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Ultrasonographic Follow-Up of Liver Cirrhosis

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Abstract: Ultrasonography and upper gastrointestinal endoscopy were prospectively used to study 100 consecutive patients with liver cirrhosis. After a period of 20 months to 55 months, 21 patients had died, 23 were lost at follow-up, and 56 patients were reevaluated. In the patients who died during follow-up, the entry liver volume, measured by means of the hepatic volumetric index, was lower as compared to the 56 cirrhotics who survived. During the study period, liver volume significantly decreased to values similar to those observed, at entry, in patients who died. Moreover, esophageal varices increased in size, and the splanchnic veins enlarged. Abdominal ultrasonography provides data regarding the natural history of liver cirrhosis, which might be used, in addition to tests of liver function and endoscopy, as prognostic factors in cirrhotic patients. **Indexing Words:** Cirrhosis · Liver volume · Splanchnic veins · Ultrasonography

Liver cirrhosis is a major health problem in Italy, accounting for 34/100,000 deaths per year. However, only limited data are available concerning the natural history of this disease and prognostic factors have not been fully recognized.[1,2]

In the last ten years ultrasonography has increasingly been used to study the abdominal structures, mainly the liver.[3] Ultrasonography has a well established role in the detection of space-occupying lesions such as tumors and cysts and in the detection of primary liver cancer at an early stage[4]; however, it is of limited value in determining the presence of diffuse hepatocellular disease.[3,5,6]

Ultrasonography may provide additional data in patients with liver cirrhosis such as a quantitative measure of liver and spleen volume,[7] and splanchnic vein diameters[8]; and it may detect the presence of spontaneous collateral circulations[9] and mild ascites.[10] No previous study has prospectively measured the changes in liver and spleen volume and splanchnic vein diameters during the course of the disease.

In the present study we followed a series of consecutive cirrhotic patients by means of ultrasonography. Upper gastrointestinal endoscopy was simultaneously performed to detect changes in the size of the esophageal varices, which is known to predict the outcome of the disease.

PATIENTS

One hundred patients suffering from liver cirrhosis, consecutively admitted to our institution from April 1983 to March 1984, were the subjects of this study. Fifty-six were males and 44 females. Their age ranged from 19 years to 77 years (median 57 years). The diagnosis of liver cirrhosis was proved by liver biopsy, in most cases carried out under laparoscopic control. The etiology of the disease was alcoholic in 44 patients, HBsAg positive postnecrotic in 29, cryptogenic in 22, and primary biliary cirrhosis in 5. None had ascites at the time of the study. Patients with liver cell carcinoma, detectable by ultrasonography and/or increased α_1-fetoprotein (more than 10×), were excluded. In addition to abdominal ultrasonography, all patients underwent an upper gastrointestinal endoscopic examination.

During 1986 to 1987, after a period of 20 months to 55 months (median 27 months), all patients were asked to repeat the ultrasound and

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endoscopic studies. However, only 56 were available at follow-up. At that time 21 patients (10 males and 11 females) had died: 6 from gastrointestinal bleeding, 11 from liver failure, 3 from hepatorenal syndrome, and 1 from primary hepatocarcinoma. Twenty-three subjects were lost at follow-up; 19 of them were still alive but refused to be reexamined. The 56 patients, who are the subjects of our longitudinal study, were reexamined as outpatients or during hospital admission. It is worth noting that from admission into the study most patients were being examined every 6 months. However, for practical purposes, only the final examination was considered in the statistical evaluation.

At the beginning of the study, all patients gave their informed consent to take part in this longitudinal study. No ethical committee is operating in our department. The protocol was submitted to and approved by the Senior Staff Committee.

METHODS

Ultrasonography

A high-resolution real-time scanner (Aloka SSD-250) was used, equipped with a 3.5-MHz linear array probe that provides a dynamic evaluation of abdominal structures. All parameters were measured by two independent, equally skilled operators. The same equipment was used both when the patients were entered into the study and when they were reexamined.

a. Liver. The hepatic volumetric index (HVI), modified for real-time scanners, was used to determine, semiquantitatively, the volume of the liver. This index is calculated on the basis of the three maximum diameters of the liver: (anteroposterior $\times$ craniocaudal $\times$ transverse)/27.[11] This formula does not provide a real estimation of liver volume but gives a number (in units) that is related to the actual size of the liver.[12] Only recently has the use of the three maximum diameters to estimate liver volume been fully been validated using computed tomography (CT).[13] The parenchymal echo pattern of the liver was also considered: echogenicity and attenuation were graded from 0 (normal) to 3 (markedly increased), as described by Sandford et al.[14]

b. Spleen. The maximum longitudinal diameter of the spleen was measured as a semiquantitative index of the volume of the spleen.[15]

c. Splanchnic vessels. The diameters of the splanchnic veins (portal, superior mesenteric, and splenic) were measured with the patients holding their breath at the end of expiration, as previously described.[8] The diameter of the hepatic artery was measured 2 cm after its origin from coeliac axis. The presence of ectasic short and left gastric veins and a patent and enlarged umbilical vein[9] was looked for with care.

It was possible to measure the liver and spleen size in all patients, while splanchnic diameters were determined in 99 out of 100 patients in the initial examination and in all 56 patients at follow-up.

The reliability of sonographic measurements was periodically checked by means of a test phantom. The interobserver variation in the determination of liver and spleen size never exceeded 8%, while the maximum variation in vessel diameter was 1 mm. In the statistical analysis we considered the mean value of the estimated liver and spleen size. Whenever different, the lower estimated vessel caliber was used.

Endoscopy

Only the sizes of esophageal varices were evaluated. It was graded from 0 (absent) to 3 (large).[16]

Statistical Analysis

Results are expressed as mean $\pm$ standard error (SE) or median and ranges. Differences in the mean entry values among patients who died and patients who survived at follow-up were tested for significance by means of Student's t test for unpaired data. Changes in the mean values of the patients actually reexamined were tested for significance by means of paired t test. The comparison in the prevalence of esophageal varices between patients who died and patients who survived was carried out by means of chi-square test. Changes in the prevalence and grade of esophageal varices and in liver echo pattern were analyzed by Wilcoxon matched-pairs signed rank test.

RESULTS

HVI at entry was lower in the 21 patients who died, in comparion to the basal value of HVI in the 56 patients who survived ($0.1 > p > 0.05$; unpaired t test). In the course of follow-up, liver volume decreased by approximately 10% (Table 1). After a period of 20 months to 55 months, the HVI was reduced to values comparable to those observed at entry in patients who subsequently died.

TABLE 1
Liver and Spleen Size in Patients with Liver Cirrhosis (Mean ± SE).

	All Cirrhotics at Entry (100)	Patients Who Died (21)	Patients Reexamined (56)	
			At Entry	At Follow-Up
HVI (units)	98 ± 3	89 ± 6	101 ± 4	91 ± 5[a]
Spleen diameter (cm)	13.8 ± 3.0	13.9 ± 4.5	13.6 ± 3.9	14.5 ± 4.1[a]

[a]Significantly different from the corresponding value at entry: $p < 0.005$ (paired t test).

At follow-up, a hepatocellular carcinoma was detected by means of ultrasonography in 4/56 cirrhotic patients. All subjects had high levels of α_1-fetoprotein. All had a single, small lesion (<3 cm in diameter), which was unlikely to affect liver volume significantly.

No changes in liver echo pattern (echogenicity and attenuation) were detected at follow-up by means of the Wilcoxon matched-pairs test. Echogenicity was unchanged in 37 patients, increased in 12, and decreased in 7; while attenuation was unchanged in 28 patients, increased in 16, and decreased in 12. No relationships between echogenicity and attenuation, or between changes in these two parameters, were observed.

The size of the spleen increased slightly but significantly in the time period before the follow-up examination (Table 1). No differences were present among groups at entry.

The diameters of the splanchnic veins are given in Table 2. No differences were observed between entry values of patients who survived and patients who died. At the follow-up examination, portal, superior mesenteric, and splenic veins were significantly enlarged. A patent and enlarged umbilical vein was observed in 10 of the 100 cirrhotics while ectasic gastric veins were observed in 15. At entry, these spontaneous collateral circulations were observed in the same proportion in the group of patients who died (3/21 and 4/21) and in the group who survived (5/56 and 8/56). At the follow-up examination, 4 additional patients had a patent umbilical vein and 4 had ectasic gastric veins.

The mean diameter of the hepatic artery was 6.2 mm in all groups at entry. After two years it was 6.5 ± 0.1 ($p < 0.05$).

In the whole group of 100 patients with cirrhosis, 33 subjects had no varices at entry, while they were small in 24, medium in 24, and large in 19. Of the 21 patients who died, 18 had esophageal varices (86%) [small in 6 (29%); medium in 8 (38%), large in 4 (19%)]. In the 56 patients who were actively followed, the prevalence of varices at entry was considerably lower (61%; p vs patients who died = 0.037; chi-square test). During the time prior to the follow-up examination a remarkable increase in the prevalence and size of varices was observed ($p = 0.0007$; Wilcoxon matched-pairs test; Table 3). Among the 22 patients with medium and large varices, 7 patients had at least one episode of esophageal bleeding. After hemorrhage, 2 patients were treated with β-blockers, 3 underwent a sclerotherapy treatment, and 1 an esophageal transection. For statistical purposes in these last 4 patients who had large varices at the beginning of the study and no varices at control, the size of varices was considered unchanged.

TABLE 2
Calibers of Splanchnic Vessels in Patients with Liver Cirrhosis (Mean ± SE in mm).[a]

Veins	All Cirrhotics At Entry (100)	Patients Who Died (21)	Patients Reexamined (56)	
			At Entry	At Follow-Up
Portal	14.4 ± 0.3	14.7 ± 0.6	14.2 ± 0.3	15.2 ± 0.3[b]
Superior mesenteric	11.3 ± 0.3	11.5 ± 0.5	11.2 ± 0.4	12.0 ± 0.4[c]
Splenic	10.8 ± 0.3	11.5 ± 0.6	10.5 ± 0.5	11.1 ± 0.5[d]
Splenic (at hilum)	9.8 ± 0.3	9.4 ± 0.6	9.7 ± 0.4	10.7 ± 0.4[b]

[a]Measurements performed during suspended expiration. Footnotes *b* through *d*, significantly different from the corresponding value at entry (paired t test).
[b]$p < 0.001$.
[c]$p < 0.01$.
[d]$p < 0.05$.

DISCUSSION

This study shows that longitudinal ultrasound examinations can demonstrate changes in abdominal organs and splanchnic vessels of cirrhotic patients, probably related to the natural history of the disease.

Quantitative data can be obtained during abdominal ultrasonography in patients with liver disease,[3,5–8] but no previous study has collected this information longitudinally. Studies on the size of abdominal organs have largely been limited by technical or practical reasons. Old methods for determining liver volumes are cumbersome and time-consuming, and unsuitable for everyday practice even if they provide an accurate assessment of liver volume based on the measurement of the liver area in parallel sections, similar to the method described for CT.[17–20] Simpler methods, as the one used in this investigation,[11,12] may be performed with the real-time scanners, and give a semiquantitative estimate of liver and spleen volume. Only recently have these methods been fully validated using CT.[13]

Portal hypertension can also be detected by ultrasonography.[21] The diameter of splanchnic vessels, and particularly the diameters of the splenic and the superior mesenteric veins, have a sensitivity of 91% and a specificity of 100% in detecting portal hypertension due to liver cirrhosis,[8] although no direct correlation exists between vein diameter and portal pressure.[22,23] These results[8] were obtained by measuring the vessel diameter when patients were holding their breath at the end of expiration, and correcting the diameter obtained in individual patients according to the body surface. However, absolute values are likely to be similarly indicative, mainly in longitudinal studies.

In the present study some patients were lost to follow-up; however, patients actively followed did not differ from the total population enrolled as to the grade of esophageal varices, ultrasound findings, and etiology of the disease. Nineteen out of the 23 patients who were not reexamined were still alive, but refused reexamination. It is unlikely that the data of these 19 subjects would change the conclusions either quantitatively or qualitatively.

TABLE 3
Grade of Esophageal Varices in the 56 Patients with Liver Cirrhosis at Entry and at Follow-Up.[a]

	Follow-Up			
Grade of Esophageal Varices	0	1	2	3
At entry				
0 (Absent)	18 (32.1%)	3 (5.4%)		1 (1.8%)
1 (Small)		8 (14.3%)	2 (3.6%)	2 (3.6%)
2 (Medium)			6 (10.7%)	7 (12.5%)
3 (Large)				9 (16.1%)

[a]Entry values vs follow-up: $p = 0.0007$; Wilcoxon matched-pairs test.

The present study suggests a possible role for ultrasound liver volume measurement in predicting prognosis in cirrhotic patients. While liver volume at entry did not differ from a large previous series of control subjects (HVI: 98 ± SE 2 U),[24] in patients who died the liver volume was smaller, and in the whole population it continued to decrease. This is in keeping with the clinical observation that liver volume tends to decrease with advancing disease. In the last stages of disease, a small cirrhotic liver could be insufficient to maintain macromolecule balance at levels compatible with life. Studies are in progress to correlate changes in liver volume with changes in liver function tests, which are able to measure the functional capacity of the liver, such as the galactose elimination capacity or antipyrine clearance.[25]

Contrasting data have been reported regarding the liver echo pattern. In older studies increased echogenicity was thought to be due to an increase in the fat content of the liver, while attenuation of the ultrasound beam was related to changes in the fibrous content.[26–28] In our cirrhotic patients these parameters did not differ significantly from a series of normal subjects[24] and did not change significantly in the period before the follow-up examination. Our study supports more recent studies, which have shown that echogenicity and attenuation is of little relevance in patients with liver cirrhosis because of the poor inter- and intraobserver agreement.[29] Moreover, these signs have a low specificity in distinguishing normal, fatty, fibrotic, or cirrhotic livers.[14]

Splanchnic vein diameters were enlarged in our patients, irrespective of the outcome of the disease, in comparison to matched control subjects.[8] During the period before the follow-up examination, a further significant increase in diameter was observed. This observation, together with the finding of an increased volume of the spleen, is likely to be the expression of a progressive increase in portal pressure, which is confirmed by the increased size of esophageal varices. However, in agreement with our previous findings,[8] and in contrast with another study,[30]

ultrasonography was not able to identify the patients who had large esophageal varices and who subsequently bled from the upper gastrointestinal tract. Also, the finding of a spontaneous collateral circulation was not correlated with the risk of bleeding.

The hepatic artery was markedly enlarged in all patients at entry in comparison to a large series of control subjects, where a mean diameter of 4.6 ± SE 0.1 mm was found.[24] The finding that the hepatic artery continues to enlarge during the period prior to the follow-up examination indicates that morphologic changes, leading to increased hepatic arterial flow, go on in the course of the disease.

On the basis of our data, we stress the relevance of ultrasonography in the follow-up of patients with liver cirrhosis. Apart from surveillance in order to detect liver carcinoma in the very early stages, a semiquantitative estimate of liver volume and a precise determination of splanchnic vein diameters can be obtained. The measurement of these parameters in large series of patients, together with more accurate tests of liver function and endoscopy, might be valuable in determining the natural history of liver cirrhosis and in helping to define indices able to predict the prognosis in individual patients.

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