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Renal ultrasound elastography

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Abstract Chronic kidney disease (CKD) incidence and prevalence are increasing in Western countries, due particularly to diabetes mellitus and hypertension-related nephropathies. CKD may lead to end-stage renal failure, with extensive morbidity, mortality and increasing health costs. Primary and secondary prevention requires a better knowledge of mechanisms underlying renal scarring, the development of specific therapies to slow down the progression of the disease and the development of non-invasive diagnostic tools to characterize the process. Ultrasound elastography is a new imaging technique under development that provides information about renal stiffness. Kidney elasticity measurements with ultrasound should be performed with a quantitative technique, such as Shearwave techniques. However kidney stiffness is not only related to fibrosis, as it is also sensitive to mechanical and functional parameters such as anisotropy, vascularization, hydronephrosis and external pressure. This paper reviews the existing ultrasound elastography techniques. Elastography is a new tool under development for renal tissue characterization and needs further validation in clinical practice.

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Chronic kidney disease (CKD) incidence and prevalence are increasing in developed countries, particularly diabetes and hypertension-related nephropathies [1]. Because it is a progressive disease, CKD may lead to end-stage renal failure, with extensive morbidity, mortality and increasing health costs. This justifies developing more efficient diagnostic strategies in patients with CKD by using non-invasive methods. Non-invasive imaging could participate in this challenge in the near future using functional, structural or molecular approaches. However, adequate imaging biomarkers have to be validated first. In most types of kidney diseases, CKD progression is characterised by progressive fibrotic processes that may involve first either glomeruli (glomerulosclerosis) or the interstitial space (interstitial fibrosis) depending on the initial nephropathy [2, 3]. Detecting intrarenal fibrosis and quantifying its progression with non-invasive methods could be useful to nephrologists, in

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addition to current methods used to evaluate CKD progression, which are mainly based on quantification of the glomerular filtration rate. Similarly, in renal transplantation, the development of interstitial fibrosis and tubular atrophy (IF/TA), previously called chronic allograft nephropathy (CAN), is the major determinant of renal allograft failure [4,5].

Among imaging methods used for that purpose, diffusion-weighted MRI (DW-MRI) was recently proposed in liver fibrosis and experimental interstitial fibrosis [6,7]. Ultrasound (US) elastography which is another attractive alternative, has already been demonstrated in the liver [8–10]. Application of these new US techniques to the kidney has been shown to be possible and the first results are encouraging. However, the kidney is a much more complex organ than the liver, with two compartments and a high vasculature. Therefore, the purpose of this review is to expose the main results, advantages and limitations of US elastography for quantifying chronic degenerative processes in renal diseases and to propose new fields of application.

Technical considerations

The compression elastography technique, or also called static elastography technique, provides a qualitative strain map of the organ by comparing two US acquisitions before and after compression. Such technique is then inadequate for renal tissue stiffness assessment for two main reasons: first, the kidneys are usually located deeply in the body and therefore there is no direct access to apply an external compression easily; second there is no normal tissue to compare the abnormal tissue to in the kidney, therefore an absolute stiffness assessment of the tissue is required and quasi-static elastography does not provide quantitative data (cf. Dr Franchi’s article). MR-elastography techniques based on Shearwave propagation, where the Shearwave speed is directly related to elasticity, provide a three-dimensional mapping of the kidney tissue rigidity however the effective spatial resolution is of the order of the centimeter and since the structure sizes in the kidney are of the order of the centimeter or less, these dynamic techniques are not adequate for kidney stiffness evaluation. Elastography systems without US guidance to monitor precisely the position of samplings, such as the FibroScan® (EchoSens, Paris, France) [11], are also inappropriate for the kidney for several reasons:

• first, there is no B-mode control and the sample volume is fixed, 4 cm long between 25 mm and 65 mm below the skin surface; therefore, it is extremely difficult and hazardous to position adequately the sample volume on the renal parenchyma which is located at a variable depth. A manual adjustment could be considered in transplanted kidneys, because more superficially located, but it stays hazardous without real time sonographic control; moreover, such adjustment would require the modification of the pressure applied on the probe which would change elasticity values;

• secondly, the mechanical wave has to be applied on a rigid surface, such as the rib cage, to avoid compression effects by the probe, which is impossible for the kidney. However, this system was recently proposed to detect fibrosis in renal transplants (the results of this study are reported below) [12].

Sonographic-guided system such as Acoustic Radiation Force Impulse (ARFI) (Acuson S2000; Siemens Medical Solutions, Mountain View, CA) is another promising quantitative transient elastography technique for assessing liver fibrosis and it has recently been applied to kidney transplants [13–15]. Even if this technique is quantitative, it stays a mono-dimensional technique (Fig. 1). Recently, static two-dimensional mapping was shown to be possible which is a key point for probe positioning. In the Supersonic Shear Imaging (SSI) (Aixplorer; Supersonic Imagine, Aix-en-Provence, France) technique, a real-time and quantitative method was successfully implemented on curved arrays for in vivo tissue elasticity mapping [16]. These two last sonographic-guided systems (SSI, ARFI) are more appropriate for kidney sampling because it is possible to sample selectively the cortex or the medulla, avoiding perirenal or sinusal fat (Fig. 2).

Measuring Shearwave velocity within the kidney with any of these systems must be cautiously performed because it is sensitive to many mechanical and functional parameters.

Figure 1. Example of intrarenal Shearwave velocity measurement with the ARFI technique.

Figure 2. Example of elasticity mapping in a native kidney with the SSI technique.
such as anisotropy and vascularization. A clear assessment of these factors variation is essential to decrease the intrinsic variability of in vivo measurements, and to increase the method reproducibility. Syversveen et al. [17] showed, using ARFI, that measurement in kidney transplants was dependent on the transducer force applied on the abdominal wall (Fig. 3). Gennisson et al. [18] showed that tissue architecture, such as the degree of anisotropy, and the level of vascular and urinary pressure may have an impact on Shearwave velocity and therefore on the elasticity values of the kidney tissue (more particularly the cortex). In the kidney, the intrinsic architecture of the parenchyma is highly anisotropic. Henle loops and vasa recta within medulla and the collecting ducts within cortex and medulla are parallel and mainly oriented from the capsule to the papilla within each renal segment. The fraction of anisotropy shown with diffusion-weighted MRI is as high as 30% within the cortex and 50% within the medulla [19]. Therefore, when emission of the ultrasound beam is sent parallel to these structures, the Shearwave propagates perpendicular to these, creating multiple vascular and tubular interfaces, thus decreasing its speed of propagation and resulting in lower elasticity values. Conversely, when emission of the ultrasound beam is sent perpendicular to these structures, the Shearwave propagates at a higher speed, without interfaces, resulting in higher elasticity values.

The degree of vascular pressure also tremendously influences elasticity values. The kidney is highly vascularized, mainly the cortex, with an eighth of the cardiac blood flow being distributed into each kidney. Therefore, a significant decrease of elasticity is noted after ligation of the renal artery and, conversely, a huge increase of renal elasticity is observed after ligation of the renal vein [18]. Finally, elasticity values are also highly influenced by the degree of urinary obstruction in a linear fashion. In consequence, urinary obstruction will have to be ruled-out before attributing an increased elasticity to tissue changes.

Reproducibility

Using ARFI, the mean intra-observer coefficient of variation (CV) was 22% for observer 1 and 24% for observer 2 [15]. Inter-observer agreement, expressed as intraclass correlation coefficient (CI) was 0.31 (95% CI: −0.03 to 0.60). Using SSI, intra- and inter-observer variation coefficients of cortical elasticity were 20% and 12%, respectively [20]. CV range was 10–43% for observer 1 and 10–35% for observer 2. It is true that CV values could be larger than 30% in some cases, which is not acceptable. However, according to the distribution, these CV in our cohort of transplanted patients, we obtained for each observer CV less than 27% in 75% of cases.

Normal renal elasticity values

No reference value has been reported up to now. Normally functioning renal transplants cannot be considered as fully normal kidneys and a study focussing on native kidneys in young patients with normal renal function would be required to establish these values. The main issue acquiring reproductive elasticity values on native kidney is the depth of investigation, which does not allow good Shearwave generation and acquisition. The ARFI system being limited to 5 cm in depth cannot reach deep kidneys. In our experience, acquiring stable and reproducible elasticity maps with the SSI system can be difficult. We measured these values in a small series of volunteers with superficial native kidneys (unpublished data): cortical elasticity values were higher than medullary values (15.4 ± 2.5 kPa and 10.8 ± 2.7 kPa respectively). This was confirmed by an in vivo evaluation of pig kidneys [18].

Measurement of renal fibrosis

An increase in the extracellular matrix synthesis, with excessive fibrillary collagens, characterises the development of chronic lesions in the glomerular, interstitial and vascular compartments, leading progressively to end-stage renal failure [1]. Mechanisms participating in these processes are increasingly identified and various therapeutic interventions have been shown to prevent or to favour regression of fibrosis in several experimental models [2,21]. Therefore, development of new non-invasive methods for identification and quantification of fibrosis would be worthwhile.

Preclinical studies

To our knowledge, only one study attempted to evaluate US elastography in an experimental model [22]: it was a rat model of glomerulosclerosis induced by L-NAME administration, and the objective was to use SSI to assess kidney cortex elasticity changes and predict histopathological development of fibrosis. Three groups were studied transversally: a control group, a group after 4 weeks of L-NAME administration, and a group after 6 weeks. A fourth group was studied longitudinally before, after 4 weeks and 7 weeks of L-NAME administration. This study showed that cortical elasticity values, measured by ultrasound SSI, increase with the development of intrarenal disease (Fig. 4). When followed longitudinally, these values increased to

Figure 3. Increase of intrarenal Shearwave velocity measurements with the increase of external pressure, using the ARFI technique. Reprinted with permission from Syversveen et al., Eur Radiol 2012;22:2130–37.
approximately 76% of their baseline values 4 weeks after the onset of the model and remained stable 3 weeks later. A high degree of correlation between the enhanced renal stiffness and the degree of renal dysfunction, measured by the proteinuria/creatininuria ratio, was very encouraging, but no correlation could be found between the semi-quantitative scoring system (which is the addition of several graded items evaluated qualitatively) and SSI (which is a quantitative value changing linearly).

Study of more fibrotic models is now mandatory to evaluate how elasticity values increase according to the degree of fibrotic tissue deposit. Unfortunately, such models with advanced fibrosis are difficult to obtain in rats. For example, ureteral obstruction is a classical highly fibrotic model but it has the disadvantage of associating fibrosis with a high level of cellularity and with a decrease in the tubular flow and water retention. Therefore, it could not be applied easily to elastographic investigation because increased cellularity and increased intratubular and interstitial hydrostatic pressure, as shown above, would change and bias the elasticity values obtained within the renal parenchyma.

**Evaluation of fibrosis in native kidneys**

To our knowledge, there is no study of US elastography measurements on native kidneys, probably due to the difficulty in acquiring reproducible values due to their depth (see above).

**Evaluation of renal transplants**

The natural history of interstitial fibrosis/tubular atrophy (IF/TA) in transplanted kidneys has been well studied through protocol biopsies. The early phase, which generally occurs during the first years post-transplantation, is characterized by fibrogenesis and the emergence of tubulo-interstitial damage due to immunologic phenomena; the late phase is characterized by the worsening of parenchymal lesions (irreversible interstitial fibrosis, tubular atrophy, arteriolar hyalinosis) and the occurrence of glomerular sclerosis leading to graft lost [4,5,23]. Non-invasive markers of these pathological changes are lacking and protocol biopsies are still the only reliable tool for the diagnosis of IF/TA.

Several studies have been performed on renal transplants because more superficially located allowing more accurate measurements. Most of them were performed with low frequency probes but high frequency probes can also be used in very superficial kidneys (Fig. 5). The correlation between renal elasticity quantification and intrarenal pathological changes is quite controversial in the literature but the number of enrolled patients for biopsy is quite limited.
Figure 5. Elasticity map of a kidney transplant using the SSI technique, acquired with a 8-MHz linear probe, showing higher values in the cortex than in the medulla.

Arndt et al. [12], using the Fibroscan®, found a correlation between renal stiffness and the degree of interstitial fibrosis in a group of 20 patients (Fig. 6), which is quite surprising considering the mentioned technical limitation of this system. Conversely, using ARFI in 30 patients, Syversveen et al. [15] did not find any correlation whereas Stock et al. [24] found a positive but moderate correlation based on 18 patients only. Grenier et al. [20] used SSI on 49 consecutive kidney transplant recipients scheduled for renal biopsy, but no correlation between renal stiffness and interstitial fibrosis could be demonstrated by using either the classical semi-quantitative Banff score or the quantitative image analysis based on the reference method of Sirius red. However, in the same paper, a significant correlation was observed between cortical stiffness and the total Banff scores of chronic lesions and of all elementary lesions ($R = 0.34, P < 0.05$ and $R = 0.41, P < 0.03$, respectively).

One possible explanation for such discrepancies is the non-specificity of stiffness changes related to interstitial fibrosis. These results suggest that the degree of renal cortical stiffness does not reflect any specific intrarenal change, such as fibrosis, but rather the association of several renal microlesions, especially chronic lesions.

### Renal tumors

Only one study, to our knowledge, reported Shearwave velocity values in a small series of 12 solid renal cell carcinomas, using ARFI [25]. The values were between 1.61 m/s and 3.97 m/s (which correspond to elasticities ranging from 7.7 kPa to 47.3 kPa) without any possibility to separate the different tumor types. One example of renal tumor is shown in Fig. 7, using SSI technique. More experience is necessary to evaluate the potential role of elastography in separating benign and malignant tumors.

In summary, quantification of tissue stiffness using ultrasound is more complex within the kidney than within the liver. Due to compartmentalization and high tissue heterogeneities, only sonography-guided techniques seem appropriate. Variability of measurements is increased by the risks of applied transducer pressure on abdominal wall and by tissue anisotropy. Therefore, more experience is needed in preclinical models and in patients cohorts with pathological correlation to better understand which are the physical factors of variation and the histopathological causes of elasticity changes.

Figure 6. Parenchymal stiffness measured with Fibroscan® in renal transplants with different Banff grades showing a significant difference between patients with Banff grades 0–1 versus grade 2 ($P: 0.008$), and grade 0–1 versus grade 3 ($P: 0.046$).


Figure 7. Example of a renal cell carcinoma evaluated with SSI technique: tumor elasticity is two times higher than renal elasticity.
Disclosure of Interest

N.G. is a member of the scientific advisory board of Super-sonic Imagine, J.L.G. is a consultant for Supersonic Imagine. F.C., Y.L.B. and L.C. have no conflicting financial interests.

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