Hepatic Vein Morphology

A New Sonographic Diagnostic Parameter in the Investigation of Cirrhosis?

Sheida Vessal, MBBS, BSc, MRCP, FRCR, Shunkara Naidoo, MBBS, FRANZCR, James Hodson, MBBS, MA, MRCP, FRCR, Damien L. Stella, MBBS, FRANZCR, Robert N. Gibson, MD, MBBS, FRANZCR

Objective. The purpose of this study was to evaluate the accuracy of a new sonographic marker for the diagnosis of cirrhosis using hepatic vein wall changes. ***Methods.*** A prospective pilot study evaluating 88 patients, 38 with cirrhosis and 50 with no evidence of liver disease, was undertaken. Hard copy sonograms of the hepatic veins were obtained and reviewed in a blinded fashion by 2 radiologists. The hepatic vein morphology was assessed by 3 parameters: hepatic vein wall straightness, uniformity of hepatic vein wall echogenicity, and visualization of a complete 1-cm hepatic vein segment. The 3 parameters were compared to evaluate sensitivity and specificity for the diagnosis of cirrhosis. Interobserver and intraobserver errors for each parameter were also calculated with κ statistics to assess reproducibility. ***Results.*** There was a strong correlation between altered straightness and nonuniformity of hepatic vein wall echogenicity and cirrhosis. The straightness parameter had superior sensitivity of 97% (95% confidence interval [CI], 85%–100%) and specificity of 91% (95% CI, 78%–97%) for diagnosis of cirrhosis. Uniformity of hepatic vein wall echogenicity was the next most useful parameter, with sensitivity of 88% (95% CI, 73%–97%) and specificity of 86% (95% CI, 72%–95%). The continuous 1-cm segment of the hepatic vein had sensitivity of 68% (95% CI, 49%–83%) and specificity of 91% (95% CI, 78%–97%). Hepatic vein evaluation was found to show both good intraobserver and interobserver error. ***Conclusions.*** Hepatic vein morphology on sonography, in particular, changes in the straightness and uniformity of hepatic vein wall echogenicity, is a new sign of cirrhosis, which may increase the overall accuracy of sonographic diagnosis of cirrhosis and which appears to have a moderately high degree of reproducibility. ***Key words:*** cirrhosis; hepatic vein; liver; sonography.

Abbreviations
CI, confidence interval

Received October 12, 2008, from the Department of Radiology, University of Melbourne, Royal Melbourne Hospital, Melbourne, Victoria, Australia. Dr Naidoo is now with Western Hospital, Footscray, Victoria, Australia; Dr Hodson is now with Princess Alexandria Hospital, Harlow, England. Revision requested October 26, 2008. Revised manuscript accepted for publication March 24, 2009.

We thank the sonographers at Royal Melbourne Hospital and Ken Sharpe, PhD, and Alexandra Gorelik at University of Melbourne and Royal Melbourne Hospital for help with the statistical analysis.

Address correspondence to Sheida Vessal, MBBS, BSc, MRCP, FRCR, University Hospital North Staffordshire, Hartshill Road, Newcastle-Under-Lyme, Staffordshire ST4, England.

E-mail: sheida26@yahoo.co.uk

Radiologic assessment plays an important role in the diagnosis and follow-up of patients with cirrhosis, but conventional sonography has variable diagnostic accuracy of 76% to 93%,[1,2] and contrast-based methods such as measurement of the hepatic transit time,[3,4] liver elastography,[5] and magnetic resonance imaging spectroscopy[6] are not widely applied as yet. Liver biopsy remains the reference standard but has problems of morbidity and sampling errors.[7–10] Many different sonographic parameters have been used. Parameters concentrating on liver architecture and morphologic changes such as increased echo coarseness have long been used[11–13] but have low sensitivity.

Surface nodularity assessment provides higher specificity and sensitivity.[14] Surface nodularity is more evident in patients with ascites, which provides a fluid-organ interface allowing easier assessment of surface contour changes. The hypothesis of our study followed from that approach: the fluid content within the thin-walled hepatic veins provides an internal interface between it and the liver parenchyma, a potential natural internal fluid-organ interface visible in all patients.

We postulated that internal nodules in cirrhosis would also cause architectural distortion and hence alter the morphology of the hepatic veins. Hepatic vein morphology has not been formally described in cirrhosis; therefore, we undertook this study to show its potential as a novel noninvasive marker for the diagnosis of cirrhosis.

Materials and Methods

The sonographic analysis of hepatic veins is a routine procedure in all liver sonographic examinations at our institution, and local Ethics Committee approval was obtained for this study.

Patients

A prospective study was completed at our large tertiary referral center. Recruitment of patients was performed during 2 periods. During period 1 in 2004 and 2005, 57 patients were recruited. These included 29 patients with cirrhosis and 28 patients with no evidence of liver disease. Patients with cirrhosis were classified as those with a clinical diagnosis according to the Child-Pugh classification and a combination of biopsy, clinical examination, consistently abnormal liver function test results and abnormal serologic markers, and previous radiology with a combination of sonography and computed tomography for a minimum of 2 years. All of the patients with cirrhosis had abnormal imaging findings, biochemical and serologic diagnostic findings, and a known causative agent, and all were under active review by a hepatologist. The radiologic features included liver irregularity, parenchyma heterogeneity, and caudate lobe enlargement combined with a definite known causative factor for cirrhosis and sustained abnormal liver function test results. Great care was taken to ensure that a clinicoradiologic diagnosis of cirrhosis had been established for a minimum of 2 years.

The patient group without cirrhosis included patients undergoing sonography for other conditions with no previous liver abnormalities and documented persistently normal liver function test results.

Informed consent was obtained from all patients according to our institution's guidelines regarding research.

A second round of recruitment was completed in 2006, producing a total of 40 patients, 16 with cirrhosis and 24 with no evidence of liver disease, according to the same inclusion criteria.

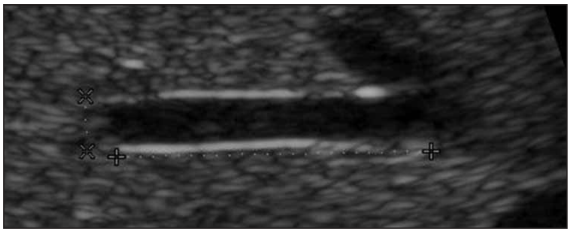
Sonographic Examination and Scan Evaluation

An HDI 5000 unit (Philips Healthcare, Bothell, WA) with a 5–2 MHz transducer was used to obtain images of the liver after an overnight fast. Images of the hepatic veins were taken by experienced unblinded sonographers. The hepatic veins were imaged to include a segment of the hepatic vein with the beam perpendicular to the hepatic vein wall to provide a strong specular echo from the wall (Figure 1). The right hepatic vein is normally easier to visualize, and the secondary branches from this vein were imaged; however, if this was not possible, the main vein was targeted.

Images were obtained during suspended respiration and captured by high-definition zoom. Both conventional imaging and real-time compound imaging were used in most cases when possible.

The inclusion criteria for a satisfactorily visualized segment of the hepatic vein included an

Figure 1. Imaging of the hepatic veins. The right hepatic vein is perpendicular to the ultrasound beam, producing a strong secular wall echo.



arbitrary figure of a minimum of 15 mm in length (the most continuous image was obtained) and a diameter of 3 mm, taken to represent a substantial diagnostic portion of the vein. Images were taken at approximately 90° to the ultrasound beam. The most continuous segment was obtained. Analysis of the hepatic vein wall was as described below: parameter 1, hepatic vein wall straightness; parameter 2, uniformity of hepatic wall echogenicity; and parameter 3, presence or absence of an uninterrupted 1-cm segment of the hepatic vein echogenic wall.

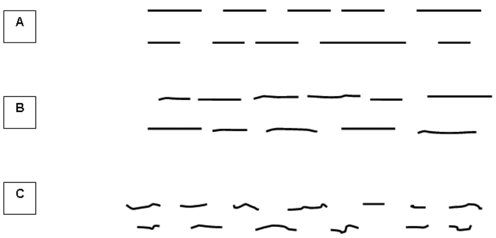
Hepatic Vein Wall Straightness

Hepatic vein wall straightness was subdivided into 3 categories: A, B, and C (Figures 2 and 3). Category A (Figure 3A) denoted a straight wall pattern, expected in normal livers with no architectural distortion. Category B (Figure 3B) had a moderate degree of irregularity producing a "slightly wavy" pattern. Category C (Figure 3C) described an increasingly distorted outline of the wall with an obvious "very wavy" pattern. Both categories B and C showed distortion of the normal straight morphologic characteristic.

Uniformity of Hepatic Vein Wall Echogenicity

In cirrhotic livers, the development of hepatic vein wall nodularity is expected to distort the wall, creating variability in the apparent wall thickness and variable echogenicity when imaged perpendicular to the beam (Figures 4 and 5). A normal hepatic vein wall would be expected to have a uniform thickness and brightness throughout a 15-mm segment. A consistent hepatic vein wall thickness was denoted "uniform" (Figures 4 and 5A), and the lack of it was deemed "nonuniform" (Figures 4 and 5B).

Figure 2. Schematic diagram showing hepatic vein straightness: A (straight), B (slightly wavy), and C (very wavy).



Complete 1-cm Segment Visualization

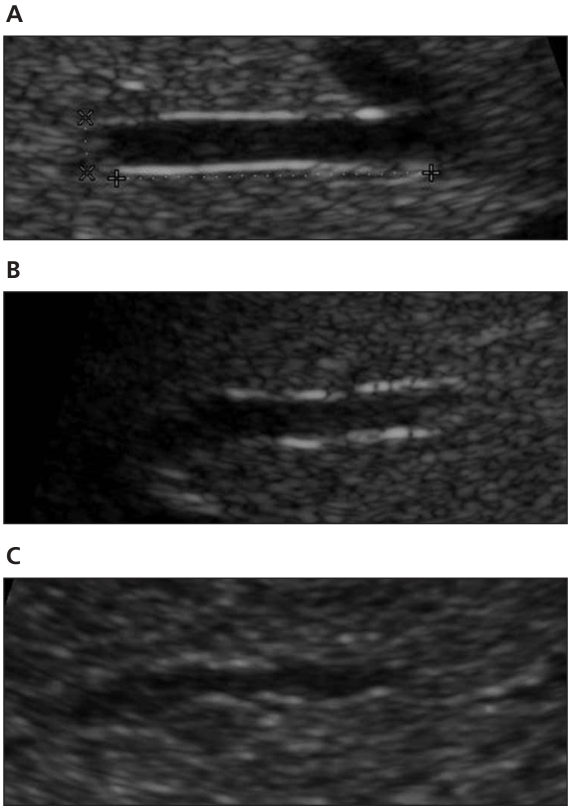
This parameter was chosen to allow increased objectivity. A positive result was denoted as a complete uninterrupted 1-cm segment of the hepatic vein wall. In cirrhosis, this line may be expected to be disrupted, creating an interrupted line (Figures 6 and 7).

Further examples of hepatic veins stratified in this format are provided (Figures 8 and 9). Each parameter was assessed by 2 specialist gastrointestinal radiologists using randomized hard copy images in a blinded fashion.

Statistical Analysis

Images from the first round, including 57 patients, were reviewed by 2 blinded specialist gastrointestinal imaging radiologists (consultants 1 and 2). The images were shown blindly and randomly. A consensus opinion categorizing the 3 parameters was obtained. After combining

Figure 3. Sonograms showing hepatic vein straightness. **A**, The hepatic wall is normal and straight (straightness category A). **B**, The hepatic wall is slightly wavy (straightness category B). **C**, The hepatic wall is very wavy (straightness category C).



these patients with those from the second round of recruitment (40), a total of 97 patients were available. All 97 films were reviewed again in 2006. This was done first individually and independently by consultants 1 and 2 and again as a combined consensus review.

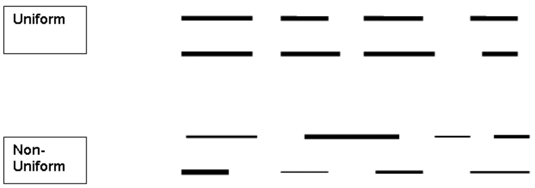
Interobserver error analysis with κ statistics was performed for the cohort of 97 patients. Intraobserver error analysis was performed for the initial round of 57 patients by comparing the consensus reviews from 2004–2005 and 2006. The proportion of potential agreement beyond chance that was achieved from the results of each parameter was described by a κ value, which was considered slight ($\kappa = 0.00–0.20$), fair ($\kappa = 0.21–0.40$), moderate ($\kappa = 0.41–0.60$), substantial ($\kappa = 0.61–0.80$), or almost perfect ($\kappa = 0.81–1.00$).[15]

The final total consensus results of 97 patients, (incorporating the 57 consensus results from 2004–2005, ie, the first data set and the additional 40 patients from 2006) was analyzed with Stata computer software (StataCorp, College Station, TX) to obtain sensitivity and specificity values with their corresponding 95% confidence intervals (CIs). Each parameter and combination of parameters was assessed again blindly and randomly. The complete data were then reevaluated with the R statistical computer package (http://www.r-project.org/) to obtain a regression tree classification. This was then used to aid clinical stratification using these potential clinical parameters.

Results

From the total of 97 images, 9 were excluded for not fulfilling the inclusion criteria because of technically inadequate images. This included 2 patients without cirrhosis and 7 with cirrhosis. Therefore, in total there were 88 patients, 50 without cirrhosis (27 female and 23 male) and 38 with cirrhosis (9 female and 29 male). In total, 8 of the 38 patients with cirrhosis had confirmatory pathologic findings at our institution. In the remaining 30, the diagnosis of cirrhosis was made by robust combined imaging and clinical and biochemical evaluation. Twelve patients had hepatitis B; 11 had alcoholic cirrhosis; 10 had hepatitis C; 3 had nonalcoholic steatohepatitis; and 2 had autoimmune hepatitis.

Figure 4. Schematic diagram showing uniformity of hepatic vein wall echogenicity: uniform morphology and nonuniform.

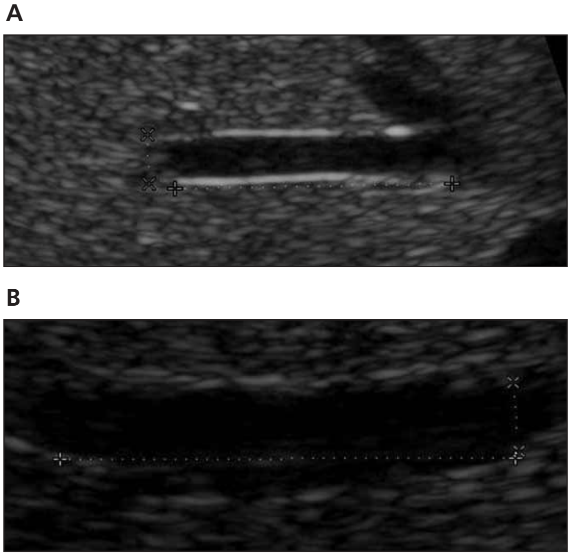


The results from the consensus readings for the 88 patients are shown in Tables 1 and 2. Both compound and conventional imaging were performed on 68 patients. The patients were all imaged as part of routine hospital sonography lists; therefore, not all patients had both compound and conventional imaging.

For the patients without cirrhosis, a positive correlation between the category A level of straightness, uniform echogenicity of the hepatic vein wall, and a positive 1-cm visualized segment finding was shown. Category C abnormal straightness was not seen in a single patient without cirrhosis.

In contrast, category B or C straightness was present in most of the cirrhotic group of patients. The 2 cases that were described as having cate-

Figure 5. Sonograms showing hepatic vein uniformity of wall echogenicity. **A**, Uniform hepatic vein wall. **B**, Nonuniform hepatic vein wall.



gory A straightness on conventional sonography interestingly showed category B straightness on compound imaging. This was likely due to the increased contrast resolution and diminishing effect of refractive errors and artifacts of compound imaging.

Nonuniform echogenicity of the hepatic vein wall was also shown to correlate with the abnormal architecture in the patients with cirrhosis. Most of the patients with cirrhosis also failed to have complete visualization of 1-cm segment of the hepatic vein wall. This parameter, however, did not appear to perform as well despite being potentially the most objective. In fact, 10 of 33 patients with cirrhosis from the compound imaging group had 1-cm segment visualization.

The straightness parameter on compound imaging showed the best sensitivity of 97% (95% CI, 85%–100%) and specificity of 91% (95% CI, 78%–97%; Table 3). The second best parameter was the uniformity of echogenicity. Interestingly, the complete 1-cm continuous segment produced too many false-negative results, reducing the sensitivity to 68%.

Interobserver error with κ statistics was assessed for each individual parameter (Table 4). Moderate κ values were obtained with compound imaging for both straightness and the 1-cm segment. The uniformity of hepatic vein wall echogenicity provided the best results (κ = 0.65, substantial agreement).

Table 5 shows the results of intraobserver agreement in which the 2 consensus reviews were compared. The straightness parameter revealed moderate agreement, with the uniformity and 1-cm segment providing substantial agreement. The highest κ value was provided by the 1-cm segment parameter (κ = 0.80).

Combining the 2 most sensitive individual parameters (lack of straightness and a nonuniform hepatic vein wall) produced sensitivity of 88% (95% CI, 73%–97%) and specificity of 95% (95% CI, 84%–99%). Combining all 3 parameters, however, diminished the sensitivity to 65% because of the number of false-negative results for the complete 1-cm segment parameter.

Figure 6. Schematic diagram showing continuous 1-cm segment morphology.

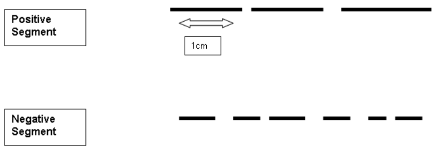
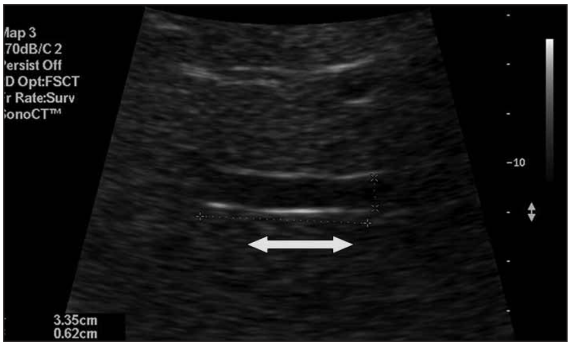


Figure 7. Sonogram showing a complete 1-cm segment (arrow).



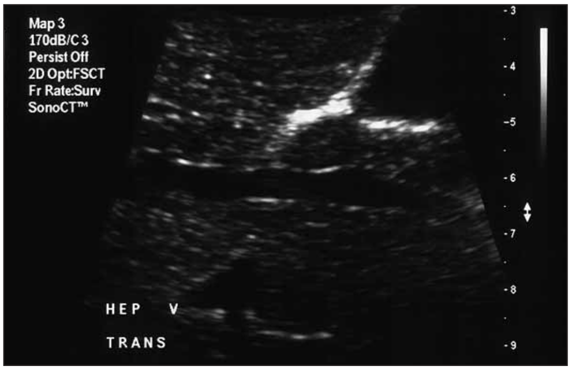


Figure 8. Sonogram showing category B straightness, a nonuniform echogenic wall, and nonvisualization of a continuous 1-cm segment.

Figure 9. Sonogram showing category C straightness, a nonuniform echogenic wall, and nonvisualization of a continuous 1-cm segment.

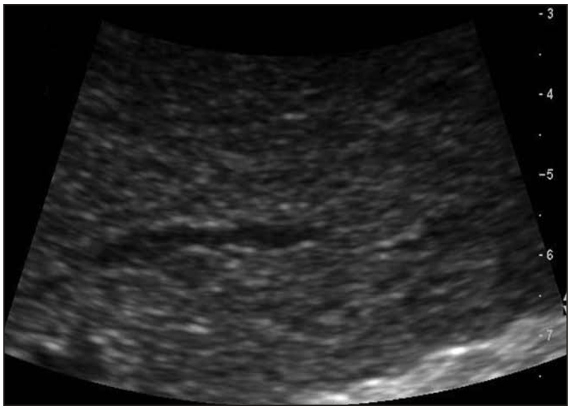


Table 1. Results for the 50 Patients Without Cirrhosis

Parameter	Compound (n = 43)	Conventional (n = 47)
Straightness	A, 39	A, 42
	B, 4	B, 5
	C, 0	C, 0
Uniformity	Uniform, 37	Uniform, 34
	Nonuniform, 6	Nonuniform, 13
1-cm segment	Positive, 39	Positive, 32
	Negative, 4	Negative, 15

Table 2. Results for the 38 Patients With Cirrhosis

Parameter	Compound (n = 23)	Conventional (n = 31)
Straightness	A, 0	A, 2
	B, 22	B, 20
	C, 11	C, 9
Uniformity	Uniform, 3	Uniform, 2
	Nonuniform, 30	Nonuniform, 29
1-cm segment	Positive, 10	Positive, 6
	Negative, 23	Negative, 25

Discussion

Many sonographic parameters have been proposed for diagnosis of cirrhosis, including morphologic and vascular-related changes.[1] Most, however, are relatively insensitive, nonspecific, or difficult to reproduce.

Vascular assessment has involved comparing changes in the mean portal vein velocity, the resistive index of the superior mesenteric artery, and dampening of the normal triphasic hepatic vein Doppler waveform pattern in patients with cirrhosis compared with controls.[16] Sonographic contrast agents have been used to show hemodynamic

Table 3. Sensitivity and Specificity of Parameters

Parameter Assessed	Compound	Conventional
Straightness	Sensitivity, 97 (85–100)	Sensitivity, 94 (79–99)
	Specificity, 91 (78–97)	Specificity, 89 (77–96)
Uniformity	Sensitivity, 88 (73–97)	Sensitivity, 94 (79–99)
	Specificity, 86 (72–95)	Specificity, 72 (57–84)
1-cm segment	Sensitivity, 68 (49–83)	Sensitivity, 81 (63–93)
	Specificity, 91 (78–97)	Specificity, 68 (53–81)
Straightness and uniformity	Sensitivity, 88 (73–97)	Sensitivity, 71 (54–85)
	Specificity, 95 (84–99)	Specificity, 98 (88–100)
Straightness and 1-cm segment	Sensitivity, 68 (49–83)	Sensitivity, 77 (59–90)
	Specificity, 98 (88–100)	Specificity, 91 (80–98)
Uniformity and 1-cm segment	Sensitivity, 65 (46–80)	Sensitivity, 74 (55–88)
	Specificity, 93 (81–99)	Specificity, 79 (64–89)
Straightness and/or uniformity	Sensitivity, 97 (85–100)	Sensitivity, 100 (89–100)
	Specificity, 81 (67–92)	Specificity, 70 (55–83)
Straightness and/or 1-cm segment	Sensitivity, 97 (85–100)	Sensitivity, 97 (83–100)
	Specificity, 84 (69–93)	Specificity, 66 (51–79)
Uniformity and/or 1-cm segment	Sensitivity, 91 (76–98)	Sensitivity, 100 (89–100)
	Specificity, 84 (69–93)	Specificity, 62 (46–75)
Straightness, uniformity, and 1-cm segment	Sensitivity, 65 (46–80)	Sensitivity, 71 (52–86)
	Specificity, 98 (88–100)	Specificity, 91 (80–98)
Straightness and/or uniformity and/or 1-cm segment	Sensitivity, 97 (85–100)	Sensitivity, 100 (89–100)
	Specificity, 79 (64–90)	Specificity, 60 (44–74)

Values are percent (95% CI).

Table 4. Interobserver Error κ Values

Parameter	Conventional κ	Compound κ
Straightness	0.57	0.50
Uniformity of echogenicity	0.65	0.60
Complete 1-cm segment	0.57	0.58

Table 5. Intraobserver Error κ Values

Parameter	Conventional κ	Compound κ
Straightness	0.60	0.50
Uniformity of echogenicity	0.64	0.69
Complete 1-cm segment	0.80	0.76

changes in patients with cirrhosis, such as the accelerated and increased peak enhancement of Levovist (SH U 806A; Schering AG, Berlin, Germany) compared with controls.[3,4] These findings are postulated to be due to the increased arterialization in cirrhosis. More recent advances include transient elastography, which indicates fibrosis by direct measurement of the liver elasticity and stiffness.[5]

Nodule formation disrupts the normal architecture of the liver parenchyma. Filly et al[17] looked at the deep (visceral) surface of the liver for nodularity, which provided sensitivity and specificity of 86% and 64%, respectively. In a more recent study of 300 patients by Colli et al,[18] surface nodularity, hepatic vein Doppler waveforms, and caudate lobe hypertrophy were measured. The surface nodularity, however, proved to be the most promising of the 3 markers.

Our results, based on hepatic vein morphology as a marker for cirrhosis, compare favorably with those reported by other groups looking at surface nodularity (Table 6). Although the study population was small, the results suggest that the use of hepatic vein wall nodularity may be superior to the use of surface nodularity.

We found excellent sensitivity and specificity (97% and 91%, respectively) using the straightness parameter alone. The second parameter, uniformity of hepatic vein echogenicity, and the combination of both parameters produced similarly high sensitivity and specificity values. The third parameter, complete visualization of a 1-cm segment, did not improve the diagnostic power of the test because of the presence of a substantial number of false-negative results.

Technically, obtaining the images was simple, time efficient, and an easily applicable addition to routine liver sonography. Only 9 patients were excluded because of technically inadequate scans. Two of these were patients without cirrhosis in whom the hepatic vein was not visualized with the beam perpendicular to the wall. An incorrect acquisition angle affects all 3 parameters. The remaining 7 of these 9 patients had confirmed cirrhosis. Indeed, 4 of these patients had highly irregular veins with narrow dimensions. In our experience, markedly cirrhotic livers with surface and architectural distortion are technically difficult to image; thus, they did not fulfill the inclusion criteria. We have therefore potentially excluded some of the most severely advanced cases, thereby testing our new parameters on less severe forms of the disease, for which the diagnosis is of more clinical value.

Our intraobserver agreement was encouraging, ranging from moderate to substantial for all 3 parameters. The time of reassessment (>1 year between consensus reviews) ensured no bias due to recall of findings. We propose that with increased use and familiarity, all 3 parameters would have improved intraobserver and interobserver agreement. A trial period using the 3 parameters in combination with other known sonographic parameters, such as surface nodularity and echo texture, is recommended when first starting to assess hepatic vein morphology.

Table 6. Summary of Studies

Study	Parameter	Sensitivity, %	Specificity, %
Di Lelio et al[14] (125 patients)	Superficial surface	88	ND
Filly et al[17] (100 patients)	Superficial surface	53	88
	Deep surface	86	64
Colli et al[18] (300 patients)	Superficial surface	54	95
This study (88 patients)	Hepatic vein wall (straightness)	97 (85–100)	91 (78–97)

Values in parentheses are 95% CIs. ND indicates not determined.

The main limitations and areas for further work shown by our study are as follows:

1. The number of patients analyzed. It is important to stress that this was a pilot study requiring further evaluation and confirmation with larger numbers of patients with cirrhosis of various causes as well as a spectrum of patients with fibrosis and steatosis. It is vital that the early phases of the disease in all cirrhotic subtypes can be diagnosed.

2. Limited clinicopathologic correlation. A large proportion of the patients recruited did not have biopsies, which was due to the noninvasive emphasis at our institution in diagnosing cirrhosis. Although a reference standard of histologically proven cirrhosis would be ideal, our inclusion criteria remained robust, differentiating the cirrhotic group from the unaffected group. All of our patients with cirrhosis had clinicoradiologic diagnosis and follow-up for a minimum of 2 years with consistently abnormal liver function test results, serologic markers, and imaging findings.

We would therefore like to obtain ethical approval to perform a rigorous pathologic confirmation. This would allow validation of hepatic vein morphology in the assessment of different stages of the disease, from fibrosis/mild cirrhosis to established cirrhosis. A grading system similar to that of our fellow pathologists could then be formed. Correlation with the sonographic changes in different subtypes of cirrhosis could also be more carefully investigated. Patients with hepatitis C, for example, are known to produce a more macronodular histologic appearance, which may produce more marked morphologic changes to the hepatic veins compared with a patient with primary biliary cirrhosis or autoimmune hepatitis, for example. Within our small number of patients, we did indeed see a trend in that the patients with hepatitis B and C had more advanced venous changes compared with any of the other groups of patients with cirrhosis. Conversely, our 2 patients with autoimmune hepatitis had the most modest changes, with category B hepatic vein straightness as well as uniformity of the hepatic vein wall, and a 1-cm segment of the wall was completely visualized.

3. Careful comparison with other known sonographic parameters. We did not formally set out to investigate this in our study. However, this is of substantial importance to accurately assess direct sensitivity and specificity in the same patient group rather than extrapolating from other studies. The most severely affected hepatic vein changes in our patient group were indeed in patients who also had surface nodularity changes but not necessarily echogenicity changes. Our numbers were too small to assess statistically.

4. Careful comparison with the degree of biochemical abnormality. Once again, this was not the goal of our study; however, it is another important avenue to carefully correlate. The most severely decompensated patients with abnormal biochemical markers did indeed have more severely affected hepatic vein morphology. Again, our numbers were too small to statistically analyze further.

These initial results reveal hepatic vein morphology, in particular straightness, to be a valuable new parameter in the assessment of patients with cirrhosis. It is a simple, reproducible, and sensitive parameter and a valuable addition to the sonographic armamentarium in the diagnosis and follow-up of patients with suspected cirrhosis.

References

1. Giorgio A, Amoroso P, Lettieri G, et al. Cirrhosis: value of caudate to right lobe ratio in diagnosis with US. Radiology 1986; 161:443–445.
2. Aubé C, Oberti F, Korali N, et al. Ultrasonographic diagnosis of hepatic fibrosis or cirrhosis. J Hepatol 1999; 30:472–478.
3. Albrecht T, Blomley MJ, Cosgrove DO, et al. Non-invasive diagnosis of hepatic cirrhosis by transit-time analysis of an ultrasound contrast agent. Lancet 1999; 353:1579–1583.
4. Albrecht T, Blomley MJ, Cosgrove DO, et al. Transit-time studies with Levovist in patients with and without hepatic cirrhosis: a promising new diagnostic tool. Eur Radiol 1999; 9(suppl 3):S377–S381.
5. Foucher J, Chanteloup E, Vergniol J, et al. Diagnosis of cirrhosis by transient elastography (FibroScan): a prospective study. Gut 2006; 55:403–408.
6. Cobbold JF, Wylezinska M, Cunningham C, et al. Non-invasive evaluation of hepatic fibrosis using magnetic resonance and ultrasound techniques. Gut 2006; 55:1670.
7. Cadranel JF, Rufat P, Degos F. Practices of liver biopsy in France: results of a prospective nationwide survey. For the

Group of Epidemiology of the French Association for the Study of the Liver (AFEF). Hepatology 2000; 32:477–481.

8. Poniachik J, Bernstein DE, Reddy KR. The role of laparoscopy in the diagnosis of cirrhosis. Gastrointest Endosc 1996; 43:568–571.
9. Piccinino F, Sagnelli E, Pasquale G, Giusti G. Complications following percutaneous liver biopsy: a multicentre retrospective study on 68,276 biopsies. J Hepatol 1986; 2:165–173.
10. Bravo AA, Sheth SG, Chopra S. Liver biopsy. N Engl J Med 2001; 344:495–500.
11. Vilgrain V. Ultrasound of diffuse liver disease and portal hypertension. Eur Radiol 2001; 11:1563–1577.
12. Taylor KJ, Carpenter DA, Hill CR, McCready VR. Gray scale ultrasound imaging: the anatomy and pathology of the liver. Radiology 1976; 119:415–423.
13. Taylor KJW, Gorelick FS, Rosenfield AT, Riely CA. Ultrasonography of alcoholic liver disease with histological correlation. Radiology 1981; 141:157–161.
14. Di Lelio A, Cestri C, Lomazzi A, Beretta L, et al. Cirrhosis: diagnosis with sonographic study of the liver surface. Radiology 1989; 172:389–392.
15. Sackett DL, Haynes RB, Guyatt GH, Tugwell P. The clinical examination. In: Clinical Epidemiology: A Basic Science for Clinical Medicine. 2nd ed. Boston, MA: Little Brown & Co; 1991:19–49.
16. Bolondi L, Li Bassi S, Gaiani S, et al. Liver cirrhosis: changes of Doppler waveform of hepatic veins. Radiology 1991; 178:513–516.
17. Filly RA, Reddy SG, Nalbandian AB, Lu Y, Callen PW. Sonographic evaluation of liver nodularity: Inspection of deep versus superficial surfaces of the liver. J Clin Ultrasound 2002; 30:399–407.
18. Colli A, Fraquelli M, Androletti M, Marino B, Zuccoli E, Conte D. Severe liver fibrosis or cirrhosis: accuracy of US detection—analysis of 300 cases. Radiology 2003; 227: 89–94.