Intravascular Volume in Cirrhosis
Reassessment Using Improved Methodology

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Previous studies of blood volume (BV) in cirrhosis have either not adjusted BV properly for body size; determined plasma volume from the dilution of labeled albumin 10–20 min postinjection, when some extravascular redistribution has already occurred; and/or not used the correct whole-body-peripheral hematocrit ratio (0.82) in calculating whole BV from plasma volume and the peripheral hematocrit. We measured BV with attention to these considerations in 19 patients with cirrhosis and reexamined the determinants of vascular volume and the relationship between vascular volume and sodium retention. BV was calculated as plasma volume (determined from extrapolated plasma activity of intravenously injected $[^{131}I]$-albumin at time 0) divided by (peripheral hematocrit $\times$ 0.82). The result was expressed per kilogram “dry” body weight, determined by subtracting the mass of ascites (measured by isotope dilution; 1 liter = 1 kg) from the actual body weight of nonedematous patients. Measured and expressed in this way, BV correlated strongly with esophageal variceal size ($r = 0.87$, $P < 0.05$), although not with net portal, right atrial, inferior vena caval, or arterial pressure, and was significantly greater in patients with sodium retention as compared to patients without sodium retention. The principal modifier of vascular volume in cirrhosis is vascular capacity, which is probably mainly determined by the extent of the portasystemic collateral circulation. Increased vascular volume in patients with sodium retention as compared to patients without sodium retention supports the “overflow” theory of ascites formation.

KEY WORDS: plasma volume; blood volume; cirrhosis; portal hypertension; ascites; esophageal varices.

A number of studies have measured intravascular (whole blood) volume in patients with cirrhosis in order to determine if the stimulus to renal sodium retention in this condition is vascular depletion (1–10). Results have generally indicated that intravascular volume is normal or increased in cirrhosis. This had led to the hypothesis that ascites formation is the result rather than the cause of sodium retention (the “overflow” theory) (11).

None of these investigations have fully satisfied the methodologic requirements for accurate measurement and expression of intravascular volume in cirrhosis. First, cirrhosis is associated with a variable degree of muscle wasting (12). Correction of intravascular volume for body size, obviously essential for a meaningful interpretation of the result, is frequently difficult in cirrhosis because of the presence of an uncertain amount of ascites and edema. For this reason, intravascular volume has usually either been given in uncorrected form (4, 8) or expressed according to height (2, 3, 7–10) in such patients. Second, measurement of plasma volume...
from dilution of an albumin marker following intravenous injection (1, 3, 6, 7, 9) overestimates this volume because albumin is in continuous circulation through the extravascular space. The longer following injection of the marker that sampling is performed, the larger will be the volume of distribution of albumin ("plasma" volume). This problem is amplified in patients with cirrhosis, as the transvascular escape rate of albumin is markedly increased in this condition (13, 14). Third, intravascular volume has commonly been calculated from plasma volume and the concentration of red cells in blood, as indicated by the hematocrit. Red cells are more dilute in the body as a whole than in the peripheral veins (15). The peripheral venous hematocrit must consequently be corrected downward to approximate the whole body hematocrit and, from that, whole blood volume. Using labeled albumin to measure plasma volume and labeled red blood cells to measure red blood cell volume, Lieberman and Reynolds demonstrated that the whole body–peripheral hematocrit ratio is lower in patients with cirrhosis (0.82) than in healthy subjects (0.91) (7). The reason for this difference is not known. Unless, however, the lower ratio is used for correction of the peripheral venous hematocrit, a falsely low whole blood volume will be obtained (1–6, 8–10).

The present study had three aims: (1) to remeasure intravascular volume in cirrhosis with attention to satisfying the above methodological considerations; (2) to examine, as far as possible, determinants of intravascular volume in this condition; and (3) to retest the hypothesis that intravascular volume depletion is the stimulus to renal sodium retention in cirrhosis.

MATERIALS AND METHODS

Patient Population. Twenty-two patients with cirrhosis proven by biopsy or subsequent autopsy were studied. Seven had no sodium retention (group 1), as indicated by absence of ascites on physical examination and no weight gain during five or more days of hospitalization while consuming an unrestricted amount of sodium. Eight patients (group 2) had mild to moderate sodium retention, defined as ascites that remitted spontaneously (one patient) or rapidly and without a rise in serum creatinine concentration in response to diuretic therapy (seven patients). Seven patients had severe sodium retention, defined as ascites that was resistant to diuretic treatment. These patients required porto-caval shunt (group 3). All had received high doses of two and often three diuretics and had urine collections documenting that diuretic unresponsiveness was due to intense tubular activity for sodium and not to increased dietary sodium intake. Patients in this group were studied prior to insertion of the shunt. All patients with sodium retention were studied when nonedematous, as defined by absence of skin pitting with digital pressure over the shins. Daily urinary sodium excretion in groups 2 and 3 was 1.3 ± 1.1 and 0.2 ± 0.4 meq, respectively. Diuretics were withheld from these patients for between two and seven days prior to study. The study was approved by the Human Investigation Committee of the Rancho los Amigos Medical Center, and patients gave informed consent.

Isotope Studies. One milliliter each of commercial human serum albumin labeled with 131I and 125I, respectively, was drawn into two calibrated glass 1.00-ml syringes. Without changing the needle, 0.50 ml of each isotope was injected into separate flasks containing 2000 ml of tap water as well as 500 mg of human serum albumin added to minimize adherence of labeled albumin to the glass. The remainder of the 131I-labeled albumin (0.50 ml) was then injected into a peripheral vein of the patient under investigation, and the remainder of the 125I-labeled albumin was injected into ascites. The coefficient of variation among counts in multiple flasks injected with isotope by this volumetric technique was 3.6%, verifying its accuracy. Ten milliliters of blood was drawn into heparinized tubes before and 10, 15, 20, and 25 min after the intravenous injection of isotope from an indwelling 18-gauge catheter in the opposite arm. Ascites was drawn from both flasks 60 min after injection. Thorough mixing was confirmed by similar counts in these specimens (<5% variation).

Blood samples were centrifuged at 2500 rpm for 20 min, and 5.0-g aliquots of plasma, ascites, and the standard solution were counted in duplicate for 2–10 min, depending on sample activity, in a gamma scintillation counter. Overlap of 125I with 131I counts was nil (<1%). Overlap of 131I with 125I count was 11%. Accordingly, 11% of the corresponding 131I count was subtracted from each 125I count. However, this correction factor proved trivial owing to the extremely small number of 131I counts in ascites 1 hr after intravenous injection.

Calculations. Body surface area was determined from a standard nomogram using the patients' height and 'dry' weight (16). 'Dry' weight was calculated as body weight on the day of the isotope study minus the mass of ascites (assuming 1.0 liter = 1.0 kg). Ideal body weight was calculated from the patient's height (7).

The transvascular escape rate of albumin was calculated as the monoexponential slope of the line (least-squares method) relating the natural logarithm of plasma counts/min to time from 10–25 min after injection of isotope (13, 14). Mean correlation coefficients of this relationship for groups 1–3 were 0.92 ± 0.11, 0.95 ± 0.08, and 0.96 ± 0.03, respectively. Plasma volume (PV) was calculated by dividing the counts in the aliquot of standard solution by the extrapolated plasma count at time 0 and multiplying by 2000 ml. Red blood cell volume was calculated as whole blood volume minus plasma volume. Whole blood volume was calculated as one minus the hematocrit (spun in triplicate for 5 min in a standard hematocrit centrifuge) times 0.96 (to correct for residual trapped plasma) times 0.82 (to approximate the whole body hematocrit) (7), divided into plasma volume. Ascites...