Renal Circulation in Cirrhosis: Observations Based on Catheterization of the Renal Vein *

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In patients with cirrhosis and advanced hepatic failure, impairment of renal function with subsequent oliguria and azotemia may develop in the absence of primary renal disease; the prognosis when this complication occurs is grave (1–7). In recent reports, we have defined some of our experiences with patients in hepatic and renal failure (7, 8). The observations of others (3–5; 9–11) and ourselves (8) suggest that reduction in effective renal plasma flow (ERPF), developing particularly in patients with severe impairment of hepatic function and relatively resistant ascites, is the most important factor leading to renal complications.

Previous estimations of renal circulatory function (ERPF) in such patients have been based on para-aminohippurate (PAH) clearance alone (3, 9, 10), which may correlate poorly with renal plasma flow when renal function is severely impaired (12). In addition, the pathophysiologic mechanisms that may reduce renal hemodynamic function in hepatic disease have not been investigated comprehensively. Reductions in "effective" blood volume (2, 4, 13), peripheral vascular resistance (6), or arterial blood pressure (1, 3, 6) have been postulated in this regard.

The purposes of the present study were to determine renal plasma flow in patients with cirrhosis and associated impairment of renal function and to report the results of simultaneous measurements of certain variables that may influence the renal circulation in such patients. These include assessments of cardiac output, arterial blood pressure, renal vein pressure, difference in oxygen content between systemic artery and renal vein, and renal extraction of PAH. In addition, glomerular filtration rate, effective renal plasma flow, systemic vascular resistance, and renal vascular resistance were determined.

Methods

Observations were made on 23 adult patients with cirrhosis. The diagnosis of cirrhosis was based on clinical and laboratory evidence and, when necessary (nine instances), was confirmed by histologic examination of hepatic tissue. Cirrhosis was associated with chronic alcoholism in 13 patients and was of uncertain etiology in the remainder. None had a history of prior renal disease or significant abnormalities on urinalysis. Patients with evidence of recent gastrointestinal bleeding, cardiac disease, arterial hypotension or hypertension, diabetes mellitus, or septicemia were not considered for the study.

Patients were assigned before the study to the following groups according to the presence of ascites and its response to therapy, as earlier work had shown that changes in renal function correlated significantly with these factors (8): Group I—no ascites or ascites responding promptly to dietary restriction of sodium and thiazide diuretics; 14 patients (seven females and seven males, ages 17 to 67 years; mean, 45 years). Group II—ascites resistant to dietary restriction of sodium and thiazide diuretics and requiring additional diuretic agents (glucocorticoids, spironolactone); nine patients (three females and six males, ages 17 to 78 years; mean, 56 years).

Two patients in group II (Cases 22 and 23) were azotemic (blood urea concentrations of 70 and 72 mg per 100 ml, respectively).

Both clinical and biochemical evidence suggested more severe liver disease in group II than in group I patients. With but one exception (Case 21), all of the group II patients had moderate to severe degrees of ascites at the time of the study. Seven group I patients had ascites,

but only of a mild or moderate degree. Two of the 14 group I patients and four of the nine group II patients had had previous episodes of hepatic precoma or coma. Serum albumin concentrations were less than 2.5 g per 100 ml in the minority (five) of group I and in the majority (seven) of group II patients; jaundice (total serum bilirubin concentration more than 3.5 mg per 100 ml) was present in four patients in group I and three in group II.

If prescribed previously, diuretics were discontinued at least 48 hours before the study. The patient fasted overnight, and all tests were performed while the patient was in the supine position with an indwelling catheter in the bladder. At least 500 ml of water was administered by mouth before the procedure. Additional fluid was given by vein as 5% solution of dextrose in water. The total water load ranged from 1,000 to 1,500 ml.

Transfemoral catheterization of the right renal vein was performed under fluoroscopic control by the Seldinger technic (14). The catheter tip was advanced as far as possible into the hilus of the kidney and then withdrawn to the point where free flow was obtained on aspiration. Since the oxygen content of renal venous blood is considerably higher than that of caval blood (15), the position of the catheter was checked by determinations of oxygen saturation of blood aspirated from the catheter through a cuvette oximeter before, during, and after the renal function studies. In 14 of 18 patients undergoing catheterization of the right renal vein, samples of blood were obtained simultaneously from the renal vein and either the radial or femoral artery for the determination of PAH extraction ratios. The oxygen content of the blood aspirated simultaneously from the right renal vein and the arterial site was measured by the method of Van Slyke and Neill (16). Pressures were recorded simultaneously via a needle in the artery and from the right renal vein or inferior vena cava by strain-gauge manometers. The zero reference point was the mid-chest level.

Clearances of inulin and PAH were determined in all patients according to the methods described by Smith (17) with the chemical modifications of Schreiner (18) and Smith and associates (19), respectively. After the oral and intravenous fluid load, priming and sustaining infusions of inulin and PAH were administered in 0.45% saline. Three or four clearance periods, each of 15 to 20 minutes, were carried out in each patient, and the mean value is reported. When urine flow rates were less than 3 ml per minute, the bladder was washed with sterile saline and emptied with air. Blood samples were aspirated simultaneously from the arterial site and the right renal vein 6 minutes before the midpoint of each clearance period for determination of inulin and PAH concentrations. Body surface area was based on body weight corrected for the weight of estimated ascites; all clearance values are corrected to a surface area of 1.73 m². The statistical significance of the results was the same for corrected and uncorrected data.

Cardiac output was determined by the indicator dilution technic immediately preceding the clearance periods and repeated, in most instances, during the clearance studies. Five mg of indocyanine green dye was injected into either the inferior or superior vena cava, and blood was sampled from the indwelling arterial needle through a densitometer. The results were calculated from the dye-dilution curve according to the method of Hamilton, Moore, Kinsman, and Spurling (20). Since individual values agreed closely, the mean value was reported when two or three estimations were made.

By using standard formulas, the following calculations were made: PAH extraction ratio (E_{PAH}) (21), renal plasma flow (RPF) (21), renal blood flow (RBF) (21), renal fraction of cardiac output (RFCO) (22), and (total) systemic vascular resistance (R_S) (23). Total renal vascular resistance (R_R) was calculated from the formula, $(Pa - Pv)/RBF \times 1,332$, where Pa is the mean arterial pressure in millimeters of Hg; Pv, the renal venous pressure in millimeters of Hg; and RBF is renal blood flow in milliliters per second corrected to 1.73 m² surface area.

Results

Inulin and PAH clearances (Table I). Patients with relatively resistant ascites (group II) had significantly lower inulin and PAH clearances than those without ascites or with ascites responding promptly to therapy (group I) ($p < 0.01$). PAH clearances were below normal in only three patients in group I, and inulin clearance was moderately reduced in one of these. In contrast, all group II patients exhibited moderate or severe reduction of PAH clearance, and inulin clearance was low in all but one.

The mean filtration fraction (F.F.) in group II was greater than that in group I (Table I). Elevated values were found in six of eight patients with resistant ascites tested (group II), but in only five of the 14 patients without ascites or with responsive ascites (group I).

Renal extraction of PAH (Table I). PAH extraction ratios were determined in 14 patients and were normal (> 0.85) or only slightly reduced (0.85 to 0.82) in all but two patients (Cases 8 and 19), both of whom had unusually low values (0.45 and 0.52, respectively). Mean values for the two groups were identical and subnormal (0.83) only because of an outstandingly low value in each group that did not affect the significance of the results. With exclusion of these values, the means were within the normal range (0.89 and 0.90, respectively).

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TABLE 1

Results of renal hemodynamic

Group and patient	Age	Sex	C_{PAH}†	C_{In}†	F.F.	E_{PAH}	RPF†	RBF†
	yrs		ml/min	ml/min		mean	ml/min	ml/min
Normal values (mean and SD or		F	592±153‡	109±13.5‡	0.194±0.039‡	0.85–0.95§ 0.905	650±150§	1,078±276§
range and mean)		M	654±163	124±25.8	0.192±0.035			
Group I								
1	43	F	624	124	0.21			
2	55	M	661	138	0.21	0.83	794	1,203
3	48	M	430	104	0.24	0.92	468	709
4	45	M	1,199	187	0.16	0.88	1,362	2,003
5	36	F	597	110	0.18			
6	56	F	631	118	0.19			
7	35	M	767	163	0.21			
8	67	M	301	73	0.24	0.45	673	935
9	60	F	579	144	0.27			
10	22	F	526	98	0.19	0.88	600	857
11	50	M	492	113	0.23	0.92	537	976
12	52	M	467	108	0.23	0.93	502	772
13	38	F	802	145	0.18	0.85	944	1,358
14	17	F	717	109	0.15			
Mean			628	124	0.21	0.83	735	1,102
Group II								
15	58	F	329	94	0.29	0.90	365	503
16	57	M	334	69	0.21	0.90	372	531
17	78	M	296	83	0.28	0.95	312	480
18	65	M	246	68	0.28			
19	67	M	133	35	0.26	0.52	256	388
20	58	F	277					
21	17	M	336	103	0.30			
22	69	F	174	35	0.20	0.82	213	288
23	39	M	243	60	0.25	0.91	266	443
Mean			263	68	0.26	0.83	297	439
Significance of difference between groups I and II			p<0.01	p<0.01	p<0.01		p<0.01	p<0.01

* Abbreviations: C_{PAH}, para-aminohippurate clearance; C_{In}, inulin clearance; F.F., filtration fraction; E_{PAH}, para-aminohippurate extraction ratio; RPF, renal plasma flow; RBF, renal blood flow; R_S (total) systemic vascular resistance; and R_R, renal vascular resistance.

† Corrected to 1.73 m².

Renal plasma flow[1] (*Table I*). The mean (total) renal plasma flow was normal in group I, but significantly lower in group II (p < 0.01); values for patients in group I exceeded those in group II without exception (Table I). Renal plasma flow values were questionably reduced in one group I patient; another (Case 4) had an unusally high value, 1,362 ml per minute. Exclusion of the latter value lowers the mean from 735 to 645 ml per minute but does not alter the significance of the difference between the two groups. Renal plasma flow was reduced from 26 to 57%

[1] Corrected to 1.73 m² surface area.

below the lower limit of normal in all patients in group II.

Renal vein and central venous pressure (*Table I*). The mean renal vein pressure was higher in group II than in group I, and the difference was statistically significant (p < 0.02). Four of nine patients with resistant ascites (group II) had pressures exceeding any in patients without ascites or with responsive ascites (group I). Renal vein pressures were elevated in one patient in group I and in four in group II.

Central venous pressures, as measured in the superior vena cava or the supradiaphragmatic

TABLE I

*studies in cirrhosis**

| Cardiac output | | Cardiac index | Rs | RR | Arterial-renal vein O₂ difference | Pressure | |
Renal fraction	L/min					Arterial (mean)	Renal vein
%	L/min	L/min/m²	dyne-sec-cm⁻⁵	dyne-sec-cm⁻⁵	vol/100 ml	mm Hg	mm Hg
17.5±4.68§	4.4–8.9‖	2.5–5.3‖	745–1,570‖	4,000–10,000¶	1.09–1.87**	75–110‖	10–14.6
	6.6	3.5	1,130	6,500	1.42	91	11.7††
	8.7	5.7	533			65	
15.9	8.9	4.4	703	5,263	1.8	88	7.0
14.6	5.3	2.9	1,184	8,805	2.0	86	8.0
27.3	8.2	4.2	817	3,290	1.7	89	6.5
	5.9	4.0	1,063		1.8	81	9.0
	6.4	5.0	786			70	
	9.1	4.6					
18.6	5.3	2.9	1,479	8,197	1.2	108	12.0
	6.0	3.5	663			80	
11.7	6.2	4.2	1,034	7,079	2.1	84	8.0
23.5	4.8	2.4	1,612	7,763	1.2	103	8.0
8.5	9.2	5.3	689	8,209	1.4	86	6.5
13.0	8.9	5.9	655	4,067	1.7	84	15.0
	8.1	5.0					
16.6	7.2	4.3	935	6,584	1.7	85	8.9
6.7	7.7	4.4	626	9,514	1.3	70	10.0
10.6	5.3	2.9	987	8,276	1.8	72	16.5
11.6	3.9	2.4	1,317	10,656	1.2	78	14.0
	5.4	2.8	1,223			88	18.0
9.3	4.5	2.4	1,772	18,300	1.7	108	19.0
	5.3	3.8	1,292			88	7.0
	4.1	2.6	1,305			78	11.0
5.2	5.6	3.2	826	15,540		66	10.0
8.0	5.5	3.2	970	11,880	2.5	89	23.0
8.6	5.3	3.1	1,146	12,364	1.7	82	14.3
p<0.02	p<0.01	p<0.01	p=0.18	p<0.01	p=0.85	p=0.65	p<0.02

‡-†† Normal values reported by: ‡ Smith (21); § Bergström and associates (12); ‖ Barratt-Boyes and Wood (24); ¶ Lauson, Bradley, and Cournand (22); ** Cargill and Hickam (15); †† Maxwell, Breed, and Schwartz (25). Where normal values are expressed as the mean and standard deviation, ± 1 SD is taken as the normal range.

portion of the inferior vena cava, tended to be slightly lower than the corresponding renal vein pressures. However, the mean values for group I (7.2 mm Hg; SE ± 0.9) and group II (9.9 mm Hg; SE ± 1.8) were not significantly different.

Arterial-renal venous oxygen difference (Table I). The average difference in oxygen content between arterial and renal venous blood was identical (1.7 vol per 100 ml) in groups I and II. This value is normal, and, with but three exceptions (Cases 3, 10, and 23), the individual values are within the normal range.

Cardiac output and cardiac index (Table I).

The mean cardiac output was higher in group I than in group II, and the difference was statistically significant (p < 0.01). Both values, however, were within the range of normal. Although cardiac outputs tended to be high normal in group I and low normal in group II, the variation of either group of values from the normal is of doubtful significance. Correction of the cardiac output for body surface area did not alter the statistical significance of the results (Table I). The mean values of cardiac indexes for both groups were within the normal range, and neither group differed significantly from the normal.
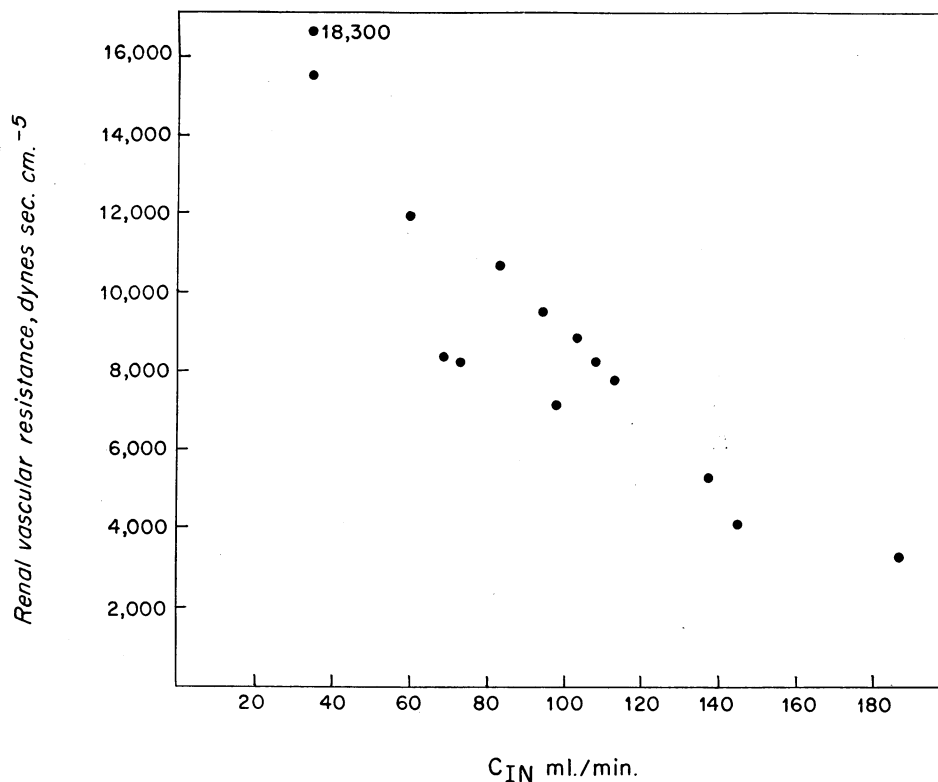
FIG. 1. COMPARISON OF RENAL VASCULAR RESISTANCE AND INULIN CLEARANCE IN PATIENTS
WITH CIRRHOSIS.

Renal fraction of cardiac output (Table I). The mean renal fraction of cardiac output was significantly higher in group I than in group II patients (p < 0.02) (Table I). Overlap between the two groups occurred in only one instance. Two patients in group I had values above and two, below the range of normal; all patients in group II had subnormal values.

Systemic vascular resistance (Table I). Mean values for systemic vascular resistance (R_S) were not significantly different in the two groups and were within the normal range. Five of 12 group I patients had R_S values below the normal range, whereas this occurred in only one group II patient (Case 15).

Renal vascular resistance (Table I). Since renal blood flow was lower in group II than in group I and the mean arterial pressures were similar in the two groups (Table I), the mean total renal vascular resistance (R_R) was higher in group II. The difference was highly significant (p < 0.01). Only one group II patient (Case 16) had a value below the highest value in group

I. With the exception of one subnormal value (Case 4), all group I patients had R_R values within the range of normal. In contrast, four of the six patients tested in group II had elevated values. Mean arterial pressures were similar in the two groups, both with regard to average values and ranges.

Comparison of individual R_R and inulin clearance values revealed a striking inverse correlation (Figure 1) as would be anticipated. Other parameters, however, including cardiac output and renal vein pressure, which were significantly different in the two groups, failed to show a significant relationship when compared individually with inulin clearance and renal plasma flow.

Discussion

Renal extraction of PAH was normal or only slightly reduced in the majority of patients in both groups. This, together with the reduced clearances of inulin and PAH measured in those with resistant ascites, confirms previous impressions that the disorder of renal function in some

patients with hepatic failure is primarily due to diminution of renal plasma flow (3, 5, 26). Several factors that might influence renal circulation were therefore considered.

The normal or only slightly reduced extraction ratios in both groups of patients militate against significant arteriovenous shunting of blood within the kidney similar to that occurring elsewhere in the body in cirrhosis (27–29). The normal arterial-renal venous oxygen differences support this, but the range of values was wide and the method relatively insensitive. Renal vein pressures were usually higher in patients with impairment of renal function, although seldom elevated far above the normal range. The degree of elevation of renal vein pressure appears insufficient alone to account for the reduction of renal plasma flow, since much more substantial increments produce less significant reductions of renal hemodynamic function in animals (30–31) and man (25). It has been suggested that the increased renal vein pressure secondary to the presence of ascites (32) or abdominal compression (33) causes reduction of glomerular filtration rate and effective renal plasma flow in man, but we have been unable to influence these measurements by the removal of ascites (8), and studies in dogs with experimentally induced ascites have yielded similar conclusions (34).

Reductions in cardiac output, peripheral vascular resistance, and arterial blood pressure (1, 3, 6) have been suggested as causes of renal failure in cirrhosis. Lancestremere and his colleagues (35) found that the cardiac output was normal or elevated under such circumstances, and our results showed that the cardiac output was usually within the normal range. There could have been a small reduction of doubtful relevance from previous values, however, as higher measurements were obtained in group I patients. Despite the normal mean cardiac output in both of our groups of patients, the renal fraction of cardiac output was significantly lower in those with impaired renal function. Diversion of a greater than normal proportion of the cardiac output to nonrenal areas is therefore implied, but no attempt was made to quantitate blood flow to other regions. Certainly, there was no significant difference between the two groups of patients with regard to mean arterial blood pressure or systemic vascular resistance. As a low systemic vascular resistance and an increase in the peripheral circulation (28, 36) have been reported in patients with cirrhosis, however, such changes in group II patients could have been masked by the contribution of elevated renal vascular resistance to the total systemic vascular resistance.

Total renal vascular resistance was significantly greater in patients with the greater impairment of renal hemodynamic function (group II) than in others (group I); this increase in resistance reflects a reduction of renal blood flow without a concomitant fall in mean arterial pressure. This increase in resistance offered by the renal vasculature, therefore, could account for the diminished total renal plasma flow and the low renal fraction of the cardiac output. Whether such a change represents a causal mechanism for the renal circulatory changes or a compensatory response to other circulatory alterations is uncertain. Similarly, the site of increased resistance within the renal vasculature, together with its possible relationship to factors more directly associated with hepatic disease, cannot be specified. Failure of inactivation or the production of a substance affecting the renal vessels as a result of hepatic failure are obvious considerations. Alternatively, Onnis, Shumacker, and Bounous (37, 38) demonstrated a dramatic reduction of renal blood flow after occlusion of the portal vein, hepatic artery, or celiac axis in dogs. As this effect was abolished by prior sympathectomy and splanchnicectomy, reflex renal vasoconstriction secondary to interference with the hepatic circulation was implicated as a cause of the diminished renal blood flow. In addition, renal circulatory failure in cirrhosis occurs particularly in patients with relatively resistant ascites, and elevated plasma angiotensinase activity has been found in patients with hepatic disease (39, 40). Interrelationships between the renin-angiotensin-aldosterone system and increased plasma angiotensinase activity or renal perfusion have been postulated, but are as yet indeterminate (41, 42).

Summary

Studies of the renal circulation were carried out in patients with cirrhosis and varying degrees of hepatic decompensation. Those with relatively resistant ascites were found to have a

disorder of the renal circulation characterized by a reduced renal plasma flow despite normal cardiac output, indicating diversion of a greater than normal proportion of the cardiac output to non-renal areas. Increased total renal vascular resistance in this group of patients suggested renal vasoconstriction as the cause of the diminished renal plasma flow.

Acknowledgment

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