Original Article
Application value of shear wave elastography technique in diagnosis of chronic allograft nephropathy

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Abstract: Objective: To investigate the application of shear wave elastography (SWE) in chronic allograft nephropathy. Methods: 82 patients with renal transplantation were all treated with conventional ultrasound and shear wave elastography. Group status: normal renal function group after treating with renal transplantation (Scr <134 mol/L, 36 patients), chronic allograft nephropathy (CAN) group after renal transplantation over 6 months (Scr >134 mol/L, 46 patients). Results: 1. The SWE values of renal cortex in CAN group were higher than those in normal renal function group, P<0.05. 2. There was a positive correlation between SWE values and Scr, and meanwhile, the difference between them was statistically significant, P<0.05. 3. The ROC curves of each SWE value showed that the sensitivity and specificity of Mean were as high as 92.9%. Conclusion: Shear wave elastography is helpful for the judgment of the hardness of chronic allograft nephropathy, which is expected to provide a new, noninvasive and convenient method for the monitoring of renal function and renal hardness after renal transplantation.

Keywords: Ultrasonography, renal transplantation, shear wave elastography technique

Introduction

Over the past 20 years, although the use of anti-immune therapy in renal transplantation has largely relieved acute rejection, it has not prolonged the survival time of the transplanted kidney [1]. Research shows that chronic allograft nephropathy (CAN) is the main cause to long-term graft function [2], and what's more, after excluding acute rejection and the clear causes that lead to chronic renal function damage such as glomerulonephritis relapse, obstruction or reflux, renal artery stenosis and acute CSA/FK506 poisoning, it often occurred within three months of renal transplantation and with the clinical manifestations of renal dysfunction, with or without high blood pressure and proteinuria [3, 4].

The patients often showed progressive deterioration of renal function after renal transplantation, and finally returned to dialysis. Along with the with the increase of patients suffering from chronic allograft renal failure, the need for kidney transplant patients continues to grow, making the shortage of donor organs is more prominent. Therefore, it is very important to study the

effective treatment of CAN to promote and improve the long-term survival of transplanted organs. Puncture is considered to be the gold standard for evaluation of renal transplant damage. However, it is invasive to renal, and some noninvasive methods have been used for renal transplant damage, such as Doppler ultrasound [5], and ultrasound contrast [6], MRI [7]. Wave elastography shear (SWE) is used to measure the hardness of the tissue, and the greater the Young's modulus, the harder the tissue, so it can also be used to evaluate the extent of the lesion. This paper will investigate the elasticity difference between the transplanted kidney and provide a new way for clinical diagnosis of CAN to evaluate the renal function by measuring shear wave velocity of transplant renal cortex and then quantify elastically compliant region of renal transplant interest.

Materials and methods

Research object

The experiment was carried out from February 2015 to July 2015, using a chronic allograft nephropathy (CAN) group, in which 46 patients

Table 1. The basic situation of the two groups

	Normal	CAN	P
	36	46	
Ages (years)	34.86±10.04	35.35±6.22	>0.05
Sex (male/female)	23/13	30/16	>0.05
Times of allograft (months)	20.08±13.62	31.72±29.08	>0.05
Size of allograft (length)	110.11±7.59	109.89±7.34	>0.05
Donor	health	health	

Table 2. The comparison of SWE between CAN group and control group

	Scr (µmol/L)	SWE (KPa) Mean	
		Cortex	Medulla
CAN	168.57±34.11	36.90±6.11	24.22±6.13
Normal	82.92±12.34	24.41±3.99	17.65±4.34
P	<0.05	<0.05	<0.05

were clinically diagnosed with CAN, including 30 males and 16 females, aged 23-49; and the control group, with 36 patients of renal transplantation with normal renal function, including 23 males and 13 females, aged 23-51. Patients were all chosen from the people who had undergone renal transplant in the previous 3 months to 14 years. Inclusion criteria: 1. The clinical manifestations showed that CAN occurred in the number of months or years after renal transplantation, and the main performance of the transplantation of renal function has had a slow progressive decline, which is usually accompanied by high blood pressure, proteinuria and so on, ultimately ending in renal failure. 2. Exclusion of chronic renal damage caused by a clear cause of disease: CAN needs to be identified with the following significant renal dysfunction such as acute rejection, renal glomerular nephritis recurrence, obstruction/reflux, renal vascular stenosis, acute CsA poisoning and so on. Exclusion criteria: 1. Patients with renal function indexes such as serum creatinine were examined as having acute or unstable performance in the first 3 months; 2. Patients with renal transplantation time less than 3 months, and those who have urinary tract obstruction, renal hematoma, surgical area infection and so on; 3. Patients with serious heart and lung disease, which may be influenced by renal external factors such as renal artery stenosis, renal artery stenosis, renal artery and (or) venous thrombosis and so on. All patients were examined for blood creatinine within 2 days.

SWE detection method

Use full the digital color Doppler ultrasonic diagnostic apparatus of AixPlore type made by Supersonic Imagine Company, with a convex array probe 6-1, and frequency 3.5-5.5 MHz. The inspection subject is in supine position. Firstly make routine diagnosis with routine ultrasound examination, which records graft size, cortical thickness, and the blood flow velocity of renal artery with spectral Doppler. Then ask the patient to hold their breath after inhaling, and make a routine ultrasound examination in the longitudinal section, trying to make the beam and kidney capsule as perpendicular as possible. Start SWE to measure Young's modulus value in the renal cortex in the central transplanted kidney after image stabilization with at least 3 sub-sampled in the same position and averaged as the final result.

Statistical analysis

Make statistical analysis with SPSS19.0 statistical software, marking all measurement data with $\overline{x}$±s. Test the comparison between the groups with independent sample t, and test the correlation analysis between SWE average and function of the transplanted kidney with Spearman rank. Compare CAN with the control group, establishing the ROC curve. The difference of P<0.05 was considered statistically significant.

Results

There were no significant differences in the aspects of age, gender, transplantation time, the size of allograft kidney and donor, etc. between the cases of the two groups (P>0.05). The basic situation of the two groups (**Table 1**).

The SWE values of the cortex and medulla of allograft kidney in CAN group were higher than those in the normal group (P<0.05). The comparison of SWE between CAN group and control group: (**Table 2**).

The correlation analysis between all the values of SWE and Cr:Mean was positively correlated with serum creatinine in SWE values of cortex, r=0.710, P<0.05, and positively correlated with serum creatinine in SWE values of medulla, r=0.591, P<0.05.
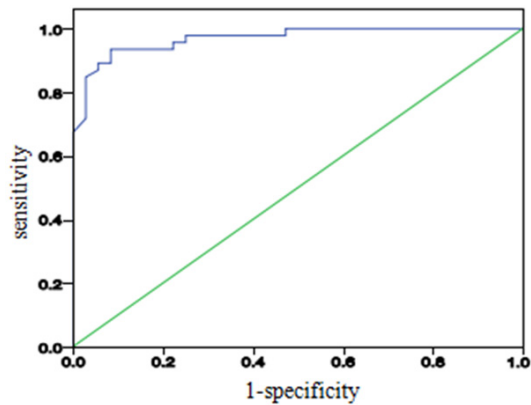
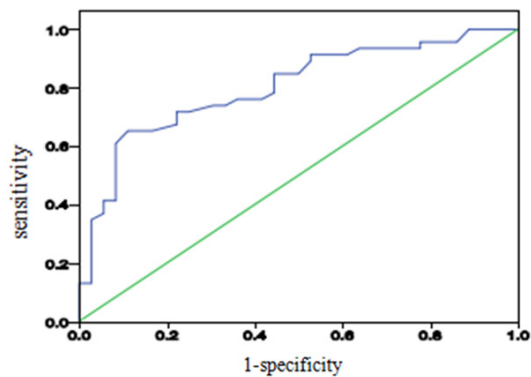**Figure 1.** The ROC curve analysis of SWE values in cortex.

Figure 2. The ROC curve analysis of SWE values in medulla.

ROC curves to Mean value of cortex and medulla SWE were drew with sensitivity as ordinate and specificity as abscissa respectively, the cut-off value for cortex was 29.05, the sensitivity, specificity, positive predictive value, negative predictive value were 93.5%, 91.7%, 93.48%, 91.67% respectively; the cutoff value for medulla was 17.65, the sensitivity, specificity, positive predictive value, negative predictive value were 84.8%, 55.6%, 71.43% and 76.92% respectively. The ROC curve analysis between SWE values in cortex and medulla: (**Figures 1**, **2** and **Table 3**).

Discussion

Shear wave elastography technology is a kind of quantitative analysis technique to obtain the absolute value of tissue elasticity, which is Young's modulus (the definition for the elasticity of objects in physics, with its unit KPa). In shear wave elastography, the shear waves are automatically emitted by the probe to collect the information of tissue stiffness, which could avoid an operator's subjective influence on the results as there is no manual pressure during the process; the tissue stiffness information (KPa value) could be directly obtained from the sampling frame, which ensures a quantitative analysis. The harder the texture of the tissue is, the faster the ultrasonic shear waves run within the tissue, and the higher the elasticity KPa value obtained [8-10]. Shear wave elastography technology is a novel method of imaging for tissue elasticity with the measurement of shear wave velocity generated by the force of acoustic radiation. Use the "Mach cone" generated by low intensity acoustic pulse after the time division to form into multiple transmitting focal zones. Use ultrafast image acquisition system (5000/sec) that could make transient elastography to integrate into a sequence of ultrasound. All these make the quantitative ultrasound elastography method, significantly reducing its operator's dependence by comparison with static elastography. A focused ultrasound beam emitted by a conventional ultrasonic probe will generate a remote acoustic radiation force or so-called pushing beam, and each acoustic intensity (I_{SPTA}) of the pushing beam can meet the internationally adopted AIUM EDA 510 (K) standards in the method of time division. The displacement of tissue generates instantaneous shear waves which spread within the medium, and the ultrasonic equipment then changes to speed imaging mode. The raw RF data are quickly obtained, and the axial displacement for the shear wave spreading within the tissue could be calculated by the comparison of continuous ultrasound images with the classic speckle-tracking algorithms. The velocity of the local shear wave group could be calculated with a one-dimensional cross-correlation algorithm, through which Young's modulus E could be deduced with the formula $E=3\rho c^2$ and two-dimensional tissue elastography produced. ρ is the density of the local tissue (regarded as constant 1000 kg·m^{-3}), and c is the shear wave velocity [11, 12].

SWE technology currently has several applications, such as the identification of the stages of liver fibrosis or liver cancer. It also has identification significance for the benign and malignant thyroid in nodules and breast. There are literature reports for measurement ranges for

Table 3. Comparison of diagnostic capability between cortex and medulla

Parameter	Sensitivity (%)	Specificity (%)	Area under the curve	Cutoff	Positive predictive value (%)	Negative predictive value (%)
Cortex	93.5	91.7	0.97	29.05	93.48	91.67
Medulla	84.8	55.6	0.802	17.65	71.43	76.92

normal kidneys and the fibrosis of transplanted kidneys [13-21] as well. Thus, SWE technology can provide clinical real-time quantitative indicators, avoiding the interference of subjective factors during the diagnostic process.

Histologically, CAN shows the following different pathological combinations: ischemic renal disease (glomerular sclerosis, etc.), transplant glomerular diseases (such as thickening or shrinking of the glomerular basement membrane, increase of mesangial matrix, etc.), interstitial fibrosis, renal tubular atrophy, atherosclerosis, hyaline degeneration of arteriole, fibrous intimal thickening of artery, and delamination or fracture of capillary basement membrane, etc. The progressive fibrosis of renal transplantation is not only the most common CAN lesion, but also the most common reason and the canal commune of the dysfunction of chronic kidney disease and renal failure. The nature is the extra cellular matrix abnormal accumulate in the glomerulus and renali interstitial which leads to the lesion of kidney, the loss of the effective nephron and the progressive loss of the kidney function. The renal parenchymal are mainly composed of glomeruli and renal interstitial, so it can make a comparatively efficient response to the variation of CAN. Normally, the blood supply of kidney cortex is abundant; the elasticity of the vascular loops and the compliance of the tissues are good [22, 23]. Kidney becoming stiff, and the elasticity and compliance decreasing, are because of changes of atrophy in the glomerulus loops, as well as basal lamina thickening, glomerular sclerosis and renal interstitial fibrosis. After the tissues are stimulated by an electromagnetic pulse, the speed of its spread and the value of SWE increased. The glomerulus of the kidney cortex is the main location of the kidney's pathological change, so the kidney cortex response to the variation of the elasticity is clearer, and the SWE kidney cortex of CAN is greater than the control group. The research outcome indicates that when the Mean in SWE measurement of kidney cortex transplantation is more

than 29.05 KPa, it should be diagnosed as CAN, as its sensibility is 93.5%, specificity is 91.7%, and area under curve is 97%. The canal commune of the end stage of renal disease is renal fibrosis, and the main pathologic change is the loss of effective nephron, then replaced by the hyperplasia of plenty fibroblasts and myofibroblasts, and this finally leads to the kidney's elasticity decrease and the stiff increase. The research uses SWE to research CAN. SWE is different from the former elasticity imaging techniques. It has the advantages of having no pressure, real time imagery, orientation survey; measurement results are free from the influence of operator and the repeatability, etc. It also can direct-response the elasticity of tissues, so the greater the measured Young's moduli is, the stiffer of the tissues.

Because of the accumulation of plenty of collagenous fiber and fibronectin, the patient has glomerular sclerosis and renal tubule interstitial fibrosis which lead to a significant increase of Young's moduli. Clinically, the percentage of patients with CAN glomerular diseases is more than 95% in chronic kidney disease, and glomerulus is mainly distributed in the renal cortex; therefore, the hardness of the renal cortex increase is more obvious, and Young's modulus values are increased more than the renal medulla. In CAN group, with the degree of impairment of renal function aggravation, the Young's modulus of the renal cortex and renal medulla of CAN patients is gradually increased, and the increase of Young's modulus of the renal cortex and renal medulla of renal atrophy patients in advanced stage was particularly evident. This shows that with the degree of kidney fibrosis getting more serious, the elasticity of kidneys is also getting worse. This is entirely consistent with the renal histopathological changes in the progression of nephropathy. Renal decompensation is in the inflammation reaction period. The damage of kidneys is lighter, with the nephron reduced 20%-25%; renal insufficiency is decompensated, renal insufficiency failure period, in the form of renal fibro-

sis, this period of pathological damage is more serious than initial stage, as the nephron reduced 50%-90%. In renal insufficiency uremia period, kidneys were almost scarred, and more than 90% of nephron function lost. CAN patients have a good correlation between Young's modulus values of renal cortex and serum creatinine values. Wherein the Mean highest correlation with Scr, r is 0.710, it means that to a certain degree, Young's modulus values may reflect the degree of renal lesions.

The advantages of this technology in kidney transplantation are: firstly, kidney transplants are usually located the side of the patients' iliac fossa. Compared with normal renal anatomical location, the distance from the location to the surface is smaller, and the influence of breathing amplitude is lessened. Intestinal gas and bone acoustic shadows also. Secondly, the renal parenchyma cortex form is more irregular, but due to a smaller sampling frame, when measuring, most tissue in the box does not contain other parts. Thirdly, this test has a deepest depth of 8.0 cm; basically it can reach the deep surface of the transplanted kidney. You can choose to measure each section of the transplanted kidney's upper pole, the pole or lower pole at will. CAN is usually used to diffuse lesions, as the main site of the lesion is the renal cortex, and it is more convenient. Taking the main lesion detection is more representative, so this study measured the cortical by pole kidney cortex, whether measured or compared, the standard is more consistent, the operating is a real-time measurement, with multiple sampling, repeated measurements, less time-consuming, and has no radiation.

This study use SWE technology detect the elastic parameters of the renal cortex of implanted kidney patients intuitively and quantitatively, value the renal cortex hardness change in early stages, and reflect changes in renal function. Combined with conventional ultrasound, it can provide quick clinical, real-time indicators. It provides another strong piece of evidence in early diagnosis and assessment of graft function. This technique is simple, inexpensive, and reproducible, can keep track the measurement without increasing the suffering of the patients, etc., it has a more extensive prospect in clinical application.

The limitations of this study are the small number of cases. Shear wave electrography in renal

transplantation research is still in its infancy, especially in the different pathological conditions of transplanted kidney. Shear wave electrography measured the value and its correlation of microscopic pathology and factors which can influence the Young's modulus values. All these need to be further studied.

Disclosure of conflict of interest

None.

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