Portal venous pressure and the serum-ascites albumin concentration gradient

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■ **CLINICAL ISSUE** Other investigators have found the serum-ascites albumin concentration gradient to be 1.1 g/dL or greater in the presence of portal hypertension and less than that in its absence.

■ **OBJECTIVE** To determine if any correlation exists between the serum-ascites albumin concentration gradient (which reflects the net serum oncotic pressure) and the portal venous pressure.

■ **METHODS** The study group comprised 15 patients who had alcoholic cirrhosis. The portal venous pressure was calculated as the difference between the measured hepatic venous wedge and inferior vena cava pressures and was expressed as the hepatic venous pressure gradient.

■ **SUMMARY** All patients had portal hypertension; the mean hepatic venous pressure gradient was 14.81 ± 6.91 (SD) mm Hg. Fourteen of the 15 patients had a serum-ascites albumin concentration gradient of at least 1.1 g/dL; the mean value was 2.168 ± .709 g/dL. No correlation was found between these variables (r = .0459, $P > .05$).

■ **CONCLUSIONS** Although the serum-ascites albumin concentration gradient is a sensitive indicator of portal hypertension in patients with alcoholic cirrhosis, it does not reflect the portal venous pressure.

■ INDEX TERMS: SERUM ALBUMIN; ASCITIC FLUID; LIVER CIRRHOSIS, ALCOHOLIC; HYPERTENSION, PORTAL ■ CLEVE CLIN J MED 1995; 62:62–67

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ASCITES CAN arise from portal hypertension or from other causes. In recent years, clinical investigators have found they could predict the presence of portal hypertension in patients with ascites by measuring the difference in albumin concentration between the serum and the ascitic fluid, ie, the serum-ascites albumin concentration gradient (SAAG). Rector[1] found the SAAG to be 1.1 g/dL or greater in portal hypertension, less in its absence.

An earlier, similar approach was to measure the total protein concentration of the ascitic fluid. Ascitic fluid with a protein concentration of 2.5 g/dL or greater was considered "exudative," ie, arising from an inflamed or tumor-laden peritoneal surface; fluid containing less was considered "transudative," ie, arising from hydrostatic forces such as portal hypertension. In a recent study of 1275 patients with ascites, the SAAG accurately identified portal hypertension in 96.7% of the patients; the ascitic fluid protein concentration correctly classified the causes of ascities (as exudative or transudative) only 55.6% of the time.[2]

The SAAG appears to retain its predictive value despite diuresis, therapeutic paracentesis, or infection in the ascitic fluid,[2] and in all types of liver disease. Several studies have found the SAAG superior to the traditional exudate-transudate concept in determining the cause of ascites and have proposed the SAAG be used as a physiologically based alternative in the classification of ascites.[3-6]

We undertook the present study to determine whether the SAAG, apart from predicting portal hypertension, correlates with the portal venous pressure. Earlier reports have shown conflicting results.[3,4,7] If such a correlation could be established, the SAAG could serve as a simple and minimally invasive test to estimate the degree of portal hypertension in these patients. It could also prove useful in assessing the prognosis of patients with chronic liver disease, since portal pressure has been suggested as an independent predictor of survival in such patients.[8]

MATERIALS AND METHODS

Fifteen patients with alcoholic cirrhosis and ascites were selected for the study. The study design was reviewed by our institution's ethics committee and was found to conform to the ethical guidelines of the 1975 Declaration of Helsinki. The criteria for inclusion were: (1) a history of consumption of at least 160 g of ethanol per day for at least 5 years; (2) evidence of cirrhosis of the liver (see below); (3) evidence of ascites by ultrasonographic examination; and (4) no history or evidence of complications (ie, hematemesis, melena, renal failure, infection, or encephalopathy) in the preceding fortnight. In eight of the 15 patients, the diagnosis of cirrhosis was established by histopathological study of liver tissue. The rest could not undergo biopsy because they had a persistently elevated prothrombin time (n = 4) or uncontrolled ascites (n = 3). These seven patients had all of the following findings, which were accepted as evidence of cirrhosis: (1) esophageal varices on endoscopy; (2) ultrasonographic features of generalized hepatocellular disease[9] and a caudate-lobe-to-right-lobe ratio of more than 0.65 (which is highly specific for cirrhosis[10]); and (3) findings on isotopic scanning suggestive of decreased or heterogeneous hepatic uptake and increased uptake by the extrahepatic reticulo-endothelial system.[11]

On admission, the patients underwent a thorough clinical examination. They gave their informed consent for the study after we explained the possible risks of the procedures involved. The blood investigations included a complete hemogram; the erythrocyte sedimentation rate; concentrations of serum electrolytes, blood urea nitrogen, serum creatinine, and fasting blood sugar; liver profile tests (concentrations of total and direct bilirubin, serum aspartate aminotransferase, serum alanine aminotransferase, serum alkaline phosphatase); and the prothrombin time.

We measured the hepatic venous wedge pressure (HVWP) and the inferior vena cava pressure (IVCP) after the patients had lain in the supine position and fasted 8 hours and had not taken diuretics for at least 48 hours. The pressure transducer was calibrated against a mercury manometer; the absolute coefficient of variation was ± 0.3 mm Hg for all pressure levels between 0 and 40 mm Hg. Throughout the procedure, we kept the pressure transducer 5 cm below the sternal notch; this served as a standard external reference point. All pressures were measured from tracings recorded on paper.

The technique for measuring the HVWP and the IVCP has been discussed in detail elsewhere.[12] Catheterization of the hepatic vein was achieved using the right internal jugular vein or the right femoral vein for access. A Mallinckrhodt end-hole catheter (St. Louis, Mo) was passed into the inferior vena cava, and the venous wall was explored for a hepatic vein opening. The catheter was advanced as far into the hepatic vein as possible. We recorded the HVWP when the catheter could be advanced no further (ie, when it became wedged). Wedging was subsequently confirmed by injection of a small amount of contrast medium (Conray 420); a "dye blush" is seen for a few seconds if the catheter is wedged. If the catheter is caught at a venous bifurcation without obstructing the flow, the dye is seen to wash away immediately. In cases where wedging could not be confirmed after injection of the dye (n = 3), the catheter was withdrawn a few centimeters and readvanced into the hepatic vein 3 to 5 minutes later in an attempt to wedge it.

HVWP readings obtained with this technique show an excellent correlation with those obtained with a balloon catheter.[13] Readings were deemed acceptable only after satisfactory radiologic confirmation of wedging. The catheter was then withdrawn, and the IVCP was recorded. The portal pressure was calculated as the difference between the

TABLE 1
LIVER FUNCTION AND RENAL CHEMISTRY

Investigation	Mean	Standard deviation
Serum bilirubin, mg/dL		
Total	3.68	4.15
Direct	2.26	2.91
Indirect	1.42	1.39
Serum aspartate aminotransferase, U/L	33.60	26.23
Serum alanine aminotransferase, U/L	24.00	8.90
Blood urea nitrogen, mg/dL	15.47	8.25
Serum creatinine, mg/dL	1.20	0.39

TABLE 2
PROTEIN AND PRESSURE VALUES

Investigation	Mean	Standard deviation
Serum albumin concentration, g/dL	2.77	0.88
Ascites albumin concentration, g/dL	0.61	0.38
Serum-ascites albumin concentration gradient, g/dL	2.17	0.71
Hepatic venous wedge pressure, mm Hg	28.07	10.44
Inferior vena cava pressure, mm Hg	13.20	5.56
Hepatic-venous pressure gradient, mm Hg	14.87	6.91

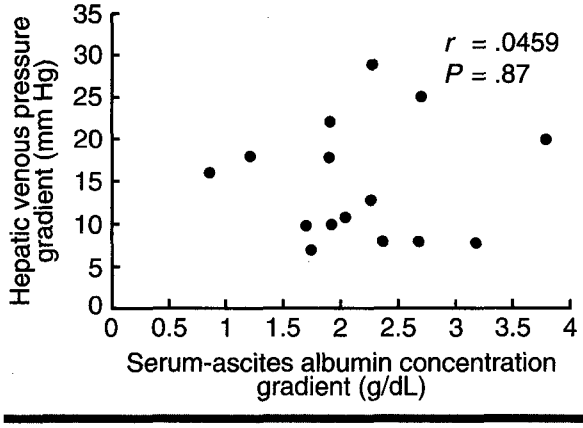

FIGURE. The hepatic venous pressure gradient (portal venous pressure) does not correlate with the serum-ascites albumin concentration gradient.

HVWP and the IVCP and expressed as the hepatic-venous pressure gradient (HVPG) in "mm Hg."

We drew approximately 10 mL of ascitic fluid and 5 mL of blood at the time of pressure measurements to measure total protein and albumin concentrations. The former was done by the biuret method[14] and the latter by the dye-binding method.[15]

All statistical analyses were performed using the EPISTAT statistics software program (distributed by the Centers for Disease Control and Prevention, Atlanta, Ga). Pearson's coefficient was used to determine the relation between the SAAG and the HVPG. A *P* value of less than .05 was considered statistically significant.

RESULTS

The mean and standard deviation values of the serum bilirubin, aspartate aminotransferase, alanine aminotransferase, blood urea nitrogen, and serum creatinine concentrations are given in *Table 1*. Ten of the 15 patients (67%) had elevated concentrations of serum bilirubin (> 1.0 mg/dL), predominantly conjugated bilirubin. Four patients (27%) had evidence of ongoing hepatitis in the form of elevated alanine aminotransferase concentrations (> 40 U/L).

The mean and standard deviation values of the serum and ascitic fluid albumin concentrations, SAAG, HVWP, IVCP, and HVPG are shown in *Table 2*. The SAAG ranged from 0.86 g/dL to 3.8 g/dL. Fourteen patients (93%) had an SAAG of 1.1 g/dL or greater. All 15 patients had portal hypertension, ie, the HVWP exceeded the IVCP by at least 6 mm Hg.[16] The calculated HVPG ranged from 7 mm Hg to 29 mm Hg. The HVPG readings of the three patients in whom the catheter could not be wedged initially were 7, 13, and 20 mm Hg.

There was no correlation between the SAAG and the HVPG (r = .0459; 95% CI –0.552 to 0.644; P = .87) when all 15 patients were analyzed together (*Figure*). We performed subgroup analysis using different ranges of the HVPG to try to identify subsets of patients in whom a positive correlation may exist between the SAAG and the HVPG. Specifically, we used the following arbitrary subgroups: (1) those with an HVPG of 10 mm Hg or greater (n = 11); (2) those with an HVPG of 15 mm Hg or greater (n = 7); (3) those with an HVPG of less than 15 mm Hg (n = 8); and (4) those with an HVPG of 20 mm Hg or less (n = 12). Since the oncotic pressure gradient

between the blood and interstitial fluid is a direct function of the corresponding capillary hydrostatic pressure gradient,[17] and since the SAAG more reliably reflects the oncotic pressure gradient when the serum globulin level is between 3.2 and 4.5 g/dL,[7] we also looked for a correlation between the SAAG and the HVPG in the subset of patients (n = 6) whose serum globulin concentrations ranged from 3.2 to 4.5 g/dL. In none of these subgroups did the SAAG correlate with the HVPG.

DISCUSSION

In this group of 15 patients with alcoholic cirrhosis, we found that the SAAG was very sensitive in predicting the presence of portal hypertension: 93% of the patients in this group, all of whom had portal hypertension, had an SAAG of 1.1 g/dL or greater. The SAAG did not correlate with the degree of portal hypertension, however.

Correlation of SAAG and portal pressure

Evidence against a correlation between the SAAG and the portal pressure was provided by earlier experiments involving the use of diuretics and albumin infusions in patients with chronic liver disease and ascites. These therapeutic measures affect the portal pressure but not the SAAG, thus ruling out a stable relationship between these two variables.

Atkinson[18] demonstrated a decrease in the intrasplenic pressure (which reflects the portal pressure[19]) in 10 of 11 periods of treatment with diuretics; the pressure reached values within the normal range in four periods. In the same experiment, the protein levels of serum and ascitic fluid remained virtually unaltered, except in one instance. Hoefs[20] also concluded from his study in patients with chronic liver disease that, although the protein concentrations of the serum and ascitic fluid increase following diuresis, the SAAG remains virtually constant, decreasing by only 20% of its initial value. Runyon et al[2] found no difference in the SAAG when it was measured before and after diuresis in 22 cirrhotic patients; they concluded that diuresis does not affect the SAAG.[2] This minimal decrease (or lack of decrease) in the SAAG following diuresis, when seen in the light of the significant fall in portal pressure found by Atkinson,[18] argues against a stable correlation between the SAAG and portal pressure.

Studies involving single and multiple injections of concentrated human serum albumin showed an increase in the plasma volume (and presumably in the portal pressure) associated with an increase in colloid osmotic pressure of the plasma and a concomitant parallel increase in the colloid osmotic pressure of the ascitic fluid, maintaining a constant osmotic pressure gradient.[21,22]

If a direct relationship exists between the SAAG and the portal pressure, phenomena that affect one of them should affect the other as well, in the same direction. These experiments, however, seem to indicate that this is not so.

On the other hand, Hoefs[3] studied the relationship between the SAAG and the portal pressure in 56 patients with chronic liver disease (resulting in most from alcohol abuse) and concluded that a direct correlation existed between the two. Subsequently, Rector and colleagues[4] also found such a correlation in 18 patients with cirrhotic ascites. Kajani and coworkers[7] found a correlation in patients with alcoholic cirrhosis, but not in those with nonalcoholic causes of cirrhosis. The portal pressure was measured by different methods in these studies. Hoefs[3] estimated the portal pressure as the difference between the transhepatic portal pressure and the IVCP; Rector et al[4] determined the net portal pressure by transhepatic portal vein puncture (four patients) or by hepatic vein catheterization (14 patients), with the pressure in the hepatic vein or inferior vena cava serving as the internal baseline. Kajani et al[7] estimated the portal pressure as the difference between the portal venous pressure measured directly at the time of orthotopic liver transplantation and the central venous pressure. These methods have been studied in the past, and a good correlation exists between the portal pressure recorded by all these techniques.[12] Hence, the difference in results between these studies and our study cannot be attributed to methodological differences.

If there really is a direct correlation between the SAAG and the portal pressure, as proposed in some of these reports, we should be able to predict the albumin content of the ascitic fluid on the basis of serum albumin concentration and the portal pressure. This would undermine the significance of a number of factors known to influence the formation of ascites in cirrhosis and, presumably, determine the concentration of albumin in the ascitic fluid.

Increased hepatic transsinusoidal pressure and low serum albumin concentrations favor the formation of ascites, as do increased splanchnic capillary pressure,[23] hyperdynamic splanchnic blood flow,[24]

adrenal and posterior pituitary hormonal effects,[25] renal handling of salt and water,[26] and, probably, impaired diaphragmatic lymph absorption and restriction of central lymph flow at venous junctions.[27]

Multiple factors also act to prevent ascites. These include an increased hepatic transsinusoidal oncotic pressure gradient; an increased splanchnic transcapillary oncotic pressure gradient; increased hepatic, splanchnic, diaphragmatic, and central lymph flow; increased visceral tissue hydrostatic pressure, and increased intra-abdominal pressure resulting from ascites.[27] In addition, portosystemic venous collaterals in the posterior peritoneum and systemic venous channels keep the ascitic fluid in equilibrium, to an extent, with the systemic circulation.[25]

Moreover, portal hypertension is a heterogeneous phenomenon in different patients, even when it results from the same cause. Witte et al[28] have described contrasting portal hemodynamic patterns in 10 patients with portal hypertension, including six in whom alcohol abuse was the presumed cause. Their patients differed from each other in portal pressure, volume of thoracic duct flow, lymph protein content in the thoracic duct, ascitic fluid protein content, the site of resistance to portal blood flow (presinusoidal or postsinusoidal), and the state of the splenic flow (hyperdynamic in some, but not in others). These features do have a bearing on the SAAG as well as on the magnitude of portal hypertension. These differences existed even among those patients in whom alcohol abuse was the sole evident cause of chronic liver disease and portal hypertension.

Possible reasons for the divergent findings

We cannot explain with certainty why our results contrast with those of some previous reports.[3,4,7] Our methods were not significantly different from those used in the other studies. Our patient population was also similar: the subjects all had alcoholic cirrhosis, and some of them also had hepatitis. However, all our subjects were natives of the Indian subcontinent, whereas the patients in the previous studies[3,4,7] were presumably predominantly Caucasian. (Although this information is not available, it would be reasonable to assume so since these studies were performed in the United States.) Whether racial differences can account for the disparity in results is a matter of conjecture.

In addition, nine of our 15 patients (60%) had serum globulin levels lower than 3.2 g/dL or higher than 4.5 g/dL; this is significant because the SAAG is a reliable reflection of the oncotic pressure gradient within this range, but tends to become narrow in the presence of a high globulin level and wide with a low globulin level.[7]

We conclude that a wide osmotic pressure gradient exists between serum and ascitic fluid in most patients with ascites caused by portal hypertension. However, the concept that the SAAG simply equilibrates with the exact level of portal pressure is physiologically misleading and simplistic, given the heterogeneous and complex pathophysiology of portal hypertension. We disagree with some earlier investigators and believe that the SAAG cannot be used as an indirect measure of portal pressure.

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