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Research Article

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Effective Plasma Volume in Cirrhosis with Ascites. Evidence that a Decreased Value Does Not Account for Renal Sodium Retention, a Spontaneous Reduction in Glomerular Filtration Rate (GFR), and a Fall in GFR during Drug-Induced Diuresis

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ABSTRACT A reduction in effective (nonportal) plasma volume is considered the basis for renal sodium retention, a spontaneous reduction in glomerular filtration rate (GFR), and a fall in GFR occurring during drug-induced diuresis in patients with cirrhosis and ascites. In the present study the concept of a reduced effective plasma volume in cirrhosis is challenged by two lines of evidence, even though effective plasma volume itself could not be measured. (*a*) Total plasma volume failed to rise in 10 patients with the spontaneous loss of ascites, the appearance of sodium in the urine, and a rise in GFR. Portal pressure remained constant in these patients as ascites left, suggesting that effective plasma volume had not increased while portal plasma volume decreased. (*b*) Reduction of GFR could not be prevented in five patients with cirrhosis and ascites while total plasma volume was prevented from falling with albumin infusions during drug-induced diuresis. Reduction of GFR during drug-induced diuresis in 15 patients with cirrhosis and ascites was completely reversed with saline infusion despite continued diuresis with the identical drugs, excluding drug nephrotoxicity as the cause for the reduced GFR.

The ascites of cirrhosis might no longer be regarded as a cause of effective plasma volume contraction, stimulating renal sodium retention and a reduction in GFR. More likely, this form of ascites is a result of plasma volume expansion and sodium retention. The causes for renal sodium retention and a spontaneous reduction in GFR remain unknown. The cause for a fall in GFR during drug-induced diuresis also remains unknown, but effective plasma volume contraction and drug nephrotoxicity seem excluded.

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INTRODUCTION

There are two renal abnormalities accompanying ascites formation in alcoholic liver disease that could be attributed to a reduction in total plasma volume. They are renal sodium retention and a reduction in glomerular filtration rate occurring spontaneously or during drug-induced natriuresis. Measurements of total plasma volume during exhibition of these phenomena, however, indicate increases above normal (1–10), and these increases cannot be accounted for by leakage of the measuring substance from the plasma during mixing (8). The presence of a reduced effective or nonportal plasma volume has been inferred as an alternative explanation (11, 12).

The purpose of the present study was to test the theory that the effective plasma volume is reduced in

patients with cirrhosis and ascites. It was felt that the following conclusions about effective plasma volume could be derived from the measurements described below even though effective plasma volume itself could not be measured. (*1*) Failure of total plasma volume to rise with the spontaneous appearance of urinary sodium and a spontaneous rise in GFR would provide evidence against the presence of a decreased effective plasma volume as a cause for these phenomena when ascites was present. This conclusion would only be acceptable if the variables influencing portal and total plasma volume, other than ascites, failed to change when ascites left spontaneously. These variables are considered to be (*a*) portal pressure, which probably influences portal volume, and (*b*) total red cell mass, (*c*) plasma oncotic pressure, and (*d*) dietary sodium intake, all of which might influence total plasma volume. If these variables remain constant, Fig. 1 graphically depicts why the total plasma volume should rise with the spontaneous loss of ascites if a decreased effective portion is associated with ascites formation. (*2*) If total plasma volume could be kept from falling with daily albumin infusions during loss of ascites with natriuretic drugs, it seems highly unlikely that effective plasma volume could be contracting simultaneously. A reduction in GFR under these circumstances would provide strong evidence against a contraction of effective plasma volume as the cause of this reduction.

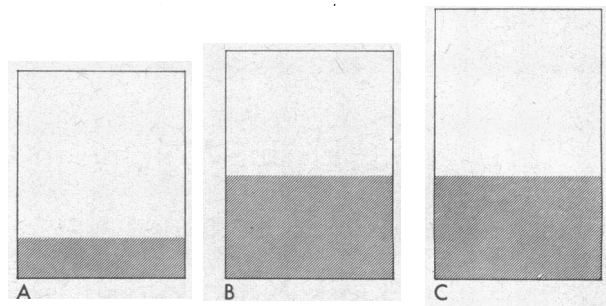

FIGURE 1 Total plasma volume comprised of portal volume (shaded area) and effective or nonportal volume (clear area). A represents the normal relative contributions of portal and effective plasma volume. B represents the theoretical proportions of portal and effective plasma volume during the sodium-retaining phase of ascites. Note that total plasma volume is increased above normal because portal plasma volume is increased; yet effective plasma volume is reduced. C represents the return of effective plasma volume to normal after the spontaneous loss of ascites with the return of normal sodium tolerance. Note that if portal plasma volume does not differ from that during the sodium-retaining phase of ascites, the increase in effective plasma volume should be detected by a rise in total plasma volume as shown.

TABLE I

Measurements Before and After the Spontaneous Loss of Ascites

	WHVP (IVCP)*		WBV‡		PV§				RBC mass‖		Clcr, 24 hr		Serum creatinine	
Patient	Before	After	Before	After	Before	After	↓Na^+	↑Na^+¶	Before	After	Before	After	Before	After
	mm Hg		*ml/kg*		*ml/kg*		*ml/kg*		*ml/kg*		*ml/min*		*mg/100 ml*	
F. S.	13(8)	13(10)	93	95	70	68	68	82	23	27	48	94	0.8	0.7
S. G.	9(19)	11(0)	89	86	63	60	60	53	26	26	100	102	1.0	0.9
E. B.	17(12)	18(0)	82	84	61	63	63	72	21	21	101	112	0.8	0.7
E. G.	16(3)	14(4)	77	107	60	79	79	78	17	28	34	96	1.2	0.8
A. H.	13(8)	14(2)	83	88	66	62	62	63	17	26	129	108	0.8	0.8
M. P.	14(9)	9(3)	75	72	57	51	51	52	18	21	35	66	1.1	1.0
R. A.	14(9)	13(6)	82	82	57	56	56	56	25	26	100	119	0.5	0.6
R. F.	11(13)	8(4)	78	87	56	61	61	63	22	26	72	96	1.0	1.1
J. J.	17(14)	10(8)	98	89	73	51	51	58	25	31	93	73	0.9	0.9
J. A.	14(11)	17(6)	81	89	60	63	63	63	21	26	83	99	0.8	0.9
Mean	14	13	84	88	62	61	61	64	22	26	80	96	0.9	0.8
±SE	0.8	1.0	2.3	2.8	1.8	2.6	2.6	3.3	1.1	0.9	10.1	5.2	0.06	0.05
Mean difference	−1		+4		−1		+2.4		+4		+17		−0.05	
±SE	0.9		3.3		3.2		1.7		1.2		8.2		0.053	
P Value	>0.20		>0.20		>0.50		>0.10		<0.01		=0.06		>0.20	

* Wedged hepatic vein pressure (WHVP) in mm Hg above inferior vena caval pressure (IVCP). Inferior vena cava pressure is in parenthesis and is referred to a baseline reference 5 cm below the sternal angle.

‡ WBV: whole blood volume in ml/kg ideal body wt.

METHODS

Chronic alcoholic liver disease causing ascites was confirmed by needle liver biopsy or at autopsy in 24 of the 30 patients studied, and by history, physical examination, and laboratory tests in all patients. In 10 patients the following measurements were made while each patient had a stable amount of ascites and was on an ad lib. water intake and a diet which contained approximately 20 mEq of sodium daily: wedged hepatic vein pressure using the inferior vena cava pressure as baseline; plasma volume using albumin-^{131}I; red cell mass using ^{51}Cr-labeled autologous red cells; 24 hr urine sodium excretion; 24 hr endogenous creatinine clearance; and serum albumin and globulin concentrations as measured by the Wolfson technique. Details of the methods used have been described previously (8). Plasma volume and red cell mass were expressed in terms of an ideal body weight formula based on height. Our normal values are 42 ±8 (SD) ml/kg and 23 ±5 (SD) ml/kg, respectively. All plasma volume measurements were made in the recumbent state before breakfast, and after overnight recumbency. Each of the 10 patients was kept on the sodium-restricted diet and a variety of diuretic agents was used to remove the ascites. When it was felt that the patient might not reform ascites upon ingestion of a diet unrestricted in sodium, plasma volume and 24 hr urine sodium excretion were remeasured while sodium in the diet was still restricted. A diet unrestricted in sodium was then prescribed and each patient was observed for 1 wk for evidence of reformation of ascites. If ascites did not reform, all the initial measurements were repeated. If ascites reformed, the patient was again placed on a diet restricted in sodium and observed for a variable period of time until it was again felt that ascites might not reform on an unrestricted sodium intake.

During drug-induced diuresis in 20 patients there developed a rise in serum urea nitrogen (SUN) of at least 50% and out of the normal range when SUN was normal before diuresis. 12 had a normal SUN before diuresis, and 8 had values above the normal range of 5–18 mg/100 ml. Diuresis was accomplished with hydrochlorothiazide, furosemide, or ethacrynic acid, each in combination with spironolactone, triamterene, or MK-870.[1] In 15 of these patients, when the SUN had risen as specified, normal saline (155 mEq of NaCl/liter) was infused intravenously to determine if re-expanding extracellular fluid (ECF) volume while continuing the same combination of diuretics would return the SUN to prediuresis levels. In the five remaining patients, SUN and serum creatinine returned to prediuresis levels after administration of the diuretics was stopped. A second diuresis was then initiated with the same or a different combination of diuretic drugs, and 12.5 g salt-poor albumin was given daily during diuresis to keep the plasma volume from falling. Diuresis was stopped when SUN and serum creatinine had risen as specified. Each of the 20 patients was on an ad lib. water intake, and a diet which contained approximately 20 mEq of sodium daily.

SUN was measured by the routine hospital laboratory using a urease method (13), and serum and urine sodium were measured in a research laboratory employing methods previously described (14). In addition, daily urine urea nitrogen was measured in those patients receiving albumin intravenously during diuresis (13). Plasma volume and

[1] Amiloride HCL, Merck Sharp & Dohme, West Point, Pa.

in 10 Patients with Chronic Alcoholic Liver Disease

24-hour urine Na			Serum albumin		Serum globulin		Hematocrit			Days to lose ascites	Body wt		
	No ascites							No ascites				No ascites	
Ascites	↓Na⁺	↑Na⁺¶	Before	After	Before	After	Ascites	↓Na⁺	↑Na⁺¶		Ascites	↓Na⁺	↑Na⁺¶
mEq	*mEq*		*g/100 ml*		*g/100 ml*		*%*	*%*			*kg*	*kg*	
5	18	61	2.0	3.2	3.8	3.4	34	31	28	36	56	51	58
1	34	132	3.3	4.0	3.6	2.3	38	37	40	58	98	76	77
1	36	92	1.9	2.6	4.3	3.4	31	38	25	118	72	63	65
2	61	214	2.2	3.4	4.6	3.5	28	32	30	223	57	67	70
1	4	123	1.0	2.0	5.6	5.4	34	37	36	186	82	76	77
2	86	201	2.8	4.8	4.2	3.5	32	38	37	126	58	53	56
25	49	132	1.9	2.9	4.5	4.7	42	39	40	15	52	52	53
1	14	153	1.5	3.6	5 0	5.0	40	38	38	63	66	64	65
22	15	164	3.0	4.6	2.9	2.8	37	46	51	48	79	75	77
2	17	100	3.7	3.8	3.7	3.1	33	33	36	245	70	70	73
6	33	137	2.3	3.5	4.2	3.7	35	36	35	112	69	65	67
2.9	8.0	15.0	0.27	0.27	0.24	0.32	1.4	1.6	1.7	15–245	4.8	3.1	2.9
			+1.2		−0.5								
			0.19		0.19								
			<0.01		<0.05								

§ PV: plasma volume in ml/kg ideal body wt.
‖ RBC mass: red blood cell mass in ml/kg ideal body wt.
¶ ↓Na⁺; ↑Na⁺: measurements made on a restricted and unrestricted sodium intake, respectively.

TABLE II

Summary of Changes in Renal Function after Drug-Induced Diuresis Unaccompanied and Accompanied by Saline Infusion in 15 Patients with Cirrhosis and Ascites

Patient	Diuretic drugs*	Diuretic period without saline	Diuretic period with saline	Normal saline infused	Body wt‡			SUN			Serum creatinine			25 hr creatinine clearance		
					A	B	C	A	B	C	A	B	C	A	B	C
		days	*days*	*liters*	*kg*			*mg/100 ml*			*mg/100 ml*			*ml/min*		
L. G.	EA, S	15	5	27	85	65½	74	12	36	13	0.9	1.8	1.0	69	26	66
M. L.	EA, S	8	7	34	61	50	55	11	38	19	1.1	1.8	1.3	40	27	43
H. M.	EA, T	7	3	20	70½	63	68	21	41	19	1.8	1.6	1.0	52	56	104
S. E.	EA, T	7	3	17	68½	63	61½	43	100	45	1.4	2.3	1.1	34	20	49
F. V.	EA, T	10	3	15	55	52	54½	14	36	12	0.9	1.5	0.7	73	62	94
J. M.	EA, T	12	5	8	70½	65	69	8	31	13	0.7	1.4	0.8	93	44	104
E. W.	EA, MK 870	20	5	16	57	51	55½	28	60	18	0.8	1.8	1.4	77	35	47
T. B.	EA, MK 870	8	5	27	71	61½	72½	37	60	47	1.3	2.0	1.5	43	24	34
G. P.	F, S	8	3	11	51	45	48½	9	22	11	1.3	1.5	0.9	41	35	68
L. S.	F, S	7	5	19	102	86½	88	12	24	17	0.8	1.6	1.4	78	40	61
S. T.	F, S	7	6	23	61	52	56	22	35	14	1.1	1.4	1.2	57	53	72
B. D.	F, S	10	5	20	65	54½	55	22	35	25	1.2	1.8	1.5	49	37	51
S. L.	F, S	10	5	19	81	65	68	15	27	16	0.8	1.7	1.3	77	34	48
J. S.§	HC, T	9	3	14	85	80½	92½	11	20	10	0.8	0.9	0.7	112	97	111
W. C.	HC, T	6	3	16	58½	51	54½	15	22	11	0.9	1.3	0.9	65	63	65
Mean ±SE		10± 1.0	4± 0.5	19± 1.7	70± 3.6	60± 3.5	65± 3.3	19± 2.7	38± 5.5	19± 3.0	1.1± 0.08	1.6± 0.08	1.1± 0.07	64± 5.6	44± 5.2	68± 6.3
Mean difference ±SE						−9 ±1.2	+4 ±0.8		+20 ±2.9	−19 ±3.5		+0.57 ±0.09	−0.51 ±0.07		−20 ±4.5	+24 ±4.1
P value						<0.01	<0.01		<0.01	<0.01		<0.01	<0.01		<0.01	<0.01

* EA = ethacrynic acid; S = spironolactone; F = furosemide; HC = hydrochlorothiazide; T = triamterene; MK 870 (Amiloride HCl).
‡ A = before diuresis; B = at the end of diuresis unaccompanied by saline infusion; C = at the end of diuresis accompanied by saline infusion.
§ This patient had ascites after an end-to-side portacaval shunt.

serum albumin concentration were also measured before and after diuresis accompanied by albumin infusions.

RESULTS

Table I summarizes the changes occurring in wedged hepatic vein pressure, inferior vena cava pressure, plasma volume, red cell mass, 24 hr urine sodium excretion, creatinine clearance, and serum protein concentration after the spontaneous loss of ascites in 10 patients with chronic alcoholic liver disease. Also included in the table are the changes in: (*a*) whole blood volume, calculated as the sum of the red cell mass measured with ^{51}Cr-labeled autologous red cells and the plasma volume measured independently with albumin-^{131}I while each patient was on a sodium-restricted diet; (*b*) peripheral venous hematocrit; (*c*) serum creatinine concentration; (*d*) body weight; and (*e*) plasma volume after resumption of a diet unrestricted in sodium. The approximate

TABLE III

Changes in Renal Function and Plasma Volume during Drug-Induced Diuresis Accompanied by Albumin Infusion

Patient	Diuresis unaccompanied by albumin infusion: Diuretics*	Wt loss	Days	SUN	Serum creatinine	Diuresis accompanied by albumin infusion: Diuretics*	Wt loss
		kg		*mg/100 ml*	*mg/100 ml*		*kg*
R. R.	EA, S	65 → 60	8	14 → 50	0.9 → 1.6	EA, S	68 → 63
G. J.	EA, MK 870	79 → 70	19	25 → 85	1.0 → 2.4	EA, MK 870	76 → 72
N. C.	F, S	54 → 49	14	31 → 77	1.1 → 2.1	EA, T	53 → 49
R. S.	HC, MK 870	88 → 83	7	15 → 45	0.8 → 2.0	EA, MK 870	85 → 78
B. H.	HC, S	60 → 51	15	11 → 21	— → 1.1	EA, S	60 → 53

* See footnote of Table I.
‡ The urine urea nitrogen excretion before diuresis represents the average of two 24 hr urine collections; the value during diuresis represents the average 24 hr excretion during the period of diuresis accompanied by a daily infusion of 12.5 g salt-poor albumin.

number of days from the time initial measurements were made to the time it was apparent that the tendency to ascites formation was lost is listed. By the method of paired comparison, utilizing the Student t test (15), there were no statistically significant mean changes in wedged hepatic vein pressure, whole blood volume, plasma volume, and venous hematocrit. Mean red cell mass rose from 22 ±1.1[2] ml/kg to 26 ±0.9 ml/kg, and the mean rise was statistically significant ($P < 0.01$). Mean creatinine clearance rose from 80 ±10.1 ml/min to 96 ±5.2 ml/min, and the mean rise was probably significant ($P = 0.06$). However, there was no change in serum creatinine concentration. There was a slight increase in mean plasma volume after resumption of a diet unrestricted in sodium, but this increase was not statistically significant. Mean serum albumin concentration rose and mean serum globulin concentration fell, and these changes were statistically significant.

Table II lists the diuretic drugs given to 15 patients, the periods of diuresis, the number of liters of saline given, and the changes in body weight, SUN, serum creatinine, and creatinine clearance, during diuresis unaccompanied and accompanied by saline administration. During infusion of saline while continuing administration of the same diuretic drugs there was a reversal in the mean rises in SUN and serum creatinine, and the mean fall in creatinine clearance, which occurred during diuresis unaccompanied by saline.

Table III summarizes the periods of drug-induced diuresis unaccompanied and accompanied by albumin administration in five patients with cirrhosis and ascites. Renal function worsened for each patient during drug-induced diuresis accompanied by albumin infusion despite a rising plasma volume in all but one patient (B. H.). Serum albumin concentration changed little, if at all. A rise in SUN due to increased synthesis of urea from catabolism of infused albumin, rather than from reduction in glomerular filtration rate, was excluded not only by a concomitant decrease in measured creatinine clearance but also by the absence of an appreciable increase in urine urea nitrogen in any patient.

[2] SEM. All subsequent variance will be SEM.

DISCUSSION

Evidence against a decreased effective plasma volume as the cause of renal sodium retention and a spontaneous reduction in glomerular filtration rate. Effective plasma volume is defined as the total plasma volume minus the plasma volume in the portal circulation. Current theory holds that the elevation of total plasma volume in patients with cirrhosis and ascites is due to portal hypertension with expansion of the splanchnic vascular bed (8). As ascites forms from the splanchnic vasculature, including the liver, there is a reduction in total and effective plasma volume (11, 12). Because the splanchnic vascular bed remains expanded, however, the reduction in effective plasma volume is undetectable by measurements of total plasma volume which are still above normal (1–8). If this theory is correct, there should be a rise in the total plasma volume in the nonascitic phase of cirrhosis as compared to the ascitic phase.

To determine whether any possible changes in total plasma volume were due to simultaneous changes in variables other than a spontaneous loss of ascites, red cell mass and serum protein concentration were measured. Furthermore, comparative measurements of total plasma volume were made on an identical sodium restricted diet, so that changes in volume could not be accounted for by changes in dietary sodium.

Of crucial importance in testing whether or not *effective* plasma volume would change with the spontaneous loss of ascites would be knowledge of portal hypertension in the ascitic and nonascitic phase of cirrhosis. If portal hypertension decreased with the spontaneous

in Five Patients with Cirrhosis and Ascites Who Previously Exhibited Diuretic-Induced Renal Insufficiency

Diuresis accompanied by albumin infusion						
Days	SUN	Serum creatinine	24 hr creatinine clearance	Plasma volume	Mean 24 hr urine urea nitrogen‡	Serum albumin
	mg/100 ml	*mg/100 ml*	*ml/min*	*ml/kg*	*g*	*g/100 ml*
5	14 → 42	1.0 → 1.8	78 → 57	61 → 67	8.8 → 6.5	2.9 → 3.8
8	34 → 58	1.4 → 2.2	50 → 32	66 → 71	5.0 → 3.8	3.6 → 3.5
7	52 → 110	1.7 → 2.6	20 → 12	28 → 34	5.4 → 2.4	5.2 → 4.5
5	16 → 28	1.0 → 1.6	70 → 33	52 → 55	4.4 → 3.4	1.7 → 2.5
5	15 → 34	0.7 → 1.4	108 → 51	66 → 59	8.0 → 8.7	2.9 → 3.4

loss of ascites, one could argue that a failure of total plasma volume to increase could be due to shrinkage of the portal plasma volume together simultaneously with an increase in effective plasma volume. If, on the other hand, portal hypertension remained constant, this would provide assurance that portal plasma volume was remaining constant. Failure to find an increase in total plasma volume under this condition would be evidence against an increase in effective plasma volume with the spontaneous loss of ascites.

In the present study, both red cell mass and serum albumin concentration increased when patients with chronic alcoholic liver disease improved to the point where ascites left spontaneously. It could be argued that the rise in red cell mass decreased the tendency for plasma volume to increase as ascites left, because there is a well-known reciprocal relationship between plasma volume and red cell mass (16). The increase in red cell mass was small, however, and calculated whole blood volume did not rise statistically significantly as ascites left. The rise in serum albumin concentration and presumably plasma oncotic pressure could only be a force favoring the expansion of total plasma volume as ascites left. Failure of total plasma volume to rise under these circumstances, therefore, provides even stronger evidence against a decrease in plasma volume during the ascitic phase of cirrhosis than if serum albumin concentration remained constant.

Because mean wedged hepatic vein pressure remained constant,[8] it can be assumed that mean portal pressure, which it parallels closely in chronic alcoholic liver disease, remained constant as ascites left spontaneously. Portal plasma volume, therefore, presumably remained constant. Even if resistance to hepatic flow decreased with the loss of ascites, and hepatic blood flow increased to the point where portal pressure did not fall, there is no reason to feel that portal plasma volume would fall under these circumstances. Hepatic blood flow was not measured in the present study because of poor hepatic extraction of Indocyanine green in patients with severe liver disease. Moreno et al., however, have made direct measurements of portal blood flow in an ascitic and a nonascitic group of patients with cirrhosis (19). Although there was an increase in mean hepatic blood flow in the nonascitic group as compared to the ascitic group (7.4 ±5.3 (SD) ml/min per kg vs. 4.9 ±5.3 (SD) ml/min per kg) the difference was small when compared to normal (20.9 ±4.1 (SD) ml/min per kg). Confirming the results of wedged hepatic vein pressure measurements in the present study, these workers did not find any difference in directly measured portal pressure in these two groups.

It is possible that blood pooled in the lower extremities was released to the remainder of the circulation when ascites was no longer compressing the inferior vena cava (18). Even if portal volume failed to contract, a portion of extremity blood might have shifted to the remainder of the circulation without a measurable change in total plasma volume. In our study we did not find any relationship between the magnitude of fall of inferior vena cava pressure and the rise in GFR. This suggests that GFR is independent of any sequestration of blood in the lower extremities that might occur due to the pressure of ascites on the inferior vena cava. Furthermore, it seems reasonable that renal sodium retention and a reduction in GFR either antedate or are coincident with the earliest formation of ascites, i.e., before ascites pressure builds up to the point of sequestering blood in the lower extremities.

In summary, failure of total plasma volume to rise with the spontaneous loss of ascites, as portal pressure remained constant, dietary sodium intake remained constant, red cell mass rose only slightly, and serum albumin concentration rose, is evidence that effective plasma volume is not decreased during the ascitic phase of cirrhosis. It follows that both renal sodium retention and a reduction in glomerular filtration rate that are found during the ascitic phase of cirrhosis cannot be explained by a decrease in effective plasma volume.

Evidence against a decrease in effective plasma volume as the cause of a reduced glomerular filtration rate during drug-induced diuresis. In the past we have considered a fall in GFR during diuresis to be a reflection of a reduction in effective plasma volume as the entire plasma volume contracts during diuresis (9). In the present study, however, total plasma volume was increased in four out of five patients receiving intravenous albumin while GFR fell during diuresis, making it highly unlikely that the effective plasma volume could be shrinking simultaneously. The only portion of the circulating plasma volume that would theoretically have to fall as ascites is disappearing during combined albumin infusion and drug-induced natriuresis is the portal plasma volume which is in equilibrium with the pool of ascites. Decreasing the effective volume while increasing the portal volume would not allow ascites to be removed from the body. That an increase in oncotic pressure from albumin infusion tended to retard GFR as plasma volume was increased during drug-induced natriuresis, thus cancelling any improvement in glomerular filtration rate brought about by the expanding effect of albumin on effective plasma volume, is unlikely

[8] We feel that wedged hepatic vein pressure should be expressed as the difference between absolute wedged pressure and inferior vena cava pressure, because of a uniform effect of ascites pressure on the inferior vena cava and portal vein. This belief has been corroborated by parallel falls in inferior vena cava and wedged hepatic vein pressure with paracentesis (17, 18).

because there was no substantial rise in serum albumin concentration in any patient.

Reversal of the reduction in GFR occurring during drug-induced diuresis in our patients, by administering saline intravenously while continuing the same diuretic drugs, excludes nephrotoxicity of these drugs as the cause of the renal insufficiency. If these drugs were nephrotoxic, one would not expect serum creatinine or SUN to fall as long as the drugs continued to be administered and thereby exert a potential nephrotoxic effect. Because reversal of the reduction in GFR occurred irrespective of which of a variety of diuretic drugs was used, it seems safe to conclude that all of the currently used diuretic drugs may induce GFR depression in cirrhosis, but none is nephrotoxic per se.

Conclusions. The cause for both renal sodium retention and a spontaneous and diuretic-induced reduction of GFR in cirrhosis should be regarded as unknown for the present. A decrease in effective plasma volume and drug nephrotoxicity seem to have been excluded by our study.

The ascites of cirrhosis might no longer be considered a cause of renal sodium retention, mediated through contraction of effective plasma volume. It may be more useful to regard ascites as a consequence of renal sodium retention superimposed on an expanded splanchnic plasma volume. This "overflow" theory of ascites would be akin to that for ascites occasionally accompanying heart failure.

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