Ultrasound-based imaging methods of the kidney—recent developments

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In recent years, several novel ultrasound (US)–based techniques have emerged for kidney diagnostic imaging, including tissue stiffness assessment with elastography, Ultrasensitive Doppler techniques, and contrast-enhanced ultrasonography to assess renal microvascularization. Renal elastography has become available with the development of noninvasive quantitative techniques, following the rapidly growing field of liver fibrosis diagnosis. With the increased incidence of chronic kidney disease, noninvasive diagnosis of renal fibrosis can be of critical value. However, it is difficult to simply extend the application of US elastography from one organ to the other due to anatomic and technical issues. Today, renal elastography appears to be a promising application that, however, still requires optimization and validation. New ultrasensitive Doppler techniques improve the detection of slow blood flow and can be used alone or after administration of US contrast agents. These microbubble-based agents are extremely well tolerated and can be administered even in cases of impaired renal function. Despite the lack of approval, they improve the characterization of atypical renal masses, complex cystic renal masses, and peripheral vascular disorders. Dynamic contrast-enhanced US is based on quantification of the signal intensity from region of interest and mathematical fits of the time-intensity curves. Perfusion-related parameters can be extracted for the monitoring of vascular changes in the renal parenchyma and in tumors in order to evaluate drug response. This estimation of renal perfusion depends on many parameters that should be kept constant for follow-up studies, and, when possible, an internal reference should be used to normalize the measurements.

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Conventional ultrasonography (US) has been available to study the kidney in routine practice for more than 40 years. It started with B-mode imaging and rapidly encompassed Color and Power Doppler US (CDUS and PDUS) and pulsed wave Doppler (PWD) to also detect renal blood flow disturbances. During the past 25 years, the performance of renal US has been continuously improved. The B-mode contrast and spatial resolution have been increased by changing the pulse sequence and the transducer capabilities. Nowadays, routine B-mode examinations are routinely performed using nonlinear harmonic imaging and spatial and frequency compounding. CDUS and power Doppler US have also benefited from increased sensitivity for the detection of deep and small vessels at much higher frame rate. However, conventional renal US still exhibits limitations for the evaluation of diffuse tissue disorders as well as for the detection of focal lesions (that will always depend on the accessibility to the ultrasound beam and on the contrast to the surrounding tissues) and for the characterization of renal masses.

Recently, new renal ultrasound-based imaging methods have been leaving the research field to become available in routine practice. Of these new technologies, we focus on ultrasound elastography, micro-Doppler techniques, and contrast-enhanced US (CEUS).

Renal elastography

Noninvasive assessment of tissue stiffness should bring additional information to improve ultrasound diagnostic capabilities.[1] Indeed, most parenchymal diseases are associated with tissue architecture changes that are affecting the tissue elasticity without necessarily changing the tissue ultrasound backscatter properties. Interstitial fibrosis is an example of such changes that has been widely studied in the liver for the detection and quantification of fibrosis in adults and children.[2–4] It seemed logical to extend this validated liver application to the noninvasive assessment of chronic kidney disease (CKD), particularly for the early stages when renal function is not yet significantly affected as well as for disease monitoring. The hypothesis that the development of the glomerular and interstitial fibrosis should lead to stiffness changes was supported by experimental findings in a rat model of CKD.[5] Renal elastography should be validated by comparison with renal pathology, glomerular filtration rate (GFR) and renal tissue stiffness changes in the course of CKD.

Several ultrasound elastography technologies have been developed over the past 15 years.[6] They all rely on the same principle with the following 3 steps: first, generation of an external (or, in rare cases, internal) constraint on the tissue; a second measurement of the very small displacement induced by the application of this constraint using US; and a third estimation of the elasticity modulus inverting the physical relationship between constraint and induced displacement. The constraint can be external (such as compression of the medium by the ultrasound transducer with obvious inter-operator variability) or internal using an acoustic radiation force impulse (ARFI).

Quasi-static elastography. The first technique consists of using external compression-decompression cycles applied by the transducer. It is called quasi-static elastography (or strain elastography). It is a qualitative technique that supposes a uniform deformation of the tissue of interest. The stiffness estimation depends on the stiffness of the tissues located inside and outside the elastographic box. The estimated parameter is the local strain that is related to local stiffness through Hooke's law involving the local stress field usually unknown in clinical conditions. The elasticity is color coded, and the color range is distributed between the softest and hardest tissues (Figure 1a), and thus the position of the elastographic box can induce additional variability. Strain elastography is widely available from many US manufacturers and is currently used mainly for breast, thyroid, and prostate stiffness evaluation.[7–9] Its value for kidney elastography is very limited due to the depth of the organ, the difficulty of applying a reproducible homogeneous external deformation, and the previously mentioned technical limitations (including the inability to achieve absolute stiffness measurements[10]).

Transient elastography. In contrast, transient elastography (Fibroscan, Echosens, Paris, France) allows quantitative evaluation of the tissue stiffness based on the measurement of the shear wave velocities (SWVs) propagating perpendicularly to the ultrasound beam direction. It uses a piston to generate a tiny shock in between the intercostal space, and a single ultrasound crystal monitors the propagation of the shear waves inside the tissue. It provides a single point measurement without imaging capabilities and has been validated for the diagnosis of liver fibrosis.[11,12] The volume of tissue involved in the measurement is at fixed depth and has a length of 30 to 40 mm, which could help to guide the site of measurement. For liver fibrosis quantification, the intercostal space allows standardization for depth and pressure applied by the device, but this placement cannot be used for renal stiffness measurements. Due to these limitations, this

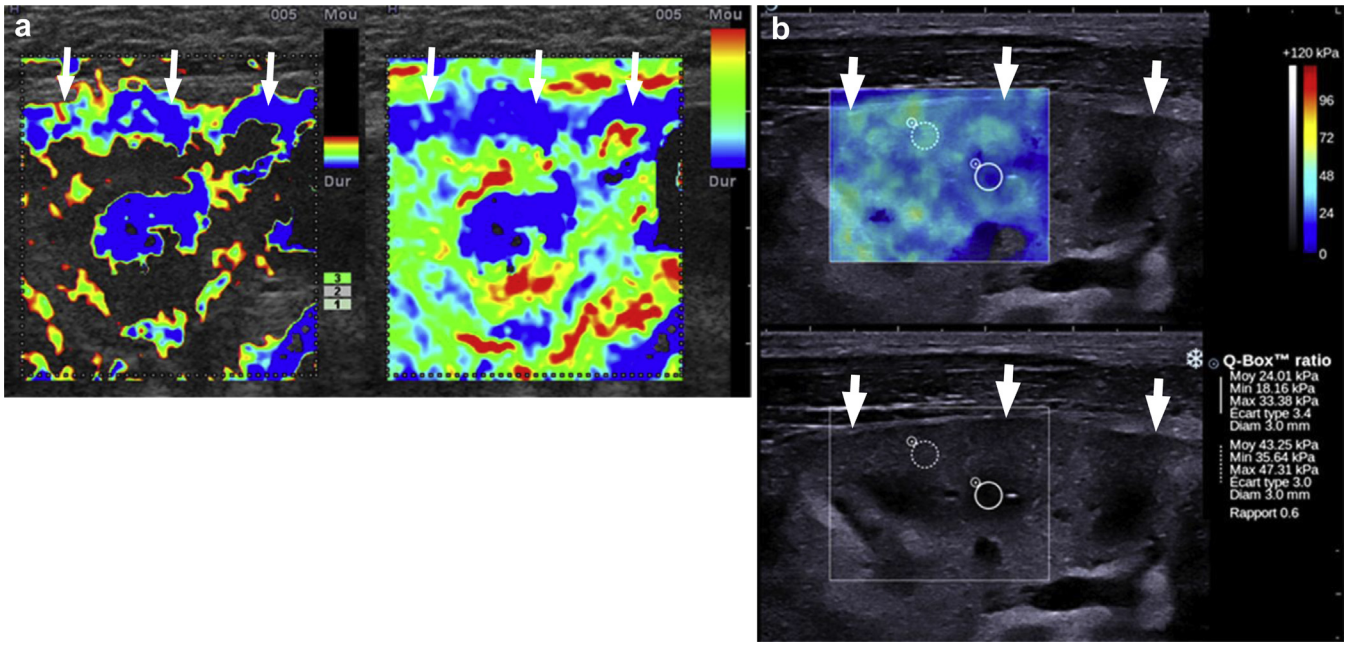

Figure 1 | Quasi-static and shear wave elastography of 2 renal transplant patients with chronic allograft nephropathy (interstitial fibrosis and tubular atrophy 3). (**a**) Using quasi-static elastography, the estimation of the elasticity is relative and qualitative and depends also on the deformation of the tissues of the color elasticity box. Soft tissues are color coded as red and orange, whereas stiff tissues are color coded as blue colors. The anterior capsule of the renal graft is indicated with white arrows. The subcapsular cortex is extremely stiff (blue colors), and the pattern of displayed elasticities is very heterogeneous. (**b**) On shear wave elastography, the upper image displays the elasticity in a color box located on the anterior renal parenchyma, and the lower image represents the morphological B-mode image in exactly the same plane. Soft tissues are color coded with blue colors, and stiff tissues are color coded with red colors. The anterior capsule of the renal graft is indicated with white arrows. The pattern of elasticities is very heterogeneous. Elasticity values ranging from 0 to 120 kPa are color coded according to the color bar on the right side of the image. Two round regions of interest are located on the cortex and the medulla to quantify the local stiffness. The mean stiffness of the cortex is greatly increased at 43.2 kPa, with an SD of 3.0 kPa (minimum, 35.6 kPa; maximum, 47.3 kPa). The mean stiffness of the medulla is also increased at 24.0 kPa with an SD of 3.4 kPa (minimum, 18.1 kPa; maximum, 33.4 kPa). For comparison, the stiffness values of a normal graft are indicated in Figure 4.