JCI The Journal of Clinical Investigation

Amendment history:
- Errata (April 1964)

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J Clin Invest. 1964;43(2):258-266. https://doi.org/10.1172/JCI104910.

Research Article

Journal of Clinical Investigation
Vol. 43, No. 2, 1964

On the Concentrating Defect in Cirrhosis of the Liver *

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The capacity of patients with cirrhosis of the liver to produce a dilute urine after a water load has been extensively investigated (1, 2). The concentrating ability of these patients has not been carefully studied, although the assumption has been made that a defect exists (1, 3).

The present studies describe the characteristics of the concentrating system in patients with cirrhosis and attempt to clarify the mechanisms involved in any existing defect.

Methods

Twenty-seven patients with cirrhosis of the liver of varying severity associated with chronic alcoholism and 17 patients with other chronic diseases were studied. Each patient was receiving at least 75 g of dietary protein and at least 1 g of dietary sodium per day. None gave a history of renal disease, and all had normal urinalysis, nonprotein nitrogen, and serum creatinine. No patients above the age of 65 were included. Except for the absence of azotemia or intrinsic renal disease, the cirrhotics represented a wide range of patients with this disease. The mean age of cirrhotics was 50 and ranged from 35 to 62 years. The degree of ascites ranged from no apparent ascites (seven patients) to massive ascites (three patients) and included varying degrees of protein depletion as estimated by degree of muscle wasting. The mean age of the 17 chronically ill patients without cirrhosis was 49 and ranged from 38 to 58 years, and they represented the only noncirrhotic patients in the medical service (180 beds) at a given time who satisfied the above criteria for inclusion in the study.

The degree of ascites and degree of muscle wasting were estimated in each cirrhotic by a scale of 0 to ++++. Age and sex were recorded.

1) Special studies were carried out in nine patients with cirrhosis to evaluate and characterize the maximal concentrating ability (U_{max}). These studies included measurement of urine osmolality (U_{osm}) starting at 14 hours after the last oral intake and 10 hours after 5 U of vasopressin in oil intramuscularly. Urine samples were obtained intermittently until a last sample was obtained after 21 to 25 hours of dehydration.

2) Volume and urea, ammonia, sodium, and potassium concentrations of U_{max} urines were measured in 11 cirrhotics. In other patients urine sodium excretion was recorded as 0 to ++++ based on the approximate percentage of the oral sodium intake excreted.

3) U_{max} after 16 hours of dehydration and 5 U of vasopressin tannate in oil was determined in the 17 patients with chronic disease other than cirrhosis. In eight of these patients selected at random, urine volume and urea, ammonia, sodium, and potassium concentrations were also determined.

4) In 16 cirrhotics, U_{max}, negative free-water clearance ($T^c_{H_2O}$), clearance of inulin (C_{In}) (four patients), or clearance of mannitol (C_{Man}) (nine patients), serum sodium, and serum potassium were measured. U_{max} was obtained after 16 hours of dehydration and 5 U of vasopressin tannate in oil. $T^c_{H_2O}$ was then determined by inducing osmotic diuresis with a rapid infusion of 10% mannitol containing approximately 200 mU of aqueous vasopressin per hour after a priming solution of inulin, or mannitol, or both, and aqueous vasopressin. At least three collection periods were obtained for measurements of C_{In} and C_{Man}.

5) Since a defect in U_{max} with normal $T^c_{H_2O}$ was noted in many patients, further studies were done on six of the above patients, and four normal healthy males, eating normal diets, as follows: after maximal osmotic diuresis was obtained, as described above, iv mannitol was stopped, and U_{osm} was determined as osmolar clearance (C_{osm}) fell.

Eight of the 16 patients were studied while on a metabolic ward where they received 2 g of dietary sodium each day. The others were patients receiving varying amounts of dietary sodium (> 1 g) on the regular medical ward.

Sodium and potassium concentrations were determined with a flame photometer.[1] Urine and plasma osmolality were determined with a cryoscopic osmometer.[2] Inulin was determined by the resorcinol method for fructose

* Submitted for publication August 27, 1963; accepted October 17, 1963.

† This investigation was carried out during tenure as a Clinical Pharmacology Trainee and was supported by grants from the U. S. Public Health Service (H-4789, H-2324, and A-2334), and by gifts from G. D. Searle Co., Chicago, Ill.

[1] Baird Associates, model DB-4, Cambridge, Mass.

[2] Fiske, model B, Bethel, Conn.

of Bacon and Bell (4) as modified by Higashi and Peters (5). Mannitol was determined by the method of Corcoran and Page (6). Urine urea and ammonia were determined in duplicate by a modification of the Van Slyke and Cullen method (7). C_{osm} was calculated from the formula $C_{osm} = (U_{osm}/P_{osm})\ V$. $T^c_{H_2O}$ was calculated from the formula $T^c_{H_2O} = C_{osm} - V$. (P_{osm} = serum osmolality; V = urine flow.)

Results

1) Data obtained from nine patients with cirrhosis indicated that dehydration beyond 16 hours did not contribute significantly to an increase in U_{max} (Table I). A mean difference of only 31 ± 11 mOsm per L (1 SE) or approximately 5% was obtained between urines voided after 21 to 25 hours of dehydration when compared with urines obtained after 16 hours of dehydration. The findings are consistent with data previously reported in hydropenic cirrhotics who demonstrated a decreased urine specific gravity and in whom dehydration beyond 16 hours did not produce a significant rise in specific gravity in any of the eight patients studied (8).

2) The mean U_{max} of 27 patients with cirrhosis obtained after 16 hours of dehydration was 651 ± 25 mOsm per L (1 SE). This value was significantly lower than the value of 812 ± 31 mOsm per L (Table II) obtained in noncirrhotics with chronic diseases ($p < 0.01$), and the value of 947 ± 25 mOsm per L previously reported in hospitalized patients without clinical evidence of renal disease (9). Although the noncirrhotic patients fulfilled the criteria of diet, age, and absence of evident renal disease, the patients studied had been, for the most part, ill for many months or years.

TABLE I

Urine osmolality (U_{osm}) during dehydration

Patient	U_{osm} 16-hr Dehydration	U_{osm} >21-hr Dehydration
	mOsm/L	
1	638	687
2	608	716*
3	648	634*
4	667	694*
5	679	680
6	488	507
7	686	694*
8	423	465*
Mean	605	636
1 SE	±32	±39

* Values represent at least 24 hours of dehydration.

TABLE II

Maximal urinary concentration (U_{max}) in noncirrhotics with chronic disease

	U_{max}	Age	Diagnosis
	mOsm/L		
1.	758	49	Cancer
2.	776	45	Cancer
3.	730	48	Cancer
4.	680	55	Diabetes
5.	780	58	Rheumatoid arthritis
6.	759	57	Chronic pulmonary disease
7.	1,000	42	Cancer
8.	720	57	Arteriosclerotic heart disease
9.	742	54	Rheumatoid arthritis
10.	790	38	Rheumatoid arthritis
11.	771	58	Rheumatoid arthritis
12.	893	43	Dermatitis
13.	1,003	56	Peripheral neuropathy
14.	1,103	35	Obesity
15.	700	43	Cancer
16.	909	49	Cancer
17.	667	57	Cancer
Mean	812	49	
SE	±31	±2	

3) The composition of U_{max} urines in 11 cirrhotics is shown in Table III. The urea concentration (U_{Urea}) ranged from 105 μmoles per ml to 370 μmoles per ml (mean = 255 ± 30). Total urea ($U_{Urea}V$) varied from 48 to 200 μmoles per minute (mean = 145 ± 20). The ratio of urea to nonurea solute varied from 19 to 68% (mean = 46 ± 5). The same values for eight noncirrhotics are given in Table IV. There were no statistically significant differences in urea or potassium excretion between the two groups. Urinary sodium concentration (U_{Na}) was significantly lower in cirrhotics ($p < 0.01$).

Neither U_{Urea} ($r = 0.483$), $U_{Urea}V$ ($r = 0.405$), nor percentage of urea per nonurea solute ($r = -0.278$) were significantly correlated with U_{max} in cirrhotics.

4) Table V summarizes the data in a group of 16 cirrhotics in whom more comprehensive studies were carried out. The mean U_{max} of this group was 688 ± 33 mOsm per L (1 SE), which is not significantly different from the U_{max} in the entire group of cirrhotics, but is significantly different ($p < 0.01$) from the patients with other chronic diseases.

The mean $T^c_{H_2O}$ for the 16 patients studied was

TABLE III

*Composition of maximal urinary concentration in cirrhotics**

Patient	U_{max}	Calculated U_{max}†	V	U_{Na}	U_K	U_{Urea}	U_{NH_4}	$U_{Urea}V$	Urea / Nonurea solute
	mOsm/L	*mOsm/L*	*ml/min*	*μEq/ml*	*μEq/ml*	*μmoles/ml*	*μEq/ml*	*μmoles/min*	%
1	687	641	0.6	83	67	279	31	167	45
2	716	641	0.5	35	46	417	31	209	68
3	465	424		13	59	232	24		28
4	634	598		139	42	172	32		43
9	728	737	0.6	32	142	333	28	200	19
10	470	428	0.5	8	34	290	27	145	65
11	535	537	0.5	152	54	105	10	53	48
12	578	528	0.5	29	107	226	15	113	43
13	618	642	0.4	118	82	120	23	48	65
14	460	407	0.7	1	56	265	14	185	54
15	790	784	0.5	69	112	370	36	185	29
Mean	607	578	0.53	62	73	255	25	145	46
SE	±35	±38	±0.02	+16	±10	±30	±3	±20	±5

* U_{max} = maximal urinary concentration; V = rate of urine flow; U_{Na} = urinary sodium concentration; U_K = urinary potassium concentration; U_{Urea} = urea concentration; U_{NH_4} = ammonium concentration; $U_{Urea}V$ = total urea.
† Urine osmolality calculated from the formula:

$$U_{osm} = (U_{Na} + U_K + U_{NH_4}) \times 2 + U_{Urea}.$$

4.8 ± 0.44 ml per minute (1 SE), which is not significantly different from the value of 5.1 ± 0.33 ml per minute obtained by Zak, Brun, and Smith (10) in normal subjects, despite the fact that the latter group was considerably younger than the group presented here.[3]

The mean glomerular filtration rate was 85 ± 9.8 ml per minute (1 SE), which is somewhat lower than the mean of 101 ± 3.8 ml per minute reported by Zak and associates (10).

Since protein depletion, potassium depletion, inadequate delivery of sodium to distal sites, age, and glomerular filtration rates are thought to affect the concentrating mechanism under some circumstances, associations involving estimates of these states were calculated and appear in Table VI. Despite the varying degrees of fluid retention and protein depletion neither U_{max} nor $T^c_{H_2O}$ was associated with degree of ascites, serum po-

[3] Values given by Zak and associates are corrected for surface area; however, recalculation to uncorrected values reveals no essential change in mean $T^c_{H_2O}$ (mean uncorrected = 5.0 ml per minute).

TABLE IV

*Composition of maximal urinary concentration in noncirrhotics**

Patient	U_{max}	Calculated U_{max}†	V	U_{Na}	U_K	U_{Urea}	U_{NH_4}	$U_{Urea}V$	Urea / Nonurea solute
	mOsm/L	*mOsm/L*	*ml/min*	*μEq/ml*	*μEq/ml*	*μmoles/ml*	*μEq/ml*	*μmoles/min*	%
1	758	688	0.2	50	40	430	39	86	63
2	776	744	0.4	142	26	330	39	132	44
3	730	702	0.3	77	68	318	47	95	45
4	680	644	0.3	68	87	240	47	72	38
5	780	681	0.8	150	60	121	26	97	18
6	759	649	0.7	184	60	109	22	76	17
7	1,000	1,014	0.3	202	138	294	20	46	28
8	720	733	0.7	136	86	239	25	90	33
9	742	699	0.8	158	76	177	27	141	25
Mean	772	728	0.5	130	71	251	32	93	35
SE	±30	±30	±0.8	±17.7	±10.7	±37	±3.5	±9.7	±5.3

* Abbreviations as in Table III.
† Urine osmolality calculated from the formula:

$$U_{osm} = (U_{Na} + U_K + U_{NH_4}) \times 2 + U_{Urea}.$$

TABLE V

*Combined data on the concentrating mechanism in sixteen cirrhotics**

Patient	Sex	Age	U_{max}	$T^c_{H_2O}$	GFR	Serum Na	Serum K	Degree of ascites	U_{Na}	Muscle wasting
			mOsm/L	*ml/min*	*ml/min*	*mEq/L*	*mEq/L*			
1	F	42	628	5.1		127	3.0	+	++	++
4†	M	60	744	4.9	139	138	4.2	++++	++++	+
5	M	51	679	8.3	112	139	4.5	0	++++	0
14	F	54	490	4.9	78	133	3.4	++	+	+++
16	F	49	700	1.7	40	142	5.0	++++	0	+++
17	F	41	619	2.4	51	141	3.8	++	0	++
18	F	43	409	3.7	78	144	4.1	++	++	+
19	M	39	853	5.4	86	142	4.1	0	+++	+
20	F	62	545	3.0	49	139	4.3	++	++	+
21	M	44	880	5.2	154	131	5.0	++	0	+
22	M	57	710	4.8	69	141	3.9	+	++++	0
23	M	60	680	5.5	108	133	3.9	+	+++	0
24	M	35	667	4.7	52	140	4.8	+	+++	+
25	F	55	728	6.4		138	4.0	0	+++	+
26	M	42	875	4.3		136	4.8	++++	0	++
27	M	54	794	7.0	87	144	5.2	0	+++	0
Mean		50	688	4.8	85	138	4.3			
SE			±33	±0.44	±9.8	±1.0	±0.11			

* U_{max} = maximal urinary concentration; $T^c_{H_2O}$ = negative free-water clearance; GFR = glomerular filtration rate; U_{Na} = urinary sodium excretion.
† Patient 4 was undergoing a spontaneous diuresis during this study.

tassium, muscle wasting, ability to excrete sodium, or serum sodium. Neither U_{max} ($r = +0.280$) nor $T^c_{H_2O}$ ($r = +0.126$) was significantly correlated with age. U_{max} was not significantly correlated with the glomerular filtration rate ($r = +0.470$), but $T^c_{H_2O}$ was ($r = +0.593$) ($p < 0.05$). As expected, there was a positive association between muscle wasting and degree of ascites ($p < 0.05$) and a negative association ($p < 0.01$) between degree of ascites and ability to excrete sodium. No significant correlation between U_{max} and $T^c_{H_2O}$ was found ($r = +0.315$).

5) In the four healthy males and in each patient with cirrhosis, straight lines were fitted to the values of $T^c_{H_2O}$ for each C_{osm} during the ascending portion of the $T^c_{H_2O}$ curve (C_{osm} rising)

TABLE VI

*Associations of clinical and laboratory findings in cirrhotic patients**

	Age	U_{max}	$T^c_{H_2O}$	Ascites	$U_{Na}V$	Muscle wasting	Serum sodium	GFR
U_{max}	0							
$T^c_{H_2O}$	0	0						
Ascites	0	0	0					
$U_{Na}V$	0	0	0	−−				
Muscle wasting	0	0	0	+	−			
Serum sodium	0	0	0	0	0	0		
GFR	0	0	+	0	0	0	0	
Serum potassium	0	0	0	0	0	0	0	0

* These data are based on 15 patients (except for GFR, which was obtained in 13 patients). Data were analyzed by correlation methods if they were scalar, otherwise by chi square. 0 = no association; + or −, positive or negative association at $p < 0.05$; −−, negative association at $p < 0.01$. U_{max} = maximal urinary concentration; $T^c_{H_2O}$ = negative free-water clearance; $U_{Na}V$ = urinary sodium excretion; GFR = glomerular filtration rate.

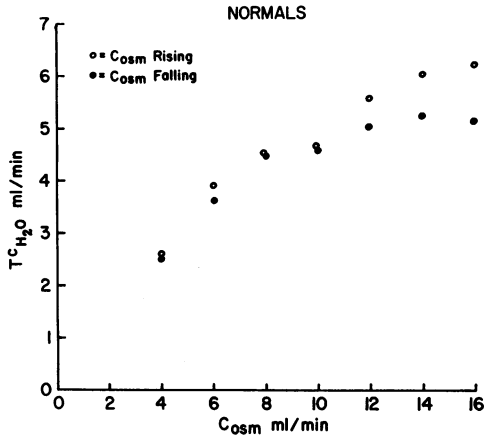

FIG. 1. GRAPH OF NEGATIVE FREE-WATER CLEARANCE ($T^c_{H_2O}$) VERSUS OSMOLAR CLEARANCE (C_{osm}) DURING OSMOTIC DIURESIS IN NORMAL SUBJECTS. All C_{osm} and corresponding $T^c_{H_2O}$ values are grouped about successive 2-ml increments in C_{osm} and represent mean values for the group.

by the method of least squares. Values of $T^c_{H_2O}$ obtained after the peak of osmotic diuresis (C_{osm} falling) were compared with expected values obtained from the calculated line.

To test the regularity of deviations of the descending points, the mean deviation was calculated and tested by *t*. In each normal subject there was no significant deviation from the calculated line, with most points in the descending portion of the curve falling directly on the calculated line.

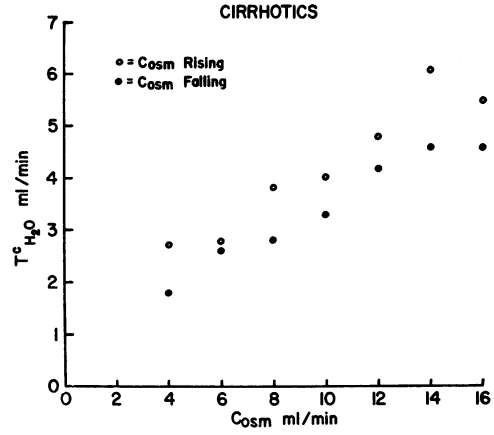

FIG. 2. GRAPH OF NEGATIVE FREE-WATER CLEARANCE ($T^c_{H_2O}$) VERSUS OSMOLAR CLEARANCE (C_{osm}) DURING OSMOTIC DIURESIS IN CIRRHOTIC SUBJECTS. All C_{osm} and corresponding $T^c_{H_2O}$ values are grouped about successive 2-ml increments in C_{osm} and represent mean values for the group.

TABLE VII

*A representative experiment measuring negative free-water clearance before and after the peak of osmotic diuresis in normal subjects**

	Vol	U_{osm}	C_{osm}	$T^c_{H_2O}$	P_{osm}
min	*ml/min*	*μOsm/ml*	*ml/min*	*ml/min*	*μOsm/ml*
0 to 95	0.8	865	2.3	1.5	
102 10% mannitol with aqueous vasopressin at 15 ml/min					
102 to 131	1.6	757	4.1	2.5	280
131 to 143	3.4	582	6.9	3.5	
143 to 152	4.3	563	8.6	4.3	
152 to 161	4.4	553	8.5	4.1	
161 to 170	5.5	542	10.4	4.9	
170 to 179	6.0	520	10.9	4.9	
179 to 192	8.0	496	12.9	4.9	
192 to 200	9.4	468	15.2	5.8	290
200 to 207	11.4	451	17.7	6.3	
Infusion stopped					
207 to 215	11.9	449	18.4	6.5	
215 to 225	10.3	453	16.1	5.8	
225 to 235	9.3	462	14.8	5.5	
235 to 245	7.9	472	13.1	5.2	
245 to 255	7.2	481	12.2	5.0	
255 to 265	7.0	488	12.0	5.0	
265 to 275	6.0	503	10.6	4.6	282
275 to 285	5.3	514	9.6	4.3	
285 to 295	4.6	543	8.8	4.2	
295 to 315	3.0	621	6.6	3.6	

* U_{osm} = urine osmolality; C_{osm} = osmolar clearance; $T^c_{H_2O}$ = negative free-water clearance; P_{osm} = plasma osmolality.

In each cirrhotic, however, the mean deviation was below the calculated line. In two cases the fall was of borderline significance ($p < 0.05$) and in one case highly significant ($p < 0.01$).

TABLE VIII

*A representative experiment measuring negative free-water clearance before and after the peak of osmotic diuresis in a cirrhotic**

Time	Vol	U_{osm}	C_{osm}	$T^c_{H_2O}$	P_{osm}
min	*ml/min*	*μOsm/ml*	*ml/min*	*ml/min*	*μOsm/ml*
0 to 52	0.5	728	1.2	0.7	283
91	Constant infusion 10% mannitol with aqueous vasopressin at 15 ml/min				
52 to 141	1.3	663	3.0	1.7	
141 to 159	1.9	598	4.0	2.1	290
159 to 174	4.6	557	8.8	4.2	
174 to 186	8.2	518	14.6	6.4	
186 to 195	9.4	500	15.7	6.3	300
195 to 225	13.9	432	20.5	6.6	
Infusion stopped					
225 to 236	13.0	404	17.5	4.5	
236 to 248	11.7	412	16.6	4.9	291
248 to 258	10.5	417	15.1	4.6	
258 to 269	8.0	425	11.7	3.7	
269 to 279	6.2	437	9.3	3.1	285
279 to 290	6.3	449	9.8	3.5	
290 to 322	4.5	483	7.6	3.1	
322 to 344	1.9	583	3.8	1.9	

* Subject no. 25. Abbreviations as in Table VII.

These findings are further illustrated by Figure 1, which shows the mean curves of $T^c_{H_2O}$ versus C_{osm} during osmotic diuresis, as C_{osm} is increasing and then as C_{osm} falls in four normal subjects, and Figure 2, which shows the same curves for cirrhotics. Except at high rates of C_{osm}, normal subjects were able to maintain their ability to conserve free water after the peak of diuresis (Table VII) when C_{osm} was falling, as shown by comparable $T^c_{H_2O}$ for a given C_{osm} at C_{osm} below 10 ml per minute (Figure 1). Cirrhotics did not improve water conservation after a mannitol infusion (Table VIII) and actually seemed to conserve water more poorly, as demonstrated by a mean $T^c_{H_2O}$ for the six patients, which was invariably lower for a given C_{osm} after the peak of osmotic diuresis (Figure 2).

Discussion

A defect in U_{max} clearly exists in patients with cirrhosis, as shown by a mean value of 651 mOsm per L obtained in this study for 27 patients, who were not rigidly salt restricted. Despite the low U_{max}, in the group studied, the mean $T^c_{H_2O}$ of 4.8 ml per minute, obtained in 16 patients, is comparable to the mean value for normal subjects reported by Zak and associates (10) and therefore is considered to be normal. The range of 1.7 to 8.3 ml per minute obtained in the present study was similar to the range of 1.5 to 7.4 ml per minute obtained in normal subjects, and the standard errors of the mean were comparable (0.44 and 0.33 ml per minute, respectively). The data of Zak and associates (10) show that a maximal $T^c_{H_2O}$ below 3.5 ml per minute occurred in 14% of the patients reported, thus indicating that such values are not necessarily "abnormally" low, but rather represent one end of the normal distribution of this measure of renal function. In the present studies a comparable group of cirrhotics (19%) exhibited a maximal $T^c_{H_2O}$ below 3.5 ml per minute.

The U_{max} in the group of cirrhotics presented was not correlated with sodium excretion, urea excretion, degree of ascites, muscle wasting, serum sodium, serum potassium, or glomerular filtration rate. The U_{max} defect does not appear to result from chronic illness per se, since a comparable group of chronically ill patients without cirrhosis exhibited a U_{max} that was significantly higher than the value for cirrhotics (though somewhat lower than normal). These data therefore suggest that the U_{max} defect is specific for the disease rather than directly related to any particular complication of the disease.

The existence of a defect in the ability to conserve water in cirrhotics is not surprising in view of the well-documented defect of free-water formation in some of these patients (1, 2). Many investigators have postulated a defective delivery of sodium to the ascending loop of Henle and distal tubule in some patients with cirrhosis (2, 11). Schedl and Bartter supported this thesis by demonstrating that a mannitol diuresis improved the ability of cirrhotics to form free water, presumably owing to increased delivery of sodium to distal sites (2).

Since the above postulate is consistent with current physiologic concepts and reinforced by experimental evidence, it is reasonable to ascribe a concentrating defect in these patients also to inadequate sodium delivery to distal sites. Furthermore, the normal $T^c_{H_2O}$ of these patients is compatible, since increased delivery during osmotic diuresis might provide the medullary interstitium with enough extra sodium to correct the pre-existing defect and produce a normal $T^c_{H_2O}$.

The data on $T^c_{H_2O}$ versus C_{osm} after the peak of osmotic diuresis (Figures 1 and 2) indicate that the above explanation is not sufficient. The ability of normal subjects studied to maintain $T^c_{H_2O}$ for a given C_{osm} shortly after the peak of osmotic diuresis is consistent with the findings in normal dogs (12). The data for cirrhotics indicate that water conservation is not improved, but is actually poorer after osmotic diuresis. This finding suggests that increased sodium delivery did not produce a fundamental correction of the defect that led to the decreased U_{max}. Furthermore, there appeared to be no shortage of sodium delivery in many of the patients, since they were excreting significant quantities of sodium in their urine each day. This finding also indicates that delivery of sodium to the distal nephron is not the only factor involved in water conservation in these patients. The normal $T^c_{H_2O}$ in these patients indicates that insensitivity to antidiuretic hormone (ADH) is not responsible for defective U_{max} and also indicates that a normal capacity to

reabsorb sodium exists in the ascending loop of Henle. A normal $T^c_{H_2O}$ is not consistent with the hypothesis that decreased urea excretion was responsible for the U_{max} defect, since subjects with this abnormality have a marked decrease in $T^c_{H_2O}$ (13). Furthermore, urea excretion was not abnormal in the present studies.

Increased body hydration and low total body potassium have been associated with defects in U_{max} (14–16). Although cirrhotics tend to have both, individuals with these entities also have decreased $T^c_{H_2O}$, which places them in a different category from the patients presented. Furthermore, neither U_{max} nor $T^c_{H_2O}$ was correlated with serum potassium, muscle wasting, or degree of ascites in the present studies.

The positive correlation of $T^c_{H_2O}$ with glomerular filtration rate is not surprising, since this correlation might well exist in normal subjects. The lack of correlation between U_{max} and glomerular filtration rate suggests that the latter was not primarily responsible for the U_{max} defect although it may contribute in some patients.

In cirrhosis a defect apparently exists in the ability to produce a maximal U_{osm}/P_{osm} ratio within the normal range. The capacity to maintain this abnormally low maximal U/P ratio is striking as illustrated in Patient 5, who lowered U_{osm} by only 94 mOsm per L (from 679 to 585) while going from a C_{osm} of 1.5 ml per minute to 16.5 ml per minute. This is in contrast to normal subjects who drop U_{osm} quickly as C_{osm} goes up (Figure 3) (17).

The co-existence of a defect in U_{max} and a normal $T^c_{H_2O}$ has been described in one other clinical disease, sickle-cell disease in children (18, 19). The authors in one article (18) speculate that the medullary circulation in these patients is a less efficient trap and more effectively removes solute and water so that medullary hypertonicity is decreased, but the capacity to remove an increased water load from the interstitium during solute diuresis is unimpaired. These authors ruled out anoxia, defective sodium transport, and capillary vascular occlusion as responsible, but were unable to shed light on the nature of the abnormality.

Perillie and Epstein have recently shown that erythrocytes containing S-hemoglobin become sickled when they are immersed in hyperosmotic solutions (20). They suggested that the hypertonic milieu of the renal medulla promotes sickling in patients with sickle-cell disease and that this phenomenon restricts medullary blood flow by increasing blood viscosity and affects sodium transport in the loop of Henle secondary to hypoxia.

One possible explanation of the data in cirrhotics also relates to the importance of the medullary circulation that acts as a countercurrent ex-

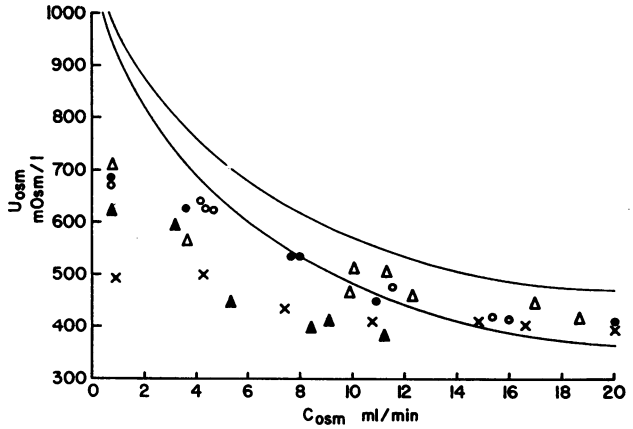

FIG. 3. GRAPH OF URINE OSMOLALITY (U_{osm}) VERSUS OSMOLAR CLEARANCE (C_{osm}) IN FIVE REPRESENTATIVE CIRRHOTIC AND NORMAL SUBJECTS. The symbols represent different patients with cirrhosis. The solid lines represent the range for normal subjects abstracted from the data of Rapoport, Brodsky, West, and Mackler (17) and Zak and associates (10).

changer. According to current thinking, increased rate of flow in the vasa recta would lead to less efficient trapping of sodium in the medulla and therefore less hypertonicity (21). Increased medullary blood flow could exist in cirrhotics in association with shunting of blood around the glomerular capillaries. This situation could exist in spite of a normal quantity of sodium being reabsorbed by the ascending loop of Henle. Vascular shunts have been demonstrated in cirrhotics and have been postulated to explain some of the frequent findings in this disease, such as spider nevi and clubbing (22).

If this is indeed the explanation for the U_{max} defect in cirrhosis, then one may explain the normal $T^c_{H_2O}$ either by postulating that a rapid mannitol infusion minimizes the effects of such shunts by decreasing circulation to the medulla, or by postulating that rapid medullary blood flow, while imposing restriction on the maximal U/P ratio, does not restrict free water reabsorption at high urine flow rates where a high U/P ratio is not required. The latter explanation seems more reasonable because of the data presented here which suggest that a mannitol infusion per se does not contribute to correction of the defect in water conservation which results in a low U_{max}. Furthermore, $T^c_{H_2O}$ formation is probably primarily dependent on simultaneous active sodium pumping in the ascending loop of Henle, limited only by a maximal U/P ratio at low flow rates and maximal $T^c_{H_2O}$ at high flow rates. Indeed, osmotic diuresis has been shown to increase rather than decrease medullary blood flow (21). If this is so, then a further increase in medullary circulation added to the postulated initial abnormally high flow in cirrhotics may explain the inability of these patients to recover their maximal ability to conserve water as rapidly as normal subjects after the peak of osmotic diuresis.

The lack of correlation between the characteristics of the concentrating system and the clinical status of patients with cirrhosis suggests that a fundamental abnormality of renal function exists in association with this disease. As is true with other complications of cirrhosis, this abnormality may be of varying severity in individual patients and apparently is not always correlated with the severity of the disease.

Summary

Most patients with cirrhosis of the liver who are not on marked dietary sodium restriction have a defect in maximal concentrating ability (U_{max}) but normal negative free-water clearance. A defective delivery of sodium to the distal nephron is not a sufficient explanation for the U_{max} defect. Increased medullary blood flow, possibly due to increased shunting of blood to the medulla, is postulated to explain the findings, since other causes for such a defect do not appear to be present.

Acknowledgments

We wish to thank Miss Ann Long and Mrs. Margaret Wilcox for supervising the care of the patients on the metabolic unit, Miss Sheila Dye for dietary supervision, and Dr. Hugo Muench for help in the statistical analysis of the data.

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