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TOPIC HIGHLIGHT

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Diagnosis of liver cirrhosis with contrast-enhanced ultrasound

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Abstract

The assessment of the extent of liver fibrosis is very important for the prognosis and clinical management of chronic liver diseases. Although liver biopsy is the gold standard for the assessment of liver fibrosis, new non-invasive diagnostic methods are urgently needed in clinical work due to certain limitations and complications of biopsy. Noninvasive imaging studies play an important role in the diagnosis of focal liver disease and diffuse liver diseases. Among them, ultrasonography is the first choice for study of the liver in clinical work. With the development of ultrasound contrast agents and contrast specific imaging techniques, contrast-enhanced ultrasound (CEUS) shows good performance and great potential in the evaluation of liver fibrosis. Researchers have tried different kinds of contrast agent and imaging method, such as arrival time of contrast agent in the hepatic vein, and quantitative analysis of the enhancement level of liver parenchyma, to evaluate the degree of liver fibrosis during the past 10 years. This review mainly summarizes the clinical studies concerning the assessment of liver fibrosis using CEUS.

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Key words: Diagnosis; Liver cirrhosis; Contrast media; Ultrasound

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INTRODUCTION

Liver fibrosis is mainly caused by chronic liver diseases such as chronic hepatitis and alcoholic liver disease. Biopsy is considered as the gold standard for estimation of fibrosis. Owing to its limitations of sampling error, inter-observer disagreement, and the risks and complications of this invasive procedure, new, reliable noninvasive diagnostic methods are necessary to take the place of liver biopsy as the first line assessment of fibrosis during clinical work[1-7]. Biochemical tests and imaging techniques are the two most active research areas for the noninvasive assessment of liver fibrosis. The biochemical tests which are based on the evaluation of a large numbers of serological markers show good performance in predicting the degree of liver fibrosis. However, there are still some limits, especially in cases of Gilbert syndrome, hemolysis and acute inflammation. Therefore, biomarkers alone are not sufficient for making a definite decision in a given patient, and the clinical data must be taken into account[8]. As to the imaging methods, ultrasonography, computed tomography (CT) and magnetic resonance imaging (MRI) are the most traditional and popular, and transient elastography is a newly developed technique which can rapidly and noninvasively measure mean tissue stiffness.

Conventional grey scale ultrasound is the first-line imaging modality in screening of liver cirrhosis. Blunt

liver edge, liver parenchymal abnormalities, and liver morphological changes are the direct signs for diagnosis of liver cirrhosis on grey scale ultrasound. Color Doppler ultrasound can supply some valuable parameters for different blood vessels in diagnosis of liver cirrhosis, but the reliability and reproducibility of the technique limits its clinical usage in noninvasive diagnosis and assessment of severity of hepatic fibrosis[9-13]. Conventional CT and MRI scans can identify irregular or nodular liver surface, liver parenchymal abnormalities and portal hypertension which are very important signs for diagnosis of hepatic cirrhosis. The diagnostic accuracies for liver cirrhosis using these imaging modalities were reported in a recent study as 70.3% for MRI, 67.0% for CT and 64.0% for ultrasound, and the sensitivities and specificities were 86.7%, 84.3%, 52.4% and 53.9%, 52.9%, 73.5%, respectively[14]. With the development of super-paramagnetic iron oxide contrast agents for MRI, Kupffer-specific imaging may prove to be a new point of view with which to diagnose and evaluate the severity of the liver cirrhosis on MRI scan[15-17].

CONTRAST-ENHANCED ULTRASOUND

Newly developed ultrasound contrast agents (UCAs) and contrast-enhanced ultrasound (CEUS) techniques show great potential in the diagnosis of focal and diffuse liver disease[18,19]. Currently, the UCAs used in clinical CEUS examination are characterized by a microbubble structure consisting of gas bubbles stabilized by a shell. Globally, there are three kinds of UCA which can be used in liver imaging : Levovist (air with a galactose/palmitic acid surfactant; SH U 508A; Schering, Berlin, Germany), SonoVue (sulfur hexafluoride with a phospholipid shell; BR1; Bracco, Milan, Italy) and Sonazoid (perfluorobutane with a lipid shell; NC100100; Amersham Health, Oslo, Norway)[18,19]. SonoVue (sulfur hexafluoride) and Sonazoid (perfluorobutane) contain low solubility gases and show higher microbubble stability than Levovist which contains air. After intravenous injection of UCA, the microbubbles act as blood pool tracers, strongly increase the ultrasound backscatter and are therefore useful for enhancement of blood echogenicity and for the assessment of blood flow in the vasculature. In addition, Levovist and Sonazoid have been proved by both *in vivo* and *in vitro* studies to be phagocytosed by the reticuloendothelial system of the liver and spleen. The liver parenchyma specific imaging can be obtained 10 min after administration of the contrast agents[20-24].

The visualization of enhancement caused by microbubbles requires contrast specific imaging techniques, which are generally based on the cancellation and/or separation of linear US signals from tissue and utilization of the nonlinear response from microbubbles. A non-linear response from microbubbles could not only be induced by microbubble disruption at high acoustic pressure but also by oscillations at low acoustic pressure. When Levovist is used as contrast agent, high mechanical index (MI) intermittent imaging with low frame rates should be used, due to the lower resistance to acoustic pressure of the air filled microbubble. When SonoVue or Sonazoid is used as contrast agent, low MI imaging could be used, which enables minimal disruption of microbubbles, real time and effective investigations of the dynamic enhancement pattern, and effective tissue signal suppression[18,19].

CEUS IN DIAGNOSIS OF LIVER CIRRHOSIS

Contrast enhanced ultrasound has been used in the diagnosis and evaluation of liver cirrhosis during the past 10 years. Researchers mainly focused their studies on the hemodynamic changes and kupffer cell function changes followed by liver fibrosis, and tried to find and prove these changes using different kinds of CEUS techniques and UCAs[25-36].

Hepatic vein arrival time

The hemodynamic changes which accompany hepatic cirrhosis mainly include arterialization of the liver, intrahepatic shunts, pulmonary arteriovenous shunts, and a hyperdynamic circulatory state. All of these changes will make the hepatic first pass of contrast agent injected into a peripheral vein faster in a cirrhotic liver compared with normal liver.

Albrecht *et al*[25] studied the hepatic vein transit time using continuous spectral Doppler ultrasonography and Levovist. They found patients with cirrhosis showed a much earlier onset of enhancement (arrival time; mean 18.3 s) and peak enhancement (mean 55.5 s) than controls (49.8 s and 97.5 s) or patients with non-cirrhotic diffuse liver disease (35.8 s and 79.7 s). All patients with cirrhosis had an arrival time of the bolus of less than 24 s, whereas the arrival time was 24 s or more in 22 of the 23 other participants. Taking a hepatic vein arrival time of 24 s as the diagnostic criteria for liver cirrhosis, the sensitivity and specificity were 100% and 96%, respectively. They also found that peak enhancement was higher in patients with cirrhosis (mean 48.7 units) than in the other two groups (12.5 and 12.3 units, respectively). They concluded that analysis of liver transit time of a bolus of UCA provides useful information about haemodynamic changes in patients with cirrhosis, and measurement of the arrival time of the bolus allows discrimination of patients with cirrhosis from controls and from patients with non-cirrhotic diffuse liver disease, and has potential as a non-invasive test for cirrhosis. Bang *et al*[26] compared pulse inversion imaging with spectral Doppler quantification in assessment of the arrival of a contrast agent in the hepatic veins in six patients. They found the hepatic vein arrival times measured by two different methods were within 2 s apart in five patients and within 5 s apart in one patient. They believe pulse inversion imaging will be a simple and accurate method for evaluation of hepatic vein arrival time. Sugimoto *et al*[27] evaluated hepatic vein arrival time using Levovist and pulse inversion imaging in 15 patients. They found that the time-acoustic intensity curves for hepatic vein could be classified as a gradual-rising curve which was seen in

all controls and non-cirrhotic patients and a rapid-rising curve which was seen in all cirrhotic patients. They also showed that the hepatic vein arrival time was significantly earlier in cirrhotic patients compared with normal and hepatitis patients (18 s *vs* 31 s, 30 s), respectively. They believe CEUS and hepatic vein transit time is a useful noninvasive diagnosis method for liver cirrhosis with high sensitivity and specificity.

With the development of contrast specific techniques and the emergence of new generation contrast agent, real-time CEUS became a powerful tool for evaluation of liver cirrhosis. Ridolfi *et al*[28] tried to use low MI CEUS with SonoVue to evaluate the severity of chronic hepatitis C. They found the mean hepatic vein arrival time decreased progressively with increasing severity of liver disease, all patients with liver cirrhosis had a hepatic vein arrival time of 17 s or less, whereas values of 18 s or more were recorded for all controls and for almost all patients (20/22) with non-cirrhotic liver disease. But within the group of chronic hepatitis C, Metavir scores of fibrosis and necro-inflammatory changes had no significant effect on hepatic vein arrival times. They concluded that hepatic vein arrival time might be a simple and non-invasive method for reliably excluding cirrhosis with signs of portal hypertension, but not for assessing the severity of either chronic hepatitis C or cirrhosis. Lim *et al*[29] compared Levovist and SonoVue in evaluation of hepatic vein arrival time in 40 hepatitis C-related liver disease patients and 25 normal volunteers. They found that mean hepatic vein arrival times in control, mild hepatitis, moderate or severe hepatitis, and cirrhosis groups were 38.3, 47.5, 29.5 and 17.6 s, respectively, with Levovist; and 29.4, 27.4, 22.9 and 16.4 s, respectively, with SonoVue. The hepatic vein arrival time decreased as severity increased in imaging with both contrast agents. There was no significant difference in hepatic vein arrival time between mild and moderate hepatitis groups with SonoVue; however, there were significant differences in hepatic vein arrival time between all patient groups using Levovist. Hepatic vein arrival time of SonoVue was shorter than that of Levovist in all groups except the cirrhosis group where the hepatic vein arrival time of the two contrast agents was similar. Although hepatic vein arrival time seems to fulfill the task of diagnosis of liver cirrhosis, some researchers also found that the hepatic vein transit time was accelerated in the liver with metastatic liver tumors[37-39]. This is the main limitation of using hepatic vein transit time to diagnose liver cirrhosis since there may be many other situations which will also result in similar hemodynamic changes.

Some researchers also studied the micro-hemodynamic changes which follow liver cirrhosis using CEUS. Giuseppetti *et al*[33] used the destruction and replenishment CEUS technique to evaluate the changes in hepatic parenchymal blood flow in cirrhotic patients and normal patients. Pulse inversion harmonic imaging was obtained at progressively increasing pulse intervals of 2, 4, 7 and 10 s in the same scan plane during infusion of Levovist (300 mg/mL, 150 mL/h). Pulse intervals *vs* signal intensity (PI-SI) plots were made to illustrate the speed of blood in the liver parenchyma. They found the slope of the PI-SI plot of the Child A cirrhotic patients was significantly lower than the slope of the normal controls and of the Child C cirrhotic patients; conversely, no significant differences were found between the slope of the patients with Child C cirrhosis and of the normal controls. The slope of the patients with liver cirrhosis presented with a significantly higher variability than was observed in the normal controls. They explained their findings by suggesting the slope of the PI-SI plot obtained by placing the ROI in a region of parenchyma reflects the average speed of both the arterial and the venous components of the microcirculation. They thought that liver perfusion was provided mainly by the portal circulation in most patients with Child A cirrhosis, and because the velocity of the portal blood flow is reduced, an overall reduction of the average velocity of the parenchymal blood is observed. In patients with Child C cirrhosis and advanced disease, however, the portal component of the hepatic blood flow can be markedly reduced, with increased arterial perfusion and significant portosystemic venous and arteriovenous shunting. These hemodynamic changes can cause a prevalence of the arterial component of the microcirculation, with higher velocity flows, causing an overall increase of the average velocity of the parenchymal blood.

Enhancement level of liver parenchyma

Some researchers have tried to use enhancement level of liver parenchyma on CEUS to diagnose liver cirrhosis based on the theory of diminished or function damage of Kupffer cells accompanied with the hepatic cirrhosis. Fujita *et al*[34] used Levovist and stimulated acoustic emission imaging, and studied 114 patients with alcoholic liver disease and other chronic liver disease. They compared the enhancement level of the hepatic parenchyma and right kidney at 20 s, 90 s, and 5 min after injection of Levovist. The contrast patterns of the liver and kidney were divided into three patterns. In pattern A, only the kidney was strongly enhanced at 20 s, both liver and kidney were strongly enhanced at 90 s, and only the liver was enhanced at 5 min. In pattern B, both the liver and the kidney were strongly enhanced at 20 s and 90 s, but only the liver was strongly enhanced at 5 min. In pattern C, both the liver and the kidney were strongly enhanced at 20 s and 90 s, and both organs were weakly enhanced at 5 min. They found 83% of normal livers showed pattern A, whereas pattern B was found in 60%-86% of patients with chronic liver disease, and almost all of the patients with alcoholic liver cirrhosis had pattern C. They supposed that Kupffer cell dysfunction in liver cirrhosis resulted in slower clearance of contrast agent and thus weak enhancement of liver parenchyma in pattern C. Gasparini *et al*[35] studied 10 normal volunteers, 16 Child A and 16 Child C cirrhotic patients with CEUS using Levovist. They found the enhancement level of liver

parenchyma in late phase (7 min after administration of contrast agent) decreased significantly both in patients with Child A ($P < 0.05$) and Child C ($P < 0.001$) cirrhosis compared with normal liver, and a statistically significant signal intensity decrease was also observed from the patients with Child A to those with Child C cirrhosis ($P < 0.01$). Their explanation was that the decreased uptake of the Levovist microbubbles by the reticuloendothelial system in cirrhotic liver due to impaired functional capacity of the Kupffer cells secondary to increased portosystemic shunting of blood resulted in the observed difference between the groups. Kaneko *et al*[36] compared the parenchyma enhancement with the degree of liver dysfunction using pulse-inversion ultrasonography and Levovist. They found there was a significant inverse correlation between the gray scale of the liver parenchyma and the hepatic fibrosis index ($r = -0.809$, $P < 0.01$). The average signal intensity of the liver parenchyma was 144.5 in a normal liver, 133.6 in chronic hepatitis, and 102.6 in liver cirrhosis, demonstrating a significant difference between a normal and cirrhotic liver ($P < 0.01$). They concluded that the signal intensity of a microbubble disruption of the liver parenchyma in the late phase of enhancement with Levovist could reflect the degree of hepatic fibrosis.

CONCLUSION

In conclusion, hepatic vein arrival time and enhancement level of liver parenchyma in late phase may be valuable clues for the diagnosis of liver cirrhosis. Most researchers believe that the hemodynamic changes in cirrhotic liver mainly happen within the liver which results in faster hepatic vein transit time on CEUS compared with normal liver. Taking a hepatic vein arrival time of less than 21 s as the diagnostic criteria, the sensitivity, specificity, positive predictive value and negative predictive value of CEUS in diagnosis of liver cirrhosis was 100%, 80%, 74% and 100%, respectively. Many researchers also pointed out that the hepatic vein arrival time correlated with the severity of liver fibrosis. Different contrast agents result in different hepatic vein arrival time on CEUS. The second generation contrast agent SonoVue, has faster hepatic vein arrival time than Levovist in normal and hepatitis patients. Finally, hepatic metastasis will also result in a faster hepatic vein arrival time on CEUS, which is another limitation of hepatic vein arrival time in the diagnosis of liver cirrhosis. Enhancement level of liver parenchyma in late phase of CEUS shows a negative correlation with the severity of liver cirrhosis. Due to dysfunction of Kupffer cells in cirrhotic liver, the enhancement of liver parenchyma in late phase was much darker than normal liver. In conclusion, CEUS may be an easy and valuable non-invasive method for diagnosis and assessment of liver cirrhosis.

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