Renovascular Impedance Correlates with Portal Pressure in Patients with Liver Cirrhosis

<table>
<thead>
<tr>
<th>Purpose:</th>
<th>To prospectively evaluate, in patients with liver cirrhosis, the correlation between the renovascular impedance measured by using color flow and pulsed wave Doppler ultrasonography (US) and the portal pressure measured by using the hepatic venous pressure gradient (HVPG).</th>
</tr>
</thead>
<tbody>
<tr>
<td>Materials and Methods:</td>
<td>The study was approved by the senior staff committee (comparable to institutional review board) of the university hospital, and written informed consent was obtained from all patients. Thirty-one patients with cirrhosis (22 men, nine women; mean age, 57.6 years ± 8.8 [standard deviation]) and esophageal varices were consecutively enrolled in the study. Having fasted, the patients underwent color flow and pulsed wave Doppler US of the right interlobar renal artery (RRA) and the left interlobar renal artery (LRA). The resistance index (RI) and pulsatility index (PI) were determined. On the same day, with fluoroscopic guidance, a 5-F balloon-tipped catheter was advanced, via the right basilic vein, into the right hepatic vein; HVPG was calculated as the difference between the wedged and free hepatic pressures. All measurements were performed in triplicate, and permanent tracings were recorded. Correlations were made by using the Pearson test. The positive predictive value of renovascular impedance for detection of severe portal hypertension was determined.</td>
</tr>
<tr>
<td>Results:</td>
<td>Mean RI and PI values were 0.67 ± 0.07 and 1.21 ± 0.25, respectively, for the RRA, and 0.68 ± 0.07 and 1.24 ± 0.26, respectively, for the LRA. All patients had portal hypertension (mean HVPG, 19.3 mm Hg ± 4.7; range, 11.5–33.5 mm Hg). Neither portal pressure nor renal impedance correlated with Child-Pugh score for cirrhosis. Renal artery impedance indexes correlated with the HVPG (for RRA RI: R = 0.424, P = .03; for RRA PI: R = 0.402, P = .04; for LRA RI: R = 0.352, P = .05; for LRA PI: R = 0.393, P = .02). A higher-than-normal renal impedance had a high positive predictive value (RRA RI and PI, 100%; LRA RI, 92%; LRA PI, 84%) for the detection of severe portal hypertension.</td>
</tr>
<tr>
<td>Conclusion:</td>
<td>Renovascular impedance had a direct correlation with HVPG.</td>
</tr>
</tbody>
</table>
Cirrhosis of the liver is characterized by a profound disarrangement of the parenchyma and intrahepatic circulation, which leads to portal hypertension. In later stages of the disease, the hemodynamic disturbances also involve the splanchnic and systemic circulatory beds (1,2). Splanchnic vascular resistance progressively decreases owing to arteriolar vasodilatation induced by portal hypertension. In patients with compensated cirrhosis, the effective arterial volume—and consequently the arterial pressure—is maintained by increases in plasma volume and cardiac output. During the later stages of cirrhosis, however, the splanchnic vasodilatation is so pronounced that both the effective arterial volume and the arterial pressure decrease. Consequently, the arterial pressure is maintained by the activation of endogenous vasoconstrictor systems, which results in renal vasoconstriction and sodium and fluid retention. These events eventually cause the clinical appearance of ascites and renal dysfunction (3).

Color flow and pulsed wave Doppler ultrasonography (US) is a noninvasive examination widely used to study the splanchnic hemodynamics in liver cirrhosis. This examination enables the accurate study of renal hemodynamics, which has been validated in different pathologic conditions (4). Calculation of the renovascular impedance—expressed in terms of the resistance index (RI) and the pulsatility index (PI)—with use of Doppler tracings at the level of the interlobar arteries yields an estimation of renal arterial vasoconstriction (4,5). Patients with cirrhosis have significantly higher renal RI and PI values compared with healthy subjects (5,6), and renovascular impedance increases as the liver disease progresses (7). These increases are marked in patients with ascitic cirrhosis (6). Collì et al (8) found that in patients who have compensated (ie, Child-Pugh class A) cirrhosis without ascites, high renovascular impedance correlates with the presence of esophageal varices. It has also been found that impedance values higher than the threshold for normal have prognostic value in the identification of patients who are at high risk for refractory ascites (9), hepatorenal syndrome (6,10), and death (6). Existing evidence therefore suggests that portal venous pressure is the initiating event that causes renal vasoconstriction.

We hypothesized that there is a correlation between hepatic venous pressure gradient (HVPG), which is the clinical equivalent of the portal pressure (11), and renovascular impedance, but specific data were not available. Thus, the purpose of our study was to prospectively evaluate, in patients with liver cirrhosis, the correlation between renovascular impedance, as measured by using color flow and pulsed wave Doppler US, and portal pressure, as measured by using the HVPG.

Materials and Methods

Patients

The study population consisted of 31 patients with cirrhosis (22 men, nine women; mean age, 57.6 years ± 8.8 [standard deviation]; age range, 36–70 years) who were consecutively referred to our facility (Università di Bologna, Policlinico S. Orsola-Malpighi) from December 1, 2003, to January 10, 2005, for measurement of the HVPG before they began receiving β-blockers. β-Blockers were considered the primary treatment to reduce portal pressure in patients with cirrhosis and high risk for hemorrhage—namely, those with medium (F2 or tortuous varices occupying less than 30% of esophageal lumen) or large (F3 or tortuous varices occupying more than 30% of esophageal lumen) (12) esophageal varices who had never had bleeding from varices. A first hemorrhage caused by variceal rupture is prevented when the treatment induces an HVPG decrease of at least 20% compared with the baseline value. For this reason, measurement of the HVPG before and after 1–3 months of therapy is considered the reference standard for testing the effectiveness of the medical treatment (13), and this procedure is routinely applied at our university hospital.

This study was approved by the senior staff committee of our university hospital (comparable to institutional review board). The nature of the study was explained to the patients, each of whom provided written informed consent, in keeping with the principles of the Declaration of Helsinki (2000 revision of Edinburgh).

Laboratory and Clinical Assessment

Disease severity was assessed by two hepatologists (N.C. and D.M., with, respectively, 5 and 15 years of experience performing this evaluation) by using the Child-Pugh continuous score (14), which takes into account five conventional clinical (hepatic encephalopathy and ascites) and laboratory (albumin, international normalized ratio, and bilirubin values) parameters. Each variable is assigned a score of 1–3 according to the grade of abnormality. Thus, patients with compensated cirrhosis (class A) receive a total score of 5–6, those with slightly moderate decompensated cirrhosis (class B) receive a score of 7–9, and those with severely decompensated disease (class C) receive a score of 10–15.
Recent (performed within 1 week from study enrollment) laboratory tests, including bilirubin level, albumin level, international normalized ratio, and creatinine level measurements, were performed in all patients as part of the routine follow-up, and the results were collected by the two hepatologists (N.C., D.M.). The same physicians also reviewed the clinical history of each patient to look for the origin of liver disease, endoscopic findings, previous episodes of ascites, and ongoing medical treatment.

**Color Flow and Pulsed Wave Doppler US Measurement of Renovascular Impedance**

After fasting overnight, the patients were transferred to the US examination room and asked to lie supine for 10 minutes. Thereafter, Doppler US measurements of the right interlobar renal artery (RRA) and the left interlobar renal artery (LRA) were obtained by one experienced operator (A.B., with 7 years of experience) by using last-generation duplex US equipment (Technos; Esaote Ansaldo, Genoa, Italy) with a 4.5–7.0-MHz convex probe provided with the color and pulsed wave Doppler device (Technos). During the patient’s suspended normal respiration, measurements were performed in three renal areas (upper, middle, and lower poles)—each measured three times—and the results were expressed as the average of the measurements in the three areas.

The positions for the measurements were identified by using power and color flow Doppler US. The size of the sample volume was 2.0 mm. To minimize sampling error, the pulsed wave Doppler spectrum was increased by using the lowest frequency-shift range possible that does not cause aliasing; the wall filter was set on a low frequency (100 MHz). The RI and PI were automatically calculated on traces of 4–6 seconds by using the arterial Doppler US spectrum to avoid errors due to flow fluctuations (15). RI was calculated as 
\[
S_{\text{peaksyst}} - S_{\text{min dias}} / S_{\text{peaksyst}},
\]
where \(S_{\text{peaksyst}}\) is the peak systolic frequency shift and \(S_{\text{min dias}}\) is the minimal diastolic frequency shift. PI is calculated as 
\[
(S_{\text{peaksyst}} - S_{\text{min dias}}) / S_{\text{mean}},
\]where \(S_{\text{mean}}\) is the mean frequency shift. We considered normal values of renovascular impedance to be RI values lower than 0.70 and PI values lower than 1.20 (16,17).

**HVPG Measurement**

Immediately after undergoing US, the patients were transferred to the angiography room and underwent hepatic vein catheter placement. The procedures were performed by three experienced radiologists (A.C., C.R., and F.L., with 6, 28, and 30 years of experience, respectively). With the patient in a state of local anesthesia, a 7-F venous catheter introducer was placed in the basilic vein of the right forearm by using the Seldinger technique. With fluoroscopic control, a 5-F balloon-tipped catheter (Meditech–Boston Scientific Cork, Cork, Ireland) was advanced into the main right hepatic vein to measure the wedged and free hepatic venous pressures by connecting the catheter to an external electromechanical transducer and a polygraph (PowerLab; ADI Instruments, Milford, Mass). The HVPG was calculated as the difference between the wedged hepatic venous pressure and the free hepatic venous pressure. All measurements were performed in triplicate, and permanent tracings were recorded (11). A hepatologist (A.B.), who had 5 years of experience in HVPG measurement, evaluated the pressure tracings and assessed the pressure values. Clinically significant portal hypertension was defined as an HVPG of 10 mm Hg or higher according to the definition established by a consensus on portal hypertension (13).

**Mean Arterial Pressure Measurement**

During hepatic vein catheter placement, the arterial pressure was automatically measured every 5 minutes by using an external electronic sphygmomanometer. The mean arterial pressure was calculated as follows:
\[
\frac{P_s + (2 \cdot P_d)}{3},
\]where \(P_s\) is the systolic pressure and \(P_d\) is the diastolic pressure. The heart rate was derived by means of continuous electrocardiogram monitoring; data were recorded in the patients’ files (A.B.).

**Statistical Analyses**

After the end of the examinations, the data obtained at Doppler US and hepatic vein catheter placement in the patients were combined and entered into a database. Statistical analyses were performed by using the SPSS 10.0 statistical package (SPSS, Chicago, Ill). All results are expressed as means ± standard deviations. Comparisons between subgroups were performed by using the Student t test for unpaired data for parametric variables and the Fisher exact test for frequencies. Correlations were determined by using the Pearson test. \(P < .05\) was considered to indicate a significant difference. The intraobserver coefficient of variation for the reported US parameters was less than 5%.

To assess the diagnostic accuracy of higher-than-normal renal RI and PI values in the prediction of an HVPG of 16 mm Hg or higher, the following parameters were determined: sensitivity (ie, number of true-positive test results divided by number of all patients with the disease), specificity (ie, number of true-negative test results divided by number of all patients without the disease), positive predictive value (ie, number of true-positive test results divided by number of all patients with positive test results), and negative predictive value (ie, number of true-negative test results divided by number of all patients with negative test results).

**Results**

The cause of liver disease was hepatitis C virus related in 20 (64%) of the 31 patients, cryptogenic in four (13%), alcohol related in three (10%), hepatitis B virus related in two (6%), and hepatitis C virus and alcohol related in two (6%). All patients had F2 or F3 esophageal varices (22 medium-size and nine large varices), and none had bleeding from varices. The mean Child-Pugh score was 6.9 ± 1.8 (range, 5–11). Fourteen (45%) of the 31 patients had had previous episodes of ascites, and five (16%) had slight ascites at US and were receiving spironolactone (100–200 mg/d, five patients), with or without furosemide (25 mg/d, two patients), on a long-term basis. The mean serum creatinine level was 0.90 mg/dL ± 0.17.
None of the patients had a creatinine level higher than values in the upper range of normal (normal range, 0.60–1.20 mg/dL).

**Renovascular Impedance at Color Flow and Pulsed Wave Doppler US**

Measurement of renovascular impedance (Table) in the RRA was feasible in only 26 patients owing to suboptimal visualization of the right kidney due to overlying bowel gas. Impedance in the LRA was measured in all patients. In the RRA, the mean RI and PI values were 0.67 ± 0.07 and 1.21 ± 0.25, respectively. In the LRA, the mean RI and PI values were 0.68 ± 0.07 and 1.24 ± 0.26, respectively. Eleven patients had renovascular impedance indexes higher than the accepted normal values for both the RRA and the LRA; the LRA PI was higher than normal in 19 patients. Twenty patients had normal renovascular impedance; the LRA PI was normal in 12 patients.

Renovascular impedance had a tendency to be higher in patients with a higher Child-Pugh score (RRA RI: R = 0.277, P = .18; RRA PI: R = 0.320, P = .11; LRA RI: R = 0.330, P = .08; LRA PI: R = 0.251, P = .17). Patients with ascites had slightly higher RI and PI values compared with patients without ascites, but the difference was not statistically significant. Renovascular impedance did not correlate with mean arterial pressure or serum creatinine level.

**HVPG Results**

All patients had findings of clinically significant sinusoidal portal hypertension. The mean HVPG was 19.3 mm Hg ± 4.7 (range, 11.5–33.5 mm Hg) (Table). The portal pressure values did not differ significantly between the patients with and those without ascites. Twenty-four patients had HVPG values higher than 16 mm Hg. HVPG did not correlate with Child-Pugh score.

**Correlations between Renovascular Impedance and HVPG**

The renovascular impedance indexes in both the RRA and the LRA showed positive correlations with the HVPG (Figs 1, 2). A renovascular impedance higher
than normal had low sensitivity but high specificity in the prediction of an HVPG of 16 mm Hg or higher. The RI and PI in the RRA had a sensitivity of 52% (11/21), a specificity of 100% (5/5), a positive predictive value of 100% (5/5), and a negative predictive value of 33% (5/15). The RI in the LRA had a sensitivity of 46% (11/24), a specificity of 86% (6/7), a positive predictive value of 92% (11/12), and a negative predictive value of 32% (6/19). The PI in the LRA had a sensitivity of 67% (16/24), a specificity of 57% (4/7), a positive predictive value of 84% (16/19), and a negative predictive value of 33% (4/12). None of the patients with less severe portal hypertension (ie, HVPG < 16 mm Hg) had an RRA renovascular impedance higher than normal (Fig 3).

Mean Arterial Pressure
The mean arterial pressure for the entire study population was 97 mm Hg ± 9 (Table). Patients with ascites had a significantly lower mean arterial pressure (89 mm Hg ± 7) compared with patients without ascites (99 mm Hg ± 8, P = .01).

Discussion
To our knowledge, our study is the first in which a correlation between HVPG and renovascular impedance, as measured by using color flow and pulsed wave Doppler US, was directly demonstrated. From a pathophysiologic standpoint, our findings support the results of many previous Doppler US studies: In the study by Colli et al (8), the finding of high renovascular impedance in patients with well-compensated cirrhosis helped to predict the presence of esophageal varices, which develop only when the portal pressure increases above a threshold value of 10 mm Hg (18). Also, Perney et al (19) found that in patients with cirrhosis, renovascular impedance increases after food ingestion, and this may be explained by the brisk increase in portal pressure observed in patients with cirrhosis after a meal (20, 21).

We observed a correlation between renovascular impedance and HVPG and a lack of an inverse correlation between renovascular impedance and mean arterial pressure. These findings are in agreement with previous hypotheses that renal vasoconstriction may be modulated by not only a reduction in effective circulating volume but also systems that are not fully elucidated, depending on the increase in portal pressure, which have been defined as hepatorenal reflexes (22–24). Nonetheless, many other factors regulate the renal vascular tone in cirrhosis (2, 3), and this may explain the lack of a more close correlation between HVPG and renovascular impedance in the present study.

Another finding of the current study was that higher-than-normal PI and RI values in the right kidney had a 100% positive predictive value in the prediction of an HVPG of 16 mm Hg or higher.
Even when the results obtained for the left kidney were not completely concordant, the positive predictive values were very high (92% for RI, 84% for PI). We believe that this finding is of interest, because an HVPG of 16 mm Hg or higher has been recognized to be associated with a higher risk of developing complications of portal hypertension (25,26). We hypothesize that the reported prognostic value of a high renovascular impedance in terms of the occurrence of renal complications of cirrhosis and mortality (6,10) may be explained by a worsened portal hypertensive state.

In contrast to previously published data, a significantly higher renovascular impedance was not observed in the patients with ascites compared with those without ascites in our series. This result may be explained by a limitation of this study: It mainly included patients with compensated cirrhosis; only five patients had ascites, and none had severe or refractory ascites, which is more commonly associated with increased renovascular impedance (9). One additional limitation was the fact that, even though we did not consider the presence of an abnormal creatinine level an exclusion criterion, none of the patients whom we examined had increased creatinine levels. Thus, our findings may be valid for only those patients who have cirrhosis without renal failure. On the other hand, increased creatinine levels in patients with cirrhosis—especially those with hepatitis C virus–related disease—may be due to not only renal vasoconstriction but also interstitial nephritis or vasculitis, either of which also causes increases in renovascular impedance (4). The absence of patients with overt renal failure in the present series resulted in the avoidance of confounding factors, and we observed abnormal renovascular impedance in up to one-third of the patients in our study group.

In conclusion, the present study data demonstrate the existence of a correlation between HVPG and renovascular impedance in patients with cirrhosis. Although patients with clinically significant portal hypertension may have normal renovascular impedance, the finding of high renovascular impedance, which is indicative of renal vasoconstriction, in patients who have liver cirrhosis with normal renal function can be considered an indication of severe portal hypertension. Routine examination of renovascular impedance in patients with cirrhosis may help to noninvasively identify a subgroup of patients with portal hypertension who are at high risk for complications.

References