

Research Article

Evaluation of Changes Liver Hemodynamics with Color Doppler Ultrasound in the Cholestatic Patients

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Abstract

Background/Aim: This study is aimed to determination of frontier findings warning physicians related to hemodynamic changes having development possibility in liver resulted from cholestasis by using such a method of color Doppler ultrasonography (RDUS) which is non invasive and reliable.

Patients and Methods: In this context; 42 patient groups having high hepatic enzyme level, 41 patient groups having elevated hepatic enzyme level and bilirubin, and 24 control groups constituted from healthy persons are examined with RDUS. In all cases congetion index (CI), fibrosis index (FI), hepatic vascular index (HVI), hepatic artery resistive index (HA-RI), hepatic artery pulsatility index (HA-PI), portal vein velocity (PVV), portal vein diameter (PVD) and spleen length are evaluated.

Results: According to these parameters, statistical difference among the control group, patient group of elevated hepatic enzyme level, and cholestasis patient group are evaluated. According to the FI, HVI, HA-PI parameters, between the patient group of high hepatic enzyme level and control group are determined significant difference ($p < 0,05$). On the other hand, according to the CI, HA-RI, PV diameter, and spleen length parameters, these groups are not observed any significant difference ($p > 0,05$). Between the patient group of high hepatic enzyme level and the cholestasis patient group, and between the control group and the cholestasis patient group are obtained significant difference as statistical in all parameters ($p < 0,05$). According to the CI, FI, HA-RI, HA-PI, PVV, and HVI parameters, these groups are determined high statistical significant difference ($p < 0,001$). While CI, FI, HA-RI, HA-PI, PVD, and spleen length have increased in the cholestasis patient group; in turn, PVV and HVI have decreased.

Conclusion: Those results that RDUS have a utility and reliable modality on the changes happened in hepatic hemodynamy that might appeared by presence of biliary cirrhosis and its progression developed in the cholestatic patients.

Keywords: Cholestasis; Biliary Cirrhosis; Hepatic Artery; Portal Vein; Color Doppler Ultrasound.

Introduction

Cholestasis is accumulation of the bile in the liver cells and bile ducts due to obstruction of bile flow into the small intestine. Decrease in bile passage into the intestine or absence of it results in accumulation of the substances in the blood that normally excreted through the bile. As a consequence, stasis in the liver ensues and this in turn leads to degeneration of hepatocytes, deterioration in the liver function tests, elongation of blood clotting time, increase in the risk of hemorrhagic diathesis, mental changes due to high bilirubin levels and tendency for infections. As pathology progresses, biliary cirrhosis can develop and septic shock and death associated with severe gastrointestinal bleedings due to secondary portal hypertension (PHT) can be seen. Despite current modern diagnostic and therapeutic approaches, biliary cirrhosis and its complications, arising in bile duct obstructions, are still serious causes of morbidity and mortality [1]. Ultrasound (US) is the primary radiologic imaging method used in diagnosis and follow up of cholestasis. Dilatation in

the bile ducts, bile stones, bile duct tumors and findings of cirrhosis such as changes in the liver parenchyma echo can be detected with US. However pathology may not be detected with ultrasound in many cases. Therefore US can be inadequate in the evaluation of biliary cirrhosis and subsequent complications such as PHT [2]. Intra and extra hepatic bile ducts and level and cause of obstruction can be assessed with computerized (CT) and magnetic resonance imaging (MRI), endoscopic retrograde cholangiography (ERCP) and magnetic resonance cholangiography (MRCP) [3]. Although of these radiologic modalities CT and MRI can visualize intraabdominal vessels, they have a limited significance in diagnosis and follow up of PHT because adequate information on direction and velocity of the flow cannot be obtained. Although angiography is considered as the gold standard in diagnosis of PHT, it is not a suitable imaging method for routine use in diagnosis and follows up because it is an invasive and expensive modality and it cannot detect blood flow rate and output. On the other hand, Doppler US is a preferable imaging method because it is noninvasive, inexpensive, and easily repeatable

and it can display hemodynamic changes easily by assessing the blood flow rate and flow characteristics [4].

In biliary cirrhosis and cirrhosis resulting from other causes, occurrence of hemodynamic changes in the liver and the other organs are expected [5]. For example splenic circulation and splenorenal shunts detection is important in the severity of the portal hypertension (of any type) of liver cirrhosis. These collateral veins are well diagnosed by Doppler US [6]. Before changes in biochemical parameters develop and in cases that are evaluated as normal by radiologic imaging methods, hemodynamic changes could have been developed asymptotically. Therefore detection of possible hemodynamic changes is crucial in early diagnosis of the disease and in monitoring the progression in patients who are already diagnosed. We investigated the detection of early and advanced phase changes in the liver hemodynamic in the cases with cholestasis by Doppler US and we studied the role of the Doppler US parameters in diagnosis and follow up of the disease progression.

Patients and Methods

Patients

Patients with cholestasis admitted subsequently in Firat University Department of Radio diagnostics between March and September 2007. Patient group that consisted of 42 patients with elevated enzyme levels, patient group that consisted of 41 cases with elevated bilirubin, patient group with cholestasis and control group that consisted of 24 healthy individuals were studied prospectively.

Methods

Cholestasis diagnosis was made on laboratory and clinical findings. Liver function tests were within normal limits in all control cases. Goal and structure of the study was described to all patients initially and their consent was obtained.

Cases with viral hepatitis and those with history of alcohol intake were not included in the study.

All cases were examined with RDUS by a single radiologist after 8 hours of fasting. Patients were examined in supine and/or lateral decubitus position. US examinations were done with LOGIQ 7 Doppler ultrasound equipment (General Electric, Yokogawa Medical and System Tokyo-Japan) and multifrequency 3.5 MHz convex transducer. PVD, PV flow velocity, HA-RI and HA-PI were measured in all cases. HVI values were calculated by proportionate PV flow velocity to HA-PI. CI was calculated with the ratio of PV area to PVH, and PI was calculated by multiplying ratio of HA-RI to portal velocity with 100. In all measurements, wall filter was kept at minimum to enable detecting slow flow signals in late diastole without allowing interferences in spectral analysis due to vessel wall vibrations. In order to minimize measurement faults, lowest possible PRF adjustments were chosen lest it lead to aliasing formation. Special attention was paid to have the angle between US beam and the vessel to be examined at possible minimum value and below 60 degrees all the time.

Statistical Evaluation

Percentage, average and standard deviation were used in statistical evaluation of enzyme elevation and characteristics of patients with cholestasis and control group. Relation between control and patient

group in terms of all Doppler parameters was evaluated using Student's t test. For evaluating the relations of Doppler parameters with each other, Pearson correlation analysis was used.

Findings

General characteristics of the cases

Age of the 43 patients with elevated enzyme (24 male, 18 female) who were evaluated with RDUS ranged between 23 and 68 (mean 44.9). Age of the 41 patients in cholestasis group (24 male, 17 female) ranged between 25-72 (mean 55.4). Control group consisted of 24 healthy individuals (13 male, 11 female) whose ages ranged between 21 and 74 (mean 43.9). In terms of age and gender, there was not any statistically significant difference between the groups (Table 1-5).

Discussion

Cholestasis can develop due to obstruction of bile flow and

Table 1:

	Gender	n	%	Total
High-enzyme level group	Female	24	57,2	42
	Male	18	42,8	
Cholestasis group	Female	17	41,5	41
	Male	24	58,5	
Control Group	Female	11	45,8	24
	Male	13	54,2	

Table 2:

Parameters	Control Group n=24	Elevated Enzyme Group n=42	Cholestasis Group n=41
CI	0,03±0,15	0,03 ± 0,14	0,08 ±0,03
FI	3,25 ±1,01	3,10±0,60	5,13 ±1,33
HVI	19,54 ± 5,26	22,71 ± 6,30	11,49 ± 2,18
HA-RI	0,65 ± 0,05	0,66 ± 0,05	0,72 ± 0,07
HA-PI	1,11 ± 0,18	1,25 ± 0,28	1,51 ± 0,24
PVV	21,16 ± 6,45	24,30 ± 6,08	17,97 ± 3,56
PVD	10,50 ± 1,06	10,92 ± 1,25	13,07 ± 1,69
Spleen length	10,45 ± 0,97	10,50± 0,99	12,155±2,05

Table 3 :

Parameters	Groups	n	Avarage	SD	P
CI	Enzyme	42	0,0345	0,1400	0,67
	Control	24	0,0329	0,1574	
FI	Enzyme	42	3,1019	0,6027	0,005
	Control	24	3,2596	1,0113	
HVI	Enzyme	42	22,7140	6,3067	0,042
	Control	24	19,5488	5,2692	
HA-RI	Enzyme	42	0,6690	0,5036	0,025
	Control	24	0,6533	0,5715	
HA-PI	Enzyme	42	1,2512	0,28927	0,041
	Control	24	1,1137	0,18619	
PVV	Enzyme	42	24,3095	6,08271	0,164
	Control	24	21,1667	6,45160	
PVD	Enzyme	42	10,9286	1,2570	0,183
	Control	24	10,5000	1,0632	
Spleen length	Enzyme	42	10,5000	0,99388	0,870
	Control	24	10,4583	0,97709	

Table 4:

Parameters	Groups	n	Avarage	SD	p
CI	Cholestasis	41	0,0861	0,03153	0,008
	Control	24	0,0329	0,1574	
FI	Cholestasis	41	5,1395	1,33687	0,001*
	Control	24	3,2596	1,0113	
HVI	Cholestasis	41	11,4990	2,18581	
	Control	24	19,5488	5,2692	
HA-RI	Cholestasis	41	0,7278	0,0752	0,001*
	Control	24	0,6533	0,0571	
HA-PI	Cholestasis	41	1,5102	0,24878	0,001*
	Control	24	1,1137	0,18619	
PVV	Cholestasis	41	17,9756	3,56713	0,001*
	Control	24	21,1667	6,45160	
PVD	Cholestasis	41	13,0732	1,69396	0,001*
	Control	24	10,5000	1,06322	
Spleen length	Cholestasis	41	12,1556	2,05058	0,001*
	Control	24	10,4583	0,97709	

Table 5:

Parameters	Groups	n	Avarage	SD	p
CI	Enzyme	42	0,0345	0,1400	0,001*
	Cholestasis	41	0,0861	0,03153	
FI	Enzyme	42	3,1019	0,6027	0,001*
	Cholestasis	41	5,1395	1,33687	
HVI	Enzyme	42	22,7140	6,30967	0,001*
	Cholestasis	41	11,4990	2,18581	
HA-RI	Enzyme	42	0,6690	0,05036	0,001*
	Cholestasis	41	0,7278	0,0752	
HA-PI	Enzyme	42	1,2512	0,28927	0,001*
	Cholestasis	41	1,5102	0,24878	
PVH	Enzyme	42	24,3095	6,08271	0,001*
	Cholestasis	41	17,9756	3,56713	
PV-CAP	Enzyme	42	10,9286	1,25704	0,001*
	Cholestasis	41	13,0732	1,69396	
Spleen length	Enzyme	42	10,5000	0,99388	0,001*
	Cholestasis	41	12,1556	2,05058	

accumulation of the bile in the liver as a result of various pathologies such as obstructive, inflammatory and genetic processes. Increased pressure in bile ducts blocks bile flow and this in turn leads to accumulation of toxic substances and macroscopic and microscopic changes in the liver. In cases where obstruction persists, fibrosis around the bile ducts can ensue, and a type of cirrhosis called biliary cirrhosis can develop. Further progression of intrahepatic fibrotic changes increase the parenchyma damage by mechanically obstructing the sinusoidal flow, nodular regeneration develops, and with the distortion of vascular structure, hepatic flow deteriorates. PHT that results in as cites, varicose bleeding and hypersplenism can develop [7].

Vanigella et al. reported that PHT and varicose bleedings develop in 40-80% of the children with biliary atresia, one of the causes of cholestasis, at age about 5. They also reported that more than half of the children with Allagille syndrome progressed to cirrhosis [8]. Mwanza et al. performed main bile duct ligation model in dogs. They induced elevated pressure and cholestasis as a result of cessation of bile flow from the gallbladder and intrahepatic bile ducts. As a consequence, they observed cirrhotic changes such as hepatocyte necrosis, degeneration and infiltration in livers of the experimental subjects. In this study, physical examination, laboratory studies and US imaging were found to be consistent with cholestasis. With Doppler US examinations that were carried out weekly until 10th week, they observed a decrease in PV volume and flow velocity and an increase in PV area and CI as duration of cholestasis prolonged [5].

Yoshioka et al. found that hepatocytes around the proliferated bile ducts atrophied on 4th week following bile duct ligation in mice [9]. Pastor et al created bile duct obstruction in rats and observed secondary biliary cirrhosis on 28th day [10]. Brodie et al. detected a decrease and an inversion in the hepatic artery diastolic flow in severe biliary cirrhosis that develops secondary to biliary atresia. They also reported that HA-RI values are correlated with degree of cirrhosis and useful in follow up of clinical course in children with biliary atresia [11]. Chawla et al reported that secondary PHT developed as a result of PV obstruction in patients with extrahepatic (such as chronic pancreatitis, local tumor invasion) or intrahepatic (such as recurrent cholangitis, primary sclerosing cholangitis) bile duct anomalies [12].

In other studies, it was reported that valuable information on severity and prognosis of the disease was obtained by evaluating the liver hemodynamic and morphology in patients with cirrhosis. A relation between hemodynamic changes in PV and histological changes in chronic hepatitis was found. Besides, it was observed that liver blood flow could be changed by diseases such as hepatocellular disorders, tumors and porto-systemic shunts [13,14]. Liver biopsy is required to make the diagnosis of cirrhosis certain in patients without prominent clinical and laboratory findings. Prognosis of cirrhosis varies depending on the cause, stage of the disease and possibilities of treatment. Child score is used to determine the prognosis. In this scoring, ascites, albumin and bilirubin levels, encephalopathy and prothrombin time are taken into account [15]. Portal angiography and splenoportography are the most valuable methods in diagnosis of PHT which often develops as a complication of cirrhosis. However, they cannot be used as convenient imaging methods because they are invasive and have a limited repeatability. Therefore a simple and noninvasive method that could provide reliable data on portal hemodynamic was needed. It was reported that Doppler US could be used as a safe, reliable, noninvasive, and easily repeatable test in assessment of portal hemodynamics [16,17].

Al-Nakshabandi a PVD wider than 13 mm showed PHT with a high specificity (reported as 100%), but a low sensitivity (45%-50%) [18]. Shi et al reported that contrary to PVV, there was not any relation among Child stages between wide PVD and high PV pressure and severity of cirrhosis [13]. Tong et al reported a relation between severe intraocular degeneration and necrosis and increase in PVD [19]. Er et al reported that a PV flow velocity of 15 cm/sec and below and a PVD of more than 13 mm were significant in diagnosis of PHT [20]. Yalınz et al. noted that PVV decreased as severity of cirrhosis worsened [16].

We found that there was not any statistically significant difference between control group and patient with elevated enzyme group in terms of PVD ($p > 0,05$, $p = 0,1$). However, we found that there was a statistically significant difference between control group and patients with cholestasis group ($p < 0,05$, $p = 0,001$) and between elevated enzyme group and patients with cholestasis group ($p < 0,05$, $p = 0,001$) in terms of PVD.

Most researchers reported that PVV decreased significantly in the patients with cirrhosis compared with healthy individuals. Sabba et al. demonstrated that though some variations existed, PVV was declined in cirrhosis compared with healthy people [21]. Kok et al. reported that PVV decreased significantly in patients with cirrhosis

and esophageal varices [22]. Aube et al. observed that there was a close relation between histological degree of fibrosis and decline in portal venous velocity [23]. Shi et al showed that as Child's classification stage increased, portal flow velocity decreased. They reported that portal flow velocity is a parameter that reflects degree of portal pressure and it is more useful in diagnosis of PHT [13]. Gaiani et al. demonstrated a significant difference between cirrhotic and non cirrhotic cases in terms of PVV [24]. Haktanır et al. reported that PV flow velocity is a useful index in diagnosis of cirrhosis [25]. Chawla et al showed that PV flow velocity is slower in cirrhotic patients compared to the patients with chronic liver disease who do not have cirrhosis yet and PVV declined as severity of the cirrhosis is increased [26].

In this study, we found that there was not any statistically significant difference between control group and patient with elevated enzyme group in terms of PVV ($p>0,05$, $p=0,1$). However, we found that there was a statistically significant difference between control group and patients with cholestasis group ($p<0,05$, $p=0,001$) and between elevated enzyme group and patients with cholestasis group ($p<0,05$, $p=0,001$) in terms of PVD.

Sacerdotal et al. showed that HA-PI values increased in patient with cirrhosis compared to healthy individuals [27]. Iwao reported that HA-PI in patients with cirrhosis and PHT was higher than control group. He considered the threshold of HA-PI in PHT diagnosis was 1.1 84% sensitivity as and 81% specificity [28]. Schneider et al. found higher HA-PI values in cirrhotic patients compared to control group. In this study a weak correlation between Child staging and HA-PI was observed. They considered threshold value of HA-PI was 1.0 with 82% sensitivity, and 74% specificity [29].

In our study we found that there was a statistically significant difference between control group and elevated enzyme group, between control group and patients with cholestasis group, between elevated enzyme group and patients with cholestasis group in term of HA-PI. We calculated that HA-PI value was 1.1 in control group; 1.25 in elevated enzyme group and 1.51 in patients with cholestasis group.

Normally, low-resistance waveform is seen in hepatic artery. Hepatic artery flow resistance is increased in chronic liver diseases and PHT [17]. Erden et al. showed that HA-RI is related with portal pressure and hepatic venous pressure gradient [30]. Previous studies indicated that HA-RI was increased in chronic liver diseases. It was showed that although increased HA-RI is closely related with deposition of large amounts of fibrotic tissue in the patients with chronic hepatitis, degeneration, inflammation and necrosis were not affected prominently. Besides this, when the patients were analyzed according to degree of liver fibrosis, changes in HA-RI do not show parallelism with the changes in PV flow velocity. As a result, it was observed that in viral hepatitis, level of HA-RI probably became apparent in presence of fibrous tissue deposits which reflect the severity and duration of the liver damage [13]. Alpern et al reported that a HA-RI higher than 0.78 was specific for PHT diagnosis, however it was not sensitive [31]. Marder et al observed an increase in pulsation and RI value because of increase in arterial bed [32].

Sacerdoti et al. reported that HA-PI (1.30) and HA-RI (0.71) values were markedly high in the patients with cirrhosis. Pierce et al. found that there was a significant difference between cirrhotic

patients and control group in terms of RI value (0.82 vs. 0.72). They reported that when RI value is considered as 0.77, sensitivity was 6% and specificity was 90% [33]. Piscaglia et al. reported that high HA-RI values were not specific for cirrhosis or PHT, however they could be useful in chronic hepatitis [34]. In another study, it was reported that HA-RI values ranged between 0.62 and 0.69 in healthy people [35]. Tanaka et al. reported that 68 hepatic RI showed an increase in acute occlusion of PV as well [36]. Walsh et al. demonstrated that HA-RI, which is thought to be related to structural deterioration in the liver, increased as the severity of the liver disease worsens [37].

In our study we found that there was not any a statistically significant difference between control group and elevated enzyme group in terms of HA-RI, however there was a statistically significant difference between control group and patients with cholestasis group, between elevated enzyme group and patients with cholestasis group in terms of HA-RI. We calculated that HA-RI value was 0.65 in control group; 0.66 in elevated enzyme group and 0.72 in patients with cholestasis group.

Iwao et al defined a parameter that represents afferent vascularity of the liver. They named it as HVI ($HVI=PVH/HA-PI$). In a study, they found that HVI values in cirrhotic patients were significantly lower compared to control group. ($8,7\pm 2,1$ and $17,2\pm 4,3$ cm/sec, respectively $p<0,001$). They found that HVI had a threshold of 12 cm/sec with 97% sensitivity and 93% specificity in the diagnosis of PHT. Also they demonstrated a significant negative correlation between HVI and Child stage [28]. Serhatlıoğlu et al. reported that HVI can be used as a reliable and objective criterion in the diagnosis, staging of cirrhosis and in monitoring the progression of cirrhosis [38].

In our study we found that there was a statistically significant difference between control group and elevated enzyme group, between control group and patients with cholestasis group, between elevated enzyme group and patients with cholestasis group in term of HVI.

Splenomegaly is one of the major characteristics of liver cirrhosis. Shi et al. found that splenomegaly is seen in 36-92% of the cases with cirrhosis [13]. Several mechanisms such as increased pooling enhanced destruction of blood cells in the spleen, dilutional effect of increased blood volume and humeral factors play role in development of hypersplenism in PHT. Tarantino et al observed between Spleen Diameter (≥ 150 mm) and development splenorenal shunt that increased risk in cirrhosis [39]. Lim et al observed that spleen dimensions increased in patients with hepatitis who develop cirrhosis [40].

In our study, 36% of the patients with cholestasis had splenomegaly and this was consisted with literature. In our study we also found that there was not any a statistically significant difference between control group and elevated enzyme group in terms of spleen dimensions, however there was a statistically significant difference between control group and patients with cholestasis group, between elevated enzyme group and patients with cholestasis group in terms of spleen dimensions.

Prognosis is poor in patients who clinically develop reverse flow in PV. Shaheen et al. reported that reverse flow occurred in 5-8% of the patients with PHT, Gaiani et al. found this rate as 4-8% [41,42].

In our study reverse flow was present in 5 cases with cholestasis (5%) and this was consistent with literature.

Sabba et al. observed a decline in PV in PHT, and an increase in PV area [21]. There was PV dilatation and decrease in velocity in PHT, CI was calculated by these. CI is ratio of PV area to average PV velocity on same section. Al-Nakshabandi reported that this index was 0.07 in normal individuals and values over 0.1 indicated portal hypertension with 95% sensitivity and specificity [18].

PV area, flow velocity and CI change in the liver cirrhosis. In a patient with cirrhosis, portal blood flow stays normal; a decline is seen in terminal phase. However, CI is 2.5 times higher than normal people because velocity is decreased. In chronic stage of the cirrhosis, a marked increase in CI and PVD is observed. CI and portal blood flow velocity allow diagnosis of liver disease noninvasively. CI is also affected by other factors such as PV pressure, portal venous resistance in the liver, portal blood flow and development of portosystemic shunt [18]. In an experimental cholestasis induced in dogs, Mwanza et al reported that CI increased as duration of cholestasis is increased [5]. Bessi et al. found a statistically significant difference in cirrhosis and PTH patients in terms of CI [43]. Haag et al demonstrated that a CI value above 0.1 has a 95% sensitivity and specificity [44]. Dragoni et al reported that CI is strongly correlated with presence and size of esophageal varices as well as with severity of cirrhosis [45].

In our study we found that there was not any a statistically significant difference between control group and elevated enzyme group in terms of CI, however there was a statistically significant difference between control group and patients with cholestasis group, between elevated enzyme group and patients with cholestasis group in terms of CI.

Doppler US is the primary imaging method in chronic liver disease such as cirrhosis. Today gold standard for the diagnosis of the liver cirrhosis is biopsy, a histopathological diagnostic method. However it has some morbidity and mortality risks [15]. Therefore another method has been searched instead of biopsy. FI (HA-RI/PVHx100) is an index calculated by multiplying the ratio of HA-RI to PVH with 100 and has been developed by Mazeher et al. to detect development of fibrosis in the liver without performing a biopsy. In this study it was found that FI has a high sensitivity (94.4%), specificity (100%) and accuracy (90%) levels, therefore it is a useful noninvasive test in diagnosis of the liver cirrhosis (5.55 ± 1.53) and in chronic hepatitis (2.63 ± 0.43) and it can decrease the need for liver biopsy [46].

Conclusion

In our study we found that there was a statistically significant difference between control group and elevated enzyme group, between control group and patients with cholestasis group, between elevated enzyme group and patients with cholestasis group in term of FI. We noted that these results were consistent with those in Mazeher et al.'s study. We concluded that fibrous tissue is increased in biliary cirrhosis. These results demonstrate that there are changes in portal, hepatic arterial hemodynamics and Doppler US parameters in normal population, patients with elevated enzyme and patients with cholestasis. We found that Doppler US has an important role in diagnosis and follow up of biliary cirrhosis developing secondary to cholestasis. Doppler US is considered as a method which has a

warning role because it can detect antecedent findings that reflect changes in hepatic hemodynamic before the possible complications of cirrhosis such as PTH occur. It attracts attention that HVI, FI and CI are sensitive in terms of the changes that occur in liver hemodynamic in the cases with cirrhosis and they correlate with the severity of the disease. Doppler US diminishes the need for invasive procedures by providing functional information about liver. Also, it enables assessment of the changes in portal blood flow which can affect the liver functions. As a result, Doppler US examination method is a very beneficial method in noninvasively defining the changes in liver hemodynamic, in follow up of the disease and in early detection of the complications such as biliary cirrhosis and PHT.

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