REVERSAL OF DIURNAL VARIATION IN RENAL FUNCTION IN CASES OF CIRRHOSIS WITH ASCITES [1, 2]

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The mechanism for control of diurnal rhythm of water and electrolyte excretion remains obscure, though the fact that such a cycle occurs was reported by Quincke (1) in 1877 who pointed out that urinary output was appreciably higher during the day in contrast to night. Campbell and Webster (2, 3) observed that the excretion of chlorides and urea was also higher during the day, though creatinine excretion remained more or less at the same level. Subsequent studies (Table I) by Kleitman (4), Simpson (5, 6), Norn (7), Manchester (8), Gerritzen (9), Brod (10), and Sirota, Baldwin, and Villarreal (11) confirmed the observations that urine flow and excretion of certain electrolytes decreased during the hours of deepest sleep in normal individuals.

This rhythm was not reversed when normal subjects slept in the daytime and took food and worked at night as reported by Campbell and Webster (2, 3), and confirmed in studies of a night watchman by Jores (12). Gerritzen (13) studied the effect of exposure of four subjects to artificial daylight during the night, and darkness during the day. In three subjects duplication of the rhythm in water and chloride excretion resulted, with two maxima occurring at noon and at midnight. In the fourth subject the rhythm was completely reversed. Borst and de Vries (14) have pointed out the difficulty in evaluating the effect of daylight and of waking on diurnal rhythm, though in some of their subjects the response to the stimulus of daylight was prompt. Jores (12) reported the relative difficulty in reversing a rhythm by a reversal of routine, and this was further supported by Joslings' (15) observation that a subject on a boat going from east to west showed a peak urinary excretion one hour earlier every day, the peak remaining at the same hour on local time. Addis and associates (16) reported nocturnal depression of endogenous creatinine clearances.

On the basis of U/P inulin ratios and creatinine clearance data, Sirota, Baldwin, and Villarreal (11) attributed the decrease in urine flow during sleep almost wholly to water reabsorption. The mechanisms of increased tubular reabsorption of water at night were not elucidated and significant diurnal variations in effective renal plasma flow were not noted (11).

Reports of a reversal of renal function (Table II) began with Wilson's (17) observation that the day and night rates of excretion of water and solids were approximately the same in the presence of debility, and especially so in cardiac or renal disease. Quincke (18) confirmed these observations several years later, noting that patients with heart or kidney disease often had a peak of diuresis during the night. Fishberg (19) attributed the nocturnal increase in urine flow in patients with nephritis and congestive heart failure to decreased renal venous pressure and increased cardiac output in the prone position. Subsequent work by Brod and Fejfar (20) and by Baldwin, Sirota, and Villarreal (21), employing clearance techniques, revealed an increased glomerular filtration rate and decreased tubular reabsorption of water during the hours of sleep in patients with congestive heart failure. In the absence of peripheral edema, or during active diuresis, no reversal of the diurnal pattern was observed (21). According to Brod and Fejfar (20), nocturia was not associated with an increase in cardiac output. Since nocturnal diuresis was always associated with an increase in

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[2] Reviewed in the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the authors are the result of their own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

TABLE I

Studies of diurnal variations of renal function in normal individuals

Investigator	Renal Functions Studied		
	No Diurnal Change	Nocturnal Depression Observed	Attributed to
(1) Quincke (1877)	—	Urine flow	—
(2,3) Campbell (1921-'22)	Creatinine excretion	Urine flow, excr. urea, Cl.	—
(4) Kleitman (1923)	Nitrogen or creatinine excr.	Urine flow, excr. of phosphates, acids and Cl	Decr. blood pressure.
(5,6) Simpson (1924,1926)	—	Urine flow, phosphate and Cl. excr., urine pH.	Acidosis of sleep with intracellular shift of chloride and water.
(7) Norn (1929)	—	Urine flow, excr. of Na., K., Cl.	Diminished activity
(8)* Manchester (1933)	Excr. of Ca., Mg., (Data on phosphate, sulfate, ammonia excr. & titratable acidity were equivocal).	Urine flow, excr. of Na., K., Cl.	Related to sleep
(9) Gerritzen (1940)	—	Urine flow, excr. urea, Cl.	Rhythmic organ function and position change.
(10) Brod (1946)	—	Urine flow, endog. creat. clear.	—
(11) Sirota (1950)	PAH clear.	Urine flow, inulin clear.	Variations in tubular reabsorption.
(14) Borst (1950)	Excr. urea, creatinine.	Urine flow, excr. Na., Cl., K.	Variations in tubular reabsorption.
(16) Addis (1951)	—	Endog. creat. clear.	Relaxation of vasc. tension with drop in filt. press.

* Data on two epileptic children on graded activity.

renal blood flow and a decrease in filtration fraction, they attributed the nocturia to the increased flow of blood to the kidneys during the period of complete rest.

Previous reports of renal function in cirrhosis (Table III) are conflicting. Leslie, Johnson, and Ralli (22) reported a depression of renal hemodynamics in cirrhosis. They observed higher rates of glomerular filtration and effective renal plasma flow in patients without ascites or during active diuresis than in the presence of actively reaccumulating ascites. Patek and associates (23), and more recently Goodyer, Relman, Lawrason, and Epstein (24) observed that mean glomerular filtration rates and effective renal plasma flows were within normal limits in this disease. Farnsworth and Krakusin (25) showed that the electrolyte excretion in patients with hepatic cirrhosis and ascites resembled that seen in cardiac failure. More recently, Goldman (26) observed a nocturnal diuresis of water and sodium in patients with congestive heart failure, glomerulonephritis, and cirrhosis of the liver. The nocturia and increased nocturnal chloride excretion in patients with cirrhosis reported by Smits (27) was attributed by Borst and de Vries (14) to semi-recumbent position at night.

During the course of water partition studies in cirrhotics with ascites, at which time renal clearances were performed, a reversal of diurnal rhythm in renal function was noted. An abstract of these observations has been published elsewhere (28).

TABLE II

Studies of diurnal variations of renal function in certain pathologic states

Investigator	Pathologic State		Renal Function Variation		
			Studied	Observed	Attributed to
Quincke[18] (1893)	Nephritis Congestive heart failure		Water excretion	Nocturia	-----
Wilson[17] (1889)	Nephritis Congestive heart failure		Water and solid excretion	Nocturia, incr. solid excr.	-----
Fishberg[19] (1939)	Nephritis Congestive heart failure		Water and electrolyte excr.	Nocturia	Decr. renal venous press., incr. cardiac output in pronepos.
Brod[10] (1946)	Glomerulonephritis		Creatinine clear.	Nocturia, decr. H_2O reabsorb.	-----
	Congestive heart failure		U/P ratios.	Nocturia, incr. GFR, decr. H_2O reabsorb.	-----
Baldwin[21] et al (1950)	Congestive heart failure	Edematous	Inulin and creatinine clear., U/P ratios, excr. Na.	Nocturia, incr. GFR, incr. Na excr.	Nocturia not related to level of GFR.
		Edema-free		Decr. urine flow, decr. GFR, decr. Na excr. (at night)	-----
Brod & Feijfar[20] (1950)	Congestive heart failure		Inulin, PAH clear. cardiac output.	Nocturia, incr. GFR, incr. ERPF, decr. F.F., No change in cardiac output	Incr. of blood flow to kidneys with diminished activity.
Smits[27] 1950)	Cirrhosis Congestive heart failure		Water and Cl excr.	Nocturia, incr. Cl excr.	Semi-recumbent position at night.
Goldman[26] (1951)	Congestive heart failure Glomerulonephritis Cirrhosis		Na, K, H_2O excr.	Nocturia, incr. Na excr., No change K excr.	Unknown humoral factors

The present paper presents further data on diurnal variations in renal hemodynamics in normal subjects and cases of cirrhosis.

METHODS

The diagnosis of Laennec's cirrhosis was made by the usual clinical and laboratory methods in the patients studied. Each of these patients had been hospitalized one or more times previously at Hines Veterans Administration Hospital, at which time the diagnosis of cirrhosis had been established. Patients selected for this study manifested no clinical evidence of cardiovascular renal disease as judged by past history, physical findings, electrocardiographic and laboratory findings. This group had in common the presence of reaccumulating ascites (Table IV), which required repeated hospital admissions and paracenteses. Normal subjects were healthy adult males who were either awaiting elective surgery or convalescing from minor surgical procedures. The subjects were allowed food and liquid *ad libitum* but were kept recumbent in bed throughout the experimental procedure. No preliminary hydration was employed. The clearance of inulin was used to estimate glomerular filtration rate (GFR) and that of para-aminohippurate to estimate effective renal plasma flow (ERPF). A priming injection of inulin and para-aminohippurate was followed by a sustaining infusion delivered at a constant rate by a pump over a 24 hour period. All solutions were infused into an antecubital vein by means of nylon tubing which permitted the patient to move about freely in bed without fear of subcutaneous extravasation of the infusate (29). Urine samples were collected by an indwelling multi-eyed catheter. At the conclusion of each clearance period, the bladder was rinsed with 60 cc. of saline to insure quantitative recovery of all urine. The spot clearance periods were 20 to 30 minutes in duration and in addition a concurrent 24 hour period was run on each patient. Two consecutive periods were run during the morning hours (9 a.m. to 12 noon) and subsequently during the late evening or early morning hours (11 p.m. to 3 a.m.). Blood samples were collected in heparinized tubes at the mid-point of each clearance period by means of an indwelling 17 gauge needle. Every attempt was made to avoid psychic or physical trauma to the patient and no

TABLE III

Summary of literature: renal hemodynamics in cirrhosis and ascites

Investigator	Number of Patients	Glomerular Filtration Rate (cc./min.)	Effective Renal Plasma Flow (cc./min.)
Patek et al * [23] (1948)	3	135 * † (91 - 172)	581 ‡ (434 - 709)
Farnsworth and Krakusin [25] (1948)	2	68 ** ‡ (61 - 74)	446 ‡ (415 - 476)
Leslie [22] (1949)	5	69 * ‡	371 ‡
Goodyer et al [24] (1950)	6	120 ** † (60 - 124)	471 † (298 - 647)

* Inulin clearance

** Mannitol clearance

† Corrected to 1.73 m^2.

‡ Uncorrected data

Note: Max. and min. values appear in parenthesis.

additional venapunctures or urethral instrumentation were performed after the experiment had begun. Inulin was determined by Harrison's (30) modification of the method of Alving, Rubin, and Miller (31). Para-aminohippurate was determined by the method of Smith and associates (32) as described by Goldring and Chasis (33).

Measurements of extracellular volume (employing a continuous infusion of mannitol over eight hours) were usually made concurrently with the day time clearance periods. Since the mannitol infusions produced a mild diuresis and as such affected urine flow values and inulin U/P ratios, these data were omitted in a consideration of diurnal variations in renal function. At plasma levels (50–150 mg. %) used to measure extracellular volume, mannitol is known to have no affect on either filtration rate or renal plasma flow (33, 34).

RESULTS

Table V summarizes day, night, and 24 hour GFR data in normal and cirrhotic subjects. Four out of the five normal subjects showed a definite

TABLE IV

Estimated severity of liver disease in patients studied for diurnal variations in renal hemodynamics

Patient	Age	Severity of Liver Dysfunction		
		Number of * Admissions	History of Jaundice	Degree of Ascites ṫ
1. J. S.	61	3	Yes	+++
2. V. G.	53	2	Yes	+
3. N. N.	49	3	Yes	++++
4. J. K.	40	2	Yes	++
5. C. R.	57	3	No	+
6. C. R.	53	2	Yes	++
7. C. N.	42	2	Yes	+
8. W. B.	41	2	Yes	++

* Hospital admissions for liver disease.

ṫ Arbitrary quantitation of severity of ascites from ṫ thru ++++

TABLE V

Diurnal variations in glomerular filtration rates in normal subjects and in cases of cirrhosis with ascites

SUBJECTS	GLOMERULAR FILTRATION RATE cc./min./1.73m²				24 Hr. G.F.R. cc./min./1.73m²
	Day	Night	Difference	% Change	
Normal Subjects					
1. K.G.	119.0	113.0	-6.0	-5.1	124.2
2. (D.M.)	(113.7)	(127.0)	(+13.3)	(+11.7)	(122.0)
3. J.M.	110.0	105.7	-4.3	-3.9	103.9
4. R.N.	140.0	119.6	-20.4	-14.3	126.3
5. V.S.	131.2	120.0	-11.2	-8.5	127.2
$\bar{x}$	126.9	117.0	-5.7	-4.0	120.7
s	±13.6	±8.0	±12.3	±6.7	±9.6
P	—	—	0.2	—	—
Patients With Cirrhosis					
1. J.S.	128.2	156.0	+27.8	+21.6	162.0
2. V.G.	126.0	139.5	+13.5	+10.7	160.6
3. N.N.	95.5	122.6	+27.1	+28.5	118.9
4. J.K.	109.3	116.5	+ 7.2	+ 6.6	130.4
5. G.R.	127.1	154.5	+17.4	+13.7	150.2
6. C.R.	82.9	99.1	+16.2	+19.6	88.0
7. C.N.	74.4	90.6	+16.2	+21.8	84.5
8. W.B.	90.1	108.6	+18.5	+20.6	104.0
$\bar{x}$	104.2	123.4	18.0	17.9	124.8
s	±21.4	±24.6	±6.8	±7.1	±31.1
P	—	—	0.01	—	—

$\bar{x}$ - mean; s - standard deviation; P - probability value

TABLE VI

Diurnal variations in effective renal plasma flow in normal subjects and in cases of cirrhosis with ascites

Subjects	Effective Renal Plasma Flow (ERPF) cc./1.73m²				24 Hr. ERPF (cc./1.73m²)
	Day	Night	Difference	% Change	
Normal Subjects					
1. K.G.	713	631	-82	-11	691
2. D.M.	1130	1161	+31	+3	1160
3. J.M.	608	690	+82	+13	634
4. R.N.	1040	1380	+340	+33	1150
5. V.S.	806	627	-179	-22	735
$\bar{x}$	859	898	+38	+3	875
s	±222	±267	±196	±21	±262
P	—	—	0.5	—	—
Patients With Cirrhosis					
1. J.K.	292	514	+222	+76	672
2. G.R.	898	1212	+314	+35	982
3. C.R.	547	639	+92	+17	580
4. C.N.	354	594	+240	+68	445
5. W.B.	717	786	+69	+9.6	723
$\bar{x}$	562	749	187	41.1	680
s	±252	±277	±104	±29.8	±199
P	—	—	0.04	—	—

$\bar{x}$ - mean; s - standard deviation; P - probability value

TABLE VII

Diurnal variations in filtration fraction in normal subjects and in cases of cirrhosis with ascites

Subjects	Filtration Fraction ($C_{1/CPAH}$)				24 Hr. F.F.
	Day	Night	Difference	% Change	
Normal Subjects					
1. K.G.	16.6	17.8	+1.2	+7	17.9
2. D.M.	10.1	10.8	+0.7	+1	10.3
3. J.M.	18.1	15.4	-2.7	-15	16.7
4. R.N.	13.5	8.7	-4.8	-35	10.9
5. V.S.	16.3	19.1	+2.8	+17	17.3
$\bar{x}$	14.9	14.3	-0.5	-3.0	14.6
s	±3.1	±4.4	±2.8	±20.0	±3.6
Patients with Cirrhosis					
1. J.K.	37.4	22.4	-15.4	-42	19.4
2. G.R.	14.2	12.8	-1.4	-9	15.3
3. C.R.	15.2	15.5	+0.3	+2	15.1
4. C.N.	21.0	15.3	-5.7	-27	19.0
5. W.B.	12.6	13.8	+1.2	+9.5	14.4
$\bar{x}$	20.1	16.0	-4.2	-13.3	16.6
s	±10.2	±3.8	±7.0	±21.1	±2.4
P	—	—	0.2	—	—

$\bar{x}$ - mean; s - standard deviation; P - probability value

tendency toward a decreased GFR during the night. However, the mean day-night difference was not statistically significant. All of the cirrhotic patients showed a nocturnal increase in GFR. The night values averaged 123.4 ± 24.6 cc./min. whereas the mean for the day period was 104.2 ± 21.4 cc./min. The mean difference of 18.0 cc./min. was highly significant with a P value of less than 0.01.

Data on diurnal variations in ERPF are shown in Table VI. In normal subjects there was no consistent change in nocturnal ERPF. Three out of five subjects showed a moderate increase whereas two showed a decrease in ERPF during the night. In striking contrast, all five of the cirrhotic patients infused with PAH showed a significant nocturnal increase in ERPF with a mean increase of 187 ± 104 cc./min. (P = 0.04).

Filtration fractions (FF) in normal and cirrhotic subjects are presented in Table VII. In normal subjects there was no consistent diurnal change in FF. Although the mean difference between the day and night FF in cirrhotic subjects was not statistically significant, it should be noted that there was a marked nocturnal fall in FF in two patients in whom the day FF values were abnormally high. On the average there was a tendency for a nocturnal decrease in FF in cirrhotic patients.

Data comparing 24 hour clearance values with those obtained during spot clearance periods are shown in Tables V, VI, and VII. In normal subjects, the 24 hour GFR calculated from the 24 hour clearance of inulin averaged 120.7 ± 9.6 cc./min., a value which fell between the day and night clearances. In cirrhotic subjects, the mean 24 hour GFR of 124.8 ± 31.1 cc./min. was actually greater than either the average day or night values. In normal subjects the 24 hour ERPF and FF values fell between those of the day and night clearance periods, whereas in cirrhotic patients these data more closely approximated those of the night clearance periods.

DISCUSSION

In normal subjects there was a tendency toward a nocturnal decrease in GFR without consistent changes in ERPF. These findings agree with those reported by Sirota, Baldwin, and Villarreal (11). In contrast to the findings in normal subjects, patients with cirrhosis and ascites showed a significant nocturnal increase in GFR and ERPF.

Both the normal subjects and cirrhotic patients were allowed food and water *ad libitum* during the renal tests. It has been shown that variations in urine flow by the administration of water with resultant flows of 1.0 up to 12.0 cc./min. had no effect on renal hemodynamics (35), and as such would rule against any influences due to the ingestion of fluids during the waking hours. All patients were maintained on high protein, high carbohydrate, low fat diets. High protein diets have been shown to increase filtration rate and renal plasma flow when fed over a 102 day period in normal subjects (36). Little information is available in the literature on the acute effects of meals on renal hemodynamics. A large beef steak meal as compared with a light breakfast was reported to have no effect on the renal plasma flow in one subject although it slightly increased the filtration rate (37). The nocturnal reversal in diurnal rhythm in cirrhotic patients would thus not seem to be related to either food or water intake during the waking hours.

The reversal of diurnal rhythm in renal hemodynamics observed in our patients with cirrhosis and ascites was similar to that reported by Baldwin, Sirota, and Villarreal (21) and Brod (10, 20) in patients with congestive heart failure. Brod and Fejfar (20) noted that the spontaneous nocturnal diuresis of cardiac patients was always accompanied by an increase in ERPF and a fall in filtration fraction. In our series of cirrhotic patients, those with abnormally high day FF values showed a similar nocturnal fall in FF. Brod and Fejfar theorized that the nocturnal improvement in renal blood flow was the result of redistribution of body water and blood flow in association with a decreased metabolic demand by muscles and viscera during the night hours.

Goldman (26) recently reported a nocturnal diuresis and natriuresis in patients with cirrhosis of the liver and ascites, in cases of congestive heart failure, and in two out of five patients with degenerative glomerulonephritis. He postulated that the nocturnal natriuresis might depend on variations in tubular metabolism controlled by a humoral agent which perhaps would be affected by the functional state of the liver.

Antidiuretic substances have previously been reported in the urine of some patients with congestive heart failure (38), cirrhosis (39), acute hepatitis (40), nephrotic edema (41), and hypertension (42). Although a diurnal variation in the secretion of ADH by the posterior pituitary could account for the nocturia in these conditions, it would fail to explain the changes in glomerular filtration rate and renal plasma flow. It has been reported that the infusion of physiologic doses of pitressin had no significant effect on renal hemodynamics in man (43).

Farnsworth and Krakusin (25) noted that in both cirrhosis with ascites and in congestive heart failure, the kidneys behaved as if the body were dehydrated. They submitted the hypothesis that a specific stimulus to salt and water retention was probably acting in both diseases. Deming and Luetscher (44) have reported an increase in excretion of desoxycorticosterone-like substances in edematous patients with heart failure or nephrosis. Evidence of increased activity of desoxycorticosterone-like hormones also has been reported in cirrhosis (45). In normal dogs, it has been shown that large doses of desoxycorticosterone expand the inulin space (46) and increase filtration rate and renal plasma flow (46, 47). It has recently been demonstrated that ACTH may effect an impressive diuresis and natriuresis in cases of nephrosis (48–51). It has been further shown by Rosenbaum, Davis, and Ferguson (52) that nocturnal oliguria and suppression of electrolyte excretion occurring in normal subjects could be eliminated or diminished as a result of cortisone therapy with an actual reversal of the rhythm. Recent work by Gaunt, Birnie and Eversole (53) has led to the theory of a reciprocal or antagonistic action between ADH and adrenal cortical hormones. It is entirely possible that the reversal of diurnal rhythm in renal function noted in various edematous states may be due to increased adrenal cortical activity during the night hours with relative neutralization of ADH effects.

In this series of eight patients with cirrhosis and ascites, four showed abnormally low day-time GFR values, whereas the rest showed rates within normal limits. Two of the four cirrhotic patients with depressed day-time filtration rates had 24 hour GFR values which were within normal limits. Two out of five patients showed an impairment in ERPF and an abnormal elevation of filtration fraction. These findings agree with those reported in the literature (22–25). It was difficult to cor-

relate any impairment of renal function with the severity of the cirrhosis, degree of ascites or with any past history of cardiovascular renal disease.

The importance of 24 hour measurement of glomerular filtration rate and renal plasma flow is pointed up by these studies in normal and cirrhotic subjects. In normal subjects, minimal diurnal variations did not result in significant differences between the 24 hour values and those obtained in spot clearance periods. In cirrhotics, however, spot clearance periods run during the day deviated markedly from 24 hour measurements of glomerular filtration rate and renal plasma flow. The mean 24 hour values in cirrhotic individuals more closely approximated the values obtained during the nocturnal clearance periods. These discrepancies are of particular importance in studies of disturbances in electrolyte excretion in edematous states.

SUMMARY

1). In a series of cases of cirrhosis with ascites a reversal of diurnal rhythm was noted with a nocturnal increase in glomerular filtration rate and effective renal plasma flow. Those patients with impaired renal flows showed a fall in FF as renal blood flow improved during the night. The possible participation of hormonal factors in the diurnal reversal is discussed.

2). Twenty-four hour measurements of renal hemodynamics were within normal limits in six out of eight patients with cirrhosis and ascites.

3). In patients with marked diurnal variations in renal hemodynamics, spot clearance periods run during the waking hours were appreciably lower than those obtained through the 24 hour clearance period. The importance of this fact in relation to electrolyte balance studies is emphasized.

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