormal histological findings were observed in 60.3% of the 73 biopsies. There were mild degree of abnormal histologic findings according to the Banff criteria, only grade I. Glomerulosclerosis, tubular atrophy, interstitial fibrosis, vascular fibrous intimal thickening, arteriolar hyaline thickening, and interstitial inflammation (i) were observed in 23 (31.5%), 27 (37.0%), 13 (17.8%), 4 (5.5%), 6 (8.2%), and 6 (8.2%) of the 73 donors, respectively. The IFTA (tubular atrophy + interstitial fibrosis) grade I was observed in 27 (37.0%) of the 73 donors (Table 2).

### 3.2. Correlation between clinical or histological findings and SWV

In univariate analyses, age, diastolic blood pressure (DBP) and depth for SWV measurement were significantly correlated with the SWV ( $r = -0.274, -0.255, -0.345, P = .019, .030, 0.003$ , respectively). Gender and cholesterol were borderline significant (male vs female 2.05 ± 0.60 vs 2.31 ± 0.56,  $P = .065$ ;  $r = -0.224, P = .057$ , respectively) (Table 2). The SWV was not correlated with any of the histological parameters. In multivariate linear regression analysis, age, gender, body mass index (BMI), and depth for SWV measurement were significantly correlated with SWV ( $P = .003, .005, .002$ , and  $.004$ , respectively) (Table 3).

### 3.3. Relationship between the kidney SWV and IFTA

IFTA did not have any association with the SWV (Table 2). Each 27 patients were selected into the IFTA score 0 group and IFTA score I group by simple random sampling which considered age

and gender. The IFTA score 1 group had a lower value of SWV than the IFTA score 0 group (2.16 ± 0.60 m/s vs 2.22 ± 0.54 m/s, respectively), although the difference was not statistically significant.

## 4. Discussion

ARFI is operator-independent and can determine tissue elasticity quantitatively.<sup>[9]</sup> The stiffer the tissue is, the faster is the SWV.<sup>[10]</sup> Tissue stiffness assessed by ultrasound-based elastography has been studied, mainly in chronic liver disease patients, and recently, it has been studied in post-transplant patients or chronic kidney disease (CKD) patients.<sup>[2-4,6,7,11-17]</sup> Several previous studies have reported about the correlations between the SWV and renal fibrosis or function.<sup>[13-16]</sup> However, studies that assess the factors affecting the SWV in normal patients have been rarely published. Prior to its application as a non-invasive tool in post-

**Table 3****Multivariate analyses of the correlation between the SWV and clinical, histological findings.**

Parameter	Coefficient	Standard error	P-value
Age (yr)	-0.018	0.006	.003
Gender (male vs female)	-0.384	0.133	.005
Body mass index (kg/m <sup>2</sup> )	0.079	0.024	.002
Diastolic blood pressure (mm Hg)	-0.007	0.006	.278
IFTA (1 vs 0)	0.034	0.122	.778
Depth for SWV measurement (cm)	-0.172	0.058	.004

IFTA=interstitial fibrosis and tubular atrophy, SWV=shear wave velocity.

transplant or CKD patients, factors influencing the SWV must be evaluated in normal patients.

Guo et al. reported that age and gender were significantly correlated with the kidney SWV in healthy volunteers.<sup>[15]</sup> In that study, the influence of age and gender was studied in a larger cohort (327 patients), although the number of patients in whom the body mass index, kidney length and depth for the SWV measurement were analyzed in detail was quite small (30 healthy volunteers). Bota et al. conducted a comparable study on 91 normal patients.<sup>[18]</sup> The study indicated that the kidney SWV values were significantly correlated with age and gender in both univariate and multivariate analyses.

Our results are in line with data published by the previous 2 studies. We found that age and gender are correlated significantly with the kidney SWV of donors. The kidney SWV decreases with the increase in age, and is significantly lower in men than in women. In our study, the mean age of donors might be lower than that of usual patients, such as CKD patients or kidney transplant patients, because of the criterion of “normal person” for kidney transplantation.

We observed that BMI and depth for the SWV measurement are significantly correlated with the SWVs. The SWV decreases with the increase in depth for the SWV measurement. These results may be due to the positive correlation between BMI and depth for the SWV measurement. Similar to our study, a previous study presented that depth for the SWV measurement on the liver in healthy volunteers influenced the value of SWV.<sup>[19]</sup>

Unlike other studies, we investigated the histological findings of donors to identify factors affecting the SWV. Any of donors had abnormal histologic findings. However, our histological findings of donors showed a mild degree of Banff score, unlike CKD patients or kidney transplant patients with a high pathological degree. We found no statistically significant correlation between histological findings and the kidney SWV, similar to previous studies.<sup>[2,17]</sup> Our center published a similar result, which suggested that the SWV values showed no significant correlation with histological renal fibrosis findings in allograft kidney.<sup>[17]</sup> In contrast to this finding, another study demonstrated that the SWV values correlated significantly with pathological parameters in CKD patients.<sup>[16]</sup> Several studies showed the SWV in CKD patients with renal fibrosis was significantly lower than that in healthy controls.<sup>[15,16]</sup> Our result showed that the SWV in the IFTA score 1 group showed a lower value than that in the IFTA score 0 group by simple random sampling that considered age and gender, although there was no significant correlation. These results suggested that interstitial fibrosis is not the main factor affecting the degree of tissue stiffness in the kidney.

Asano et al. reported that patients with a low brachial-ankle pulse wave velocity, as an indicator of arteriosclerosis in the large vessels, tended to have a high SWV in the kidney.<sup>[13]</sup> It is suspected renal blood flow dominantly influences the elasticity of the kidney in CKD patients, because the kidney is a highly vascularized organ. We investigated the influence of renal blood flow on the kidney SWV using systolic BP and diastolic BP. Unfortunately, we did not observe that BP was correlated with the kidney SWV, although diastolic BP had a borderline significant correlation with the SWV in univariate analysis. We assumed that this result is obtained because normal patients are not susceptible to reduced renal blood flow. We expect the SWV is influenced by renal blood flow in CKD patients with high pathological renal fibrosis.

Our study has some limitations. First, the number of donors' kidney is small. So, the results do not represent for normal kidney. Second, although ARFI measurements were performed by randomly assigned investigators, investigator choice might have influenced the results. Finally, the histologic finding might be influenced by subjective bias, because we identified the histologic findings by only 1 pathologist.

## 5. Conclusion

We identified factors influencing the kidney SWV as assessed by ARFI elastography as a non-invasive tool. The SWV was significantly correlated with age, gender, BMI, and depth for the SWV measurement. However, we did not observe that histological findings were correlated with the kidney SWV. For further evaluation of the kidney SWV in CKD or kidney transplant patients, we need to understand that the kidney SWV is influenced by clinical features, in particular, age, gender, BMI, and depth for the SWV measurement in normal patients.

## Author contributions

D.J.J. and Y.S.K. contributed to the research idea and study design; A.L.L., Y.T.O., W.K.H., D.J.J., and H.J.J. contributed to data acquisition; A.L.L. and D.J.J. contributed to data analysis/interpretation; A.L.L. and M.J.O. performed statistical analysis; D.J.J., Y.S.K., and Y.T.O. provided supervision and mentorship. Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved.

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## References

- Arndt R, Schmidt S, Loddenkemper C, et al. Noninvasive evaluation of renal allograft fibrosis by transient elastography—a pilot study. *Transpl Int* 2010;23:871–7.
- Syversveen T, Brabrand K, Midtvedt K, et al. Assessment of renal allograft fibrosis by acoustic radiation force impulse quantification—a pilot study. *Transpl Int* 2011;24:100–5.
- Fierbinteanu-Braticevici C, Andronescu D, Usvat R, et al. Acoustic radiation force imaging sonoelastography for noninvasive staging of liver fibrosis. *World J Gastroenterol* 2009;15:5525–32.
- Friedrich-Rust M, Wunder K, Kriener S, et al. Liver fibrosis in viral hepatitis: noninvasive assessment with acoustic radiation force impulse imaging versus transient elastography. *Radiology* 2009;252:595–604.
- Lupsor M, Badea R, Stefanescu H, et al. Performance of a new elastographic method (ARFI technology) compared to unidimensional transient elastography in the noninvasive assessment of chronic hepatitis C. Preliminary results. *J Gastrointest Liver Dis* 2009;18:303–10.
- Stock KF, Klein BS, Cong MT, et al. ARFI-based tissue elasticity quantification and kidney graft dysfunction: first clinical experiences. *Clin Hemorheol Microcirc* 2011;49:527–35.
- Stock KF, Klein BS, Vo Cong MT, et al. ARFI-based tissue elasticity quantification in comparison to histology for the diagnosis of renal transplant fibrosis. *Clin Hemorheol Microcirc* 2010;46:139–48.

- [8] Palmeri ML, Wang MH, Dahl JJ, et al. Quantifying hepatic shear modulus in vivo using acoustic radiation force. *Ultrasound Med Biol* 2008;34:546–58.
- [9] Cosgrove DO, Berg WA, Doré CJ, et al. Shear wave elastography for breast masses is highly reproducible. *Eur Radiol* 2012;22:1023–32.
- [10] Fahey BJ, Nightingale KR, Nelson RC, et al. Acoustic radiation force impulse imaging of the abdomen: demonstration of feasibility and utility. *Ultrasound Med Biol* 2005;31:1185–98.
- [11] Ebinuma H, Saito H, Komuta M, et al. Evaluation of liver fibrosis by transient elastography using acoustic radiation force impulse: comparison with Fibroscan. *J Gastroenterol* 2011;46:1238–48.
- [12] Rifai K, Cornberg J, Mederacke I, et al. Clinical feasibility of liver elastography by acoustic radiation force impulse imaging (ARFI). *Dig Liver Dis* 2011;43:491–7.
- [13] Asano K, Ogata A, Tanaka K, et al. Acoustic radiation force impulse elastography of the kidneys: is shear wave velocity affected by tissue fibrosis or renal blood flow? *J Ultrasound Med* 2014;33:793–801.
- [14] Bob F, Bota S, Sporea I, et al. Relationship between the estimated glomerular filtration rate and kidney shear wave speed values assessed by acoustic radiation force impulse elastography: a pilot study. *J Ultrasound Med* 2015;34:649–54.
- [15] Guo LH, Xu HX, Fu HJ, et al. Acoustic radiation force impulse imaging for noninvasive evaluation of renal parenchyma elasticity: preliminary findings. *PLoS One* 2013;8:e68925.
- [16] Hu Q, Wang XY, He HG, et al. Acoustic radiation force impulse imaging for non-invasive assessment of renal histopathology in chronic kidney disease. *PLoS One* 2014;9:e115051.
- [17] Lee J, Oh YT, Joo DJ, et al. Acoustic radiation force impulse measurement in renal transplantation: a prospective, longitudinal study with protocol biopsies. *Medicine (Baltimore)* 2015;94:e1590.
- [18] Bota S, Bob F, Sporea I, et al. Factors that influence kidney shear wave speed assessed by acoustic radiation force impulse elastography in patients without kidney pathology. *Ultrasound Med Biol* 2015;41:1–6.
- [19] Kaminuma C, Tsushima Y, Matsumoto N, et al. Reliable measurement procedure of virtual touch tissue quantification with acoustic radiation force impulse imaging. *J Ultrasound Med* 2011;30:745–51.