Studies on the Hemodynamic Changes in Cirrhosis of the Liver

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=國文抄錄=

肝硬變症에서의 血力學的 變化에 關한 硏究

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肝硬變症 患者 29 例에서 血漿量, 心搏出量 및 腎血漿流量을 同時에 測定하여 血力學的 變化를 觀察하였으며 다음과 같은 結論을 얻었다.

1. 平均 血漿量은 3793±895 ml 로 正常보다 增加된 것을 보았고 血液量(5266±1222 ml) 및 體重 kg 當 血液量(95.7±23.41 ml)도 亦是 增加되어 있었다. 體重 kg 當 血漿量(69.1±19.1 ml)은 增加하는 傾向을 보였고 血液量과 血漿量의 差, 即 赤血球質量은 26.4±7.05 ml 로 正常範圍內에 있었다.

2. 平均 心搏出量은 7708±2652 ml/min 로 增加되어 있었으며 心係數(4924±1998 ml/min/M^2) 心搏動量(96.2±34.2 ml/beat), 心搏動係數(62.3±27.34 ml/M^2) 및 分別心係數(1.54±0.577)도 모두 增加함을 보았다. 全末梢抵抗은 1664±753.8 dynes sec $cm^{-5}M^2$ 로 正常보다 減少되어 있었다.

3. 平均 腎血漿流量은 537±146.8 ml/min/1.73M^2로 正常 내지는 減少된 것을 보였고, 平均 creatinine clearance 는 66.7±23.0 ml/min/1.73M^2로 顯著한 低下를 보았다. filtration fraction 은 一定치 않았으나 大部分의 例에서 減少되었다. 心搏出量의 腎分別値는 相對的으로 減少하여 있었다.

4. 腎血漿流量은 全般的으로는 正常 또는 低下되어 있었으나 creatinine clearance 가 60 ml/min/1.73 M^2以下인 群과 治療에 抵抗하는 腹水群 및 窒素血症이 있는 例에서 顯著한 減少를 보였다.

5. 本實驗에서 觀察한 絲球體 濾過率의 減少, filtration fraction 의 低下 및 心搏出量의 腎分別値의 減少等은 腎臟의 輸入細動脈抵抗의 上昇을 뒷받침한다.

6. 肝硬變症에서 腎循環 障碍는 窒素血症이나 乏尿에 先行하여 일어남을 알 수 있었다.

7. 臨床像이나 肝機能 成績은 이들 血力學 變化와 相關關係가 없었고 다만 食道 靜脈瘤가 心搏出量이 增加된 例에서 觀察되었다.

8. 腎血力學 變化와 血漿量 或은 心搏出量 間에도 相關關係는 없었다.

Circulatory changes and liver-kidney interrelationship in cirrhosis of the liver have been extensively studied by many investigators. So-called "hepatorenal syndrome" was known for a long time to designate functional impairment of kidney in the terminal stage of hepato-biliary diseases. It is defined as oliguria, azotemia, hyponatremia and low urinary sodium associated with severe hepatic failure.[1]

Spontaneous occurrence of renal failure in patients with decompensated liver cirrhosis is well recognized and has emerged as a separate clinical entity. Changes in plasma volume[2,3,4,5,6] and cardiac output[7,8,9,10]

Table 1. Clinical findings (29 cases)

Case	Sex	Age	Ascites*	Jaundice	Vascul. spider	Palm. eryth.	Splenomegaly	Heart murmur	Esoph. varix
1.	F	31	I	+	—	—	+	—	—
2.	M	35	II A	—	+	—	—	—	—
3.	M	38	I	—	—	—	+	—	—
4.	M	43	III A	—	+	—	—	—	—
5.	M	52	I	—	—	—	—	+	—
6.	F	47	I	—	—	—	—	—	—
7.	M	30	II B	—	—	—	—	+	+
8.	M	54	II A	+	—	—	—	—	—
9.	F	35	III A	—	—	—	+	—	+
10.	M	41	II A	+	—	—	—	—	—
11.	M	38	I	—	—	—	—	—	—
12.	F	49	III B	—	+	—	+	—	+
13.	M	56	III A	+	+	—	—	—	—
14.	M	56	II B	—	—	—	+	+	—
15.	M	59	III B	+	+	—	—	—	—
16.	M	37	II B	+	—	—	+	—	—
17.	F	48	I	+	—	—	—	—	—
18.	M	59	I	—	—	—	—	—	—
19.	M	40	III A	+	—	—	+	—	—
20.	F	59	II B	—	—	+	+	+	—
21.	M	70	II B	+	—	—	—	—	—
22.	M	46	III B	—	—	+	—	—	—
23.	M	59	I	+	+	+	—	—	—
24.	F	36	I	—	—	—	+	—	—
25.	F	37	III A	+	+	—	—	—	—
26.	M	53	III B	+	—	—	—	—	—
27.	M	52	I	—	—	+	—	—	—
28.	M	65	I	—	—	—	+	—	+
29.	F	52	III A	—	—	+	+	—	—

* A: Responsive B: Resistant

are known to associate with renal dysfunction in the cirrhotics. The kidney from patients with this syndrome functions normally when transplanted into patients with terminal renal disease,[1] strongly suggesting functional nature of the disorder.

Most published studies are concerned with either plasma volume or cardiac output separately in correlating renal hemodynamics. Present study is performed with simultaneous measurements of renal hemodynamics and plasma volume as well as cardiac output in patients with liver cirrhosis. Principles of currently developed method by double isotope technique with external monitoring were modified and used in measurements.[11,12,13,14,40]

Correlations between these hemodynamic changes and clinical status along with various laboratory results were also evaluated.

METHODS

This study was performed on 29 subjects hospitalized at the medical wards of Seoul National University Hospital. Twenty were males and nine were females. Their ages ranged from 30 to 70 years. Diagnosis of liver cirrhosis was confirmed by clinical findings, laboratory results and liver biopsy. No patients with primary renal or cardiovascular diseases were included.

Table 2. Laboratory findings (29 cases)

Case	Sex	Age (yrs)	Asc.	Hct (%)	Proth time (%)	BSP(45min,)	Cholesterol (mg/100ml)	Bilirubin (mg/100ml)	TTT(Unit)	Serum Alb. (gm/100ml)	A.P.-ase (Unit)	SGPT (Unit)	N_3Hug/100ml	Serum Na (mEq/L)	Serum K (mEq/L)
1.	F	31	I	46	33	20	145	3. 10	12. 9	2. 3	4. 9	97	132	137	3. 8
2.	M	35	II A	39	66	13	286	0. 64	12. 8	2. 8	7. 8	54	110	139	4. 2
3.	M	38	I	47	70	11	155	1. 17	13. 0	2. 7	4. 6	28	101	136	4. 0
4.	M	43	III A	27	56	23	105	0. 62	3. 6	2. 1	5. 2	20	115	140	4. 3
5.	M	52	I	34	82	10	190	0. 48	13. 8	3. 1	6. 3	47	78	138	4. 0
6.	F	47	I	30	83	11	190	0. 39	12. 4	2. 7	1. 5	14	98	145	4. 0
7.	M	30	II B	22	28	32	125	1. 26	17. 7	3. 0	5. 9	65	113	135	3. 7
8.	M	54	II A	44	65	30	215	1. 73	10. 8	2. 5	10. 8	200	107	136	4. 4
9.	F	35	III A	23	26	29	175	0. 91	15. 0	2. 2	4. 0	53	94	139	3. 4
10.	M	41	III A	38	26	49	185	15. 20	15. 8	1. 8	8. 1	280	106	132	3. 5
11.	M	38	I	43	55	13	251	0. 73	9. 4	1. 4	10. 2	50	87	140	3. 4
12.	F	49	III B	27	73	9	200	1. 35	16. 7	2. 3	14. 7	22	126	138	4. 1
13.	M	56	III A	26	15	22	125	1. 64	11. 7	2. 9	5. 0	40	101	139	3. 9
14.	M	56	II B	25	30	28	130	1. 17	9. 4	1. 8	2. 9	40	94	135	4. 1
15.	M	59	III B	33	69	25	155	20. 60	4. 4	2. 8	8. 6	78	103	138	4. 5
16.	M	37	II B	29	64	70	160	1. 54	4. 8	2. 8	6. 4	54	120	132	3. 5
17.	F	48	I	31	55	12	150	1. 44	8. 1	2. 8	3. 6	65	84	144	4. 0
18.	M	59	I	31	90	14	168	1. 09	4. 7	3. 0	10. 3	50	110	142	4. 4
19.	M	40	III A	27	50	25	225	8. 13	20. 1	2. 6	3. 1	70	105	138	4. 2
20.	F	59	II B	29	20	14	120	1. 26	6. 8	2. 7	5. 9	25	84	140	4. 2
21.	M	70	II B	28	26	15	165	1. 53	13. 8	2. 1	4. 8	74	86	138	3. 5
22.	M	46	III B	29	26	54	160	0. 73	16. 8	2. 2	4. 0	10	102	130	4. 0
23.	M	59	I	34	47	15	210	2. 99	12. 2	2. 8	20. 9	74	112	137	3. 7
24.	F	36	I	22	64	10	150	0. 48	14. 4	3. 5	2. 1	22	92	138	3. 4
25.	F	37	III A	27	26	32	136	5. 06	16. 8	2. 0	3. 6	70	117	141	3. 7
26.	M	53	III B	33	73	35	290	3. 33	21. 6	2. 5	14. 6	190	113	138	4. 6
27.	M	52	I	42	24	16	216	0. 63	24. 4	2. 5	10. 4	20	121	133	4. 5
28.	M	65	I	32	26	17	180	1. 17	9. 9	2. 2	4. 4	17	95	127	2. 9
29.	F	52	III A	25	66	63	228	1. 16	11. 3	2. 2	3. 7	28	109	144	3. 7

(Table 1 and 2)

Patients were studied before the institution of diuretc therapy, in the state of clear consciousness, and with urine amount exceeding 500 ml per day. Ascites was classified into three grades according to its degree: grade I with none to minimal, grade II with moderate, and grade III with marked ascites. Grade II and III were further divided into two groups, A and B,; the former includes 20 patients responding to diuretic therapy and the latter consists of 9 with resistant ascites. Grade I was considered as responsive group. (Table 1)

Plasma volume, cardiac output and renal plasma flow were measured as follows.

A collimated scintillation detector was placed over the precordium and the detector was connected to a counting ratemeter and a chart recorder which could be operated at 30 K counting range, time constant of 0. 25 second and chart speed of 12 inch per minute. After recording the background curve, a dose of 10 uCi of radio-iodinated human serum albumin(RIHSA) bolus were rapidly injected. The radiocardiogram obtained by external monitoring was recorded through the counting ratemeter with chart recorder. (Fig. 1)

At the same time, 5ml of venous blood was withdrawn for calibration to determine blood volume, volume of dilution as well as to serve as blood background for renal blood flow determination. After recording the body background curve at 30 K counting range, 40 uCi of ^{131}I-sodium ortho-iodohippurate were injected. The information thus collected was recorded by the same apparatus. (Fig. 2) Ten minutes following the radio-hippuran injection, 5 ml of venous blood sample was obtained. The level of radioactiviy expressed as well as the standard for dose calculation was determined in a well-type scintillation counter.

Calculation was made by the following equations.

Plasma volume

$$PV=\frac{1\text{ ml of Standard activity}\times 1000}{1\text{ ml of plasma activity}\times 1.015}$$

Cardiac output

$$CO=\frac{Cf\times\text{blood volume}}{Cav\times T}$$

Cf: Equilibration counting rate

Cav: Average counting rate under the primary curve

T: Total time under primary curve

Renal plasma flow

$$VD=\frac{\text{Standard sample (cpm/ml)}\times 1000}{\text{At (cpm/ml)}\times Ho/Ht}$$

$$RPF=VD\times k$$

VD: Volume of dilution

k: $0.693/T\frac{1}{2}$ (disappearance constant)

Ht: Height of disappearance curve at 10 minutes after Hippuran injection

At: Measured activity of 1ml of plasma sample at 10 min ater Hippuran inj ection

Ho: Height of disappearance curve at zero time

Normal controls used in this study were derived from Radio-isotope Clinic, Seoul National University Hospital.

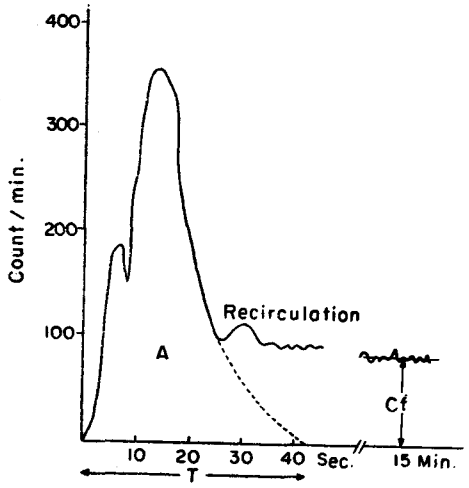

Fig. 1. Radio-cardiogram.

RESULTS

1. Plasma volume

Plasma volume, blood volume and difference between blood volume and plasma volume per kg body weight were measured in 21 cases of liver cirrhosis(Table 3).

Values for the normal controls are shown in Table 4.

The mean plasma volume for the patients (3793± 895 ml) is significantly higher than for the controls ($P<0.01$).

The mean plasma volume per kg body weight for the patients (69.1±19.1 ml) shows increased tendency comparing with the controls ($0.05<P<0.1$). (Fig. 3).

The mean blood volume for the patients(5266± 1222 ml) is significantly higher than for the controls ($P<0.01$).

The mean blood volume per kg body weight (95.7 ±23.4 1ml) is also increased significantly ($p<0.01$).

The mean difference between blood volume and plasma volume per kg body weight (26.4±7.05ml) is in lower limit of normal range.

No definite correlation was found between plasma volume and various clinical findings, i.e., esophageal

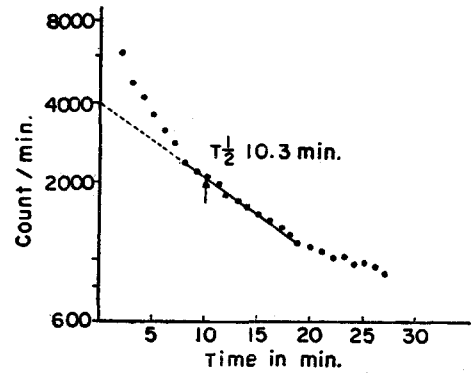

Fig. 2. Determination of the disappearance half-time of radiohippuran by external monitoring.

Table 3. Plasma volume (21 cases)

Case	Sex	Age (yrs)	Wt(kg)	Ascites	PV(ml)	PV/kg(ml)	BV(ml)	BV/kg(ml)	BV-PV/kg (ml)
2.	M	35	60	Ⅱ A	4,451	74.2	6,670	111.2	37.0
3.	M	38	56	Ⅰ	4,854	86.6	7,171	116.5	29.9
4.	M	43	63	Ⅲ A	4,355	69.0	5,650	89.6	20.6
9.	F	35	47	Ⅲ A	4,972	100.6	6,203	132.0	31.4
10.	M	41	62	Ⅲ A	5,073	81.8	7,500	120.8	39.0
11.	M	38	61	Ⅰ	3,421	56.1	5,401	88.5	32.4
12.	F	49	46	Ⅲ B	4,170	90.6	5,410	117.5	26.9
13.	M	56	63	Ⅲ A	3,406	54.0	4,370	69.3	15.3
14.	M	56	55	Ⅱ B	2,578	46.7	3,414	62.0	15.3
15.	M	59	56	Ⅲ B	3,723	66.4	5,182	92.5	26.1
16.	M	37	59	Ⅱ B	3,923	66.4	5,211	88.5	22.1
17.	F	48	42	Ⅰ	2,502	59.5	3,418	81.0	12.5
18.	M	59	55	Ⅰ	2,220	40.4	3,328	60.5	20.1
22.	M	46	62	Ⅲ D	3,020	48.7	4,022	64.9	16.2
23.	M	59	61	Ⅰ	4,932	80.9	6,950	114.0	33.1
24.	F	36	44	Ⅰ	5,457	123.8	6,712	152.5	28.7
25.	F	37	54	Ⅲ A	3,341	61.8	4,356	80.6	18.8
26.	M	53	53	Ⅲ D	3,453	65.1	4,801	90.6	25.5
27.	M	52	45	Ⅰ	3,341	57.5	5,201	89.7	32.2
28.	M	65	50	Ⅰ	3,330	66.6	5,205	104.5	37.4
29.	F	52	53	Ⅲ A	3,132	59.1	4,415	83.3	24.2
Mean					3,793	69.1	5,266	95.7	26.4
S.D.					895	19.1	1,222	23.41	7.05

Table 4. Plasma volume in normal controls

	PV	PV/kg	BV	BV/kg	BV-PV/kg
Mean	2918	49.5	4490	72.1	30.8
S.D.	258	2.4	385	7.3	3.6

varix, splenomegaly, vascular spider, palmar erythema or cardiac murmur. Furthermore, correlation was not seen between plasma volume and response of ascites to treatment (Fig. 4).

No definite correlation was found between plasma volume and liver function, i.e., prothrombin time, BSP, serum bilirubin, serum albumin, thymol turbidity and others. (Fig. 12, 13, 14 & 15)

2. Cardiac output

Cardiac output, cardiac index, stroke volume, stroke index, total peripheral resistance and fractional cardiac index were measured in 20 cases of liver cirrhosis (Table 5).

Values for the normal controls are shown in Table 6.

The mean cardiac output for the patients (7708±2652 ml/min) is significantly higher than for the controls ($P<0.01$). (Fig. 3)

The mean cardiac index (4924±1998 ml/min/M2), stroke volume (96.2±34.2 ml/beat) and stroke index (62.3±27.34 ml/beat/M^2) were also significantly higher than for the controls ($P<0.01$).

The mean total peripheral resistance (1664±753.8 dynes sec $cm^{-5}M^2$) was significantly lower than for the controls ($p<0.01$).

The mean fractional cariac index(1.54±0.577) was increased significantly ($P<0.01$).

No definite correlation was seen between cardiac output and various clinical findings, i.e., ascites, splenomegaly, vascular spider, palmar erythema or cardiac nurmur. And correlation was not found between cardiac output and response of ascites to

Table 5. Cardiac output (20 cases)

Case	Sex	Age(yrs)	MBP (mmHg)	PR (per min)	BSA (M^2)	Ascites	BV(ml)	CO (ml/min)	CI (ml/min/M^2)	SV (ml/beat)	SI (ml/beat/M^2)	TPR (dynes·sec cm^{-5} M^2)	FCI
2.	M	35	96	81	1.74	II A	6,670	3,920	2,250	48	27.6	3,410	0.59
3.	M	38	86	61	1.61	I	7,171	4,429	2'745	37	45.3	2,500	0.62
4.	M	43	86	70	1.65	III A	5,650	7,139	4,320	102	62.0	1,590	1.26
9.	F	35	76	75	1.46	III A	6,203	10,742	7,360	143	98.0	825	1.73
10.	M	41	92	80	1.74	III A	7,500	7,449	4,275	93	53.4	1,720	0.99
11.	M	38	94	76	1.75	I	5,401	6,255	3,572	83	47.4	2,100	1.16
12.	F	49	76	80	1.42	III D	5,410	14,901	10,498	186	131.0	639	2.76
13.	M	56	104	85	1.71	III A	4,370	7,070	4,131	83	48.2	2,010	1.62
14.	M	56	96	80	1.58	II D	3,414	5,001	3,159	68	39.9	2,422	1.47
15.	M	59	80	87	1.62	III B	5,182	7,619	4,683	88	54.2	1,368	1.47
16.	M	67	80	89	1.60	II B	5,211	9,120	5,701	102	63.7	1,122	1.75
17.	F	48	102	92	1.35	I	3,418	8,240	6,088	90	66.5	1,340	2.42
18.	M	59	86	70	1.63	I	3,328	5,750	3,519	82	82.2	1,945	1.90
22.	M	46	82	85	1.68	III B	4,022	7,650	4,550	90	53.5	1,441	1.90
23.	M	59	84	90	1.70	I	6,950	6,325	3,718	70	41.1	1,805	0.91
24.	F	36	82	82	1.45	I	6,712	10,519	7,274	128	88.4	902	1.57
25.	F	37	82	73	1.51	III A	4,356	9,403	6,220	129	85.5	1,055	2.16
26.	M	53	29	98	1.55	III B	4,801	7,767	4,998	79	51.0	1,470	1.62
27.	M	52	80	90	1.68	I	5,201	3,870	2,297	43	25.6	2,780	0.75
28.	M	65	76	75	1.52	I	5,205	1,1003	7,112	184	95.0	844	2.14
Mean								7,708	4,924	96.2	62.3	1,664	1.54
S.D.								2,652	1,998	34.2	27.34	753.8	0.577

Table 6. Cardiac output in normal controls

	CO	CI	SV	SI	TPR	FCI
Mean	5,857	3,533	79	48	2,083	1.09
S.D.	685	414	9	6	354	0.18

treatment. (Fig. 4) However, esophageal varix was demonstrated in 3 cases among 4 (case 9, 12, 24 and 28) with cardiac output exceeding 10 l/min.

No correlation was detected between cardiac output and liver function, i.e., prothrombin time, BSP, serum bilirubin, serum albumin, thymol turbidity and others.

3. Renal plasma flow

Renal plasma flow, endogenous creatinine clearance, filtration fraction, renal fraction of cardiac output were measured in 28 cases of liver cirrhosis(Table 7).

Values for the normal controls are shown in Table 8.

The mean renal plasma flow for the patients (537 ±146.8 ml/min/1.73 M^2) showed normal or decreased tendency. However, when renal plasma flow was compared to 2 groups: one with creatinine clearance less than 60 ml/min/1.73 M^2, the other with more than 60 ml/min/1.73 M^2, the mean renal plasma flow in the former group was significantly lower than that in the latter (Fig. 11). ($P<0.01$)

The mean endogenous creatinine clearance for the patients (66.7±23.0 ml/min/1.73 M^2) was significantly lower than for the controls. (Fig. 3).

Although filtration fraction was variable, it is slightly lower than normal in most cases.

The mean renal fraction of cardiac output (11.4± 6.27%) was relatively decreased.

No definite correlation could be found between renal plasma flow and various clinical findings, i.e., ascites in degree, esophageal varix, splenomegaly,

Table 7. Renal plasma flow (28 cases)

Case	Sex	Age (yrs)	BSA (M^2)	Ascites	Urine Micro	BUN (mg/100ml)	Cr (mg/100ml)	PSP (%) 15′	PSP (%) 60′	C_{cr} (ml/min/1.73M^2)	RPF(ml/min/1.73M^2)	FF	RBF (ml/min/1.73M^2)	CO (ml/min)	RFCO (%)
1.	F	31	1.52	I	N	12	0.9	51	76	104	702	0.17	962	—	—
2.	M	35	1.74	II A	N	16	0.8	44	65	96	763	0.13	1,210	3,920	31.0
3.	M	38	1.61	I	A	14	1.1	36	57	85	455	0.20	800	4,429	18.0
4.	M	43	1.65	III A	A	13	1.0	37	49	75	684	0.12	894	7,139	11.2
5.	M	52	1.68	I	N	13	1.0	26	77	87	790	0.11	1,160	—	—
6.	F	47	1.45	I	N	18	0.9	37	62	87	434	0.20	506	—	—
7.	M	30	1.61	II B	N	13	1.2	35	64	75	385	0.19	461	—	—
8.	M	54	1.55	II A	N	11	0.9	18	36	74	582	0.13	932	—	—
9.	F	35	1.46	III A	N	15	0.8	37	58	88	571	0.15	645	10,741	6.0
10.	M	41	1.74	III A	N	20	1.5	23	61	61	445	0.14	617	7,449	8.3
11.	M	38	1.75	I	N	19	1.3	42	71	83	680	0.12	1,307	6,255	20.8
12.	F	49	1.42	III B	N	20	1.4	26	69	92	430	0.21	884	14,901	5.9
13.	M	56	1.71	III A	N	16	1.3	33	48	81	675	0.12	900	7,070	12.7
14.	M	56	1.58	II B	N	17	1.3	27	58	63	452	0.14	525	5,001	10.5
15.	M	59	1.62	III B	N	13	1.4	20	—	92	542	0.17	759	7,619	10.0
16.	M	37	1.60	II B	N	19	1.2	17	57	69	570	0.12	720	9,120	7.9
17.	F	48	1.35	I	N	20	0.9	51	80	67	715	0.09	798	8,240	9.7
18.	M	59	1.63	I	N	15	1.0	21	48	82	582	0.14	800	5,750	13.9
19.	M	40	1.64	III A	N	15	0.8	35	51	52	498	0.11	466	—	—
20.	F	59	1.67	II B	N	48	3.6	31	54	43	248	0.18	336	—	—
21.	M	70	1.63	II B	N	46	2.0	6	31	10	334	0.03	438	—	—
22.	M	46	1.68	III B	N	42	1.9	15	30	29	293	0.10	376	7,650	4.9
23.	M	59	1.70	I	N	17	1.3	—	—	47	672	0.07	1,000	6,325	15.8
24.	F	36	1.45	I	N	12	1.1	32	61	47	419	0.11	494	1,0519	4.7
25.	F	37	1.51	III A	A	37	1.7	16	22	54	590	0.09	670	9,403	7.1
26.	M	53	1.55	III B	N	17	1.3	—	32	31	480	0.06	641	7,767	8.3
27.	M	52	1.68	I	N	30	1.3	17	45	57	338	0.17	567	3,870	14.6
28.	M	65	1.56	I	A	18	1.6	14	49	38	712	0.09	823	11,003	7.4
Mean						20.2	1.30			66.7	537	0.13	745		11.4
S.D.										23.0	146.8	0.043	237		6.27

Table 8. Renal plasma flow in normal controls

	Ccr	RPF	RFCO
Mean	121	582	18.8
S.D.	16	60	2.5

vascular spider, palmar erythema or cardiac murmur.

Renal plasma flow is definitely decreased in resistant ascites group. ($P<0.01$) (Fig. 4)

There was no specific correlation between renal plasma flow and liver function, i.e., prothrombin time, BSP, blood ammonia, serum bilirubin, serum albumin, thymol turbidity and others

Among 4 cases (case 3, 4, 25 and 28) with abnormal urinary microscopic findings, renal plasma flow was decreased in only one.

Blood urea nitrogen and serum creatinine were elevated in 5 cases (case 20, 21, 22, 25 and 27), among these creatinine clearance was less than 60 ml/min/1.73 M^2 in all and renal plasma flow was markedly reduced in all but one cases. PSP clearance was also abnormal in 4 out of 5 of these cases. Serum electr-

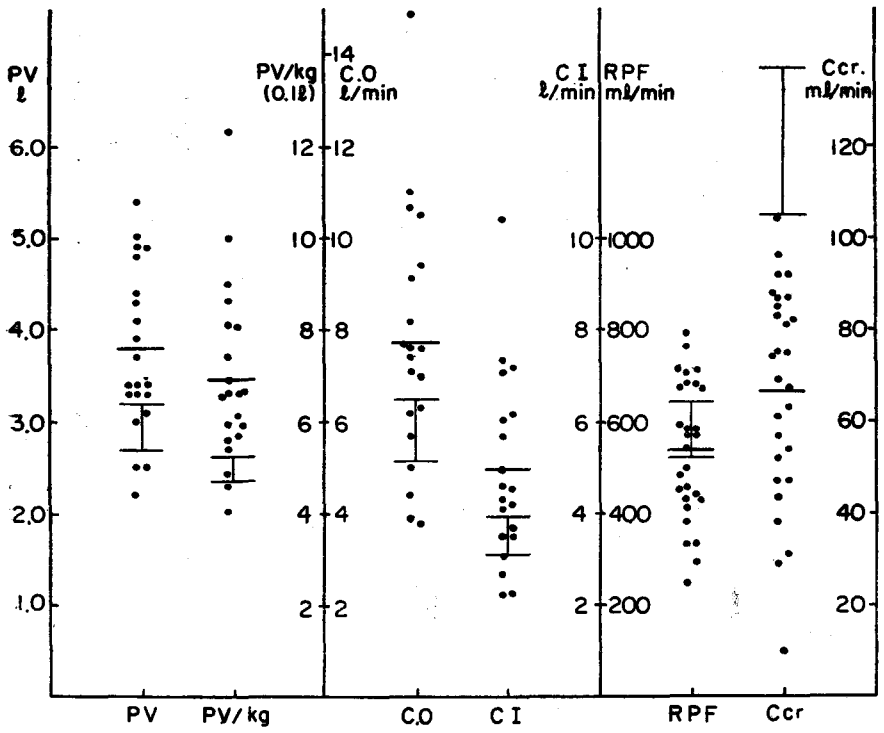

Fig. 3. PV, CO & RPF in cirrhosis

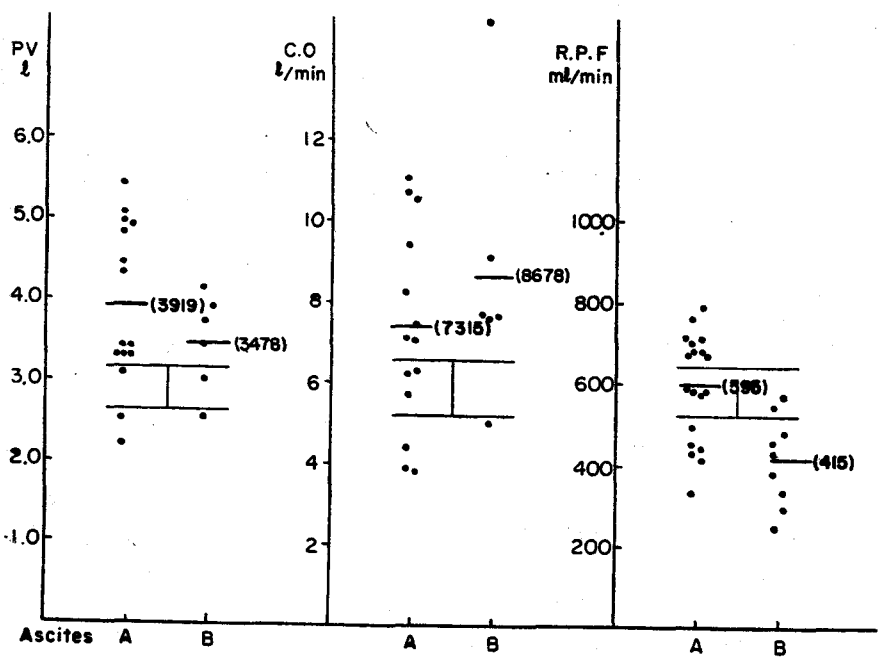

Fig. 4. PV, CO & RPF and ascites

olytes were markedly diminished in only one case (case 28), whose renal plasma flow was within normal range, however, PSP and endogenous creatinine clearance revealed abnormal values in this case.

4. Correlation of renal plasma flow with plasma volume or cardiac output

There were no definite correlations between renal plasma flow and plasma volume; renal plasma flow and cardiac output;, and plasma volume and cardiac output (Fig. 5, 6 & 7).

No correlation was found between creatinine clearance and plasma volume or cardiac output(Fig. 9 & 10).

No Definite correlation was found between renal plasma flow and creatinine clearance (Fig. 8).

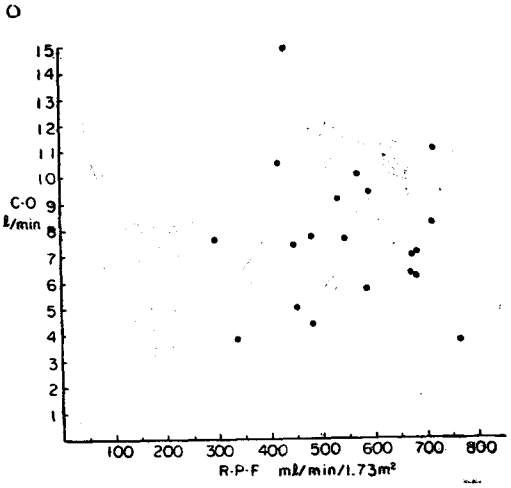

Fig. 7. CO vs RPF

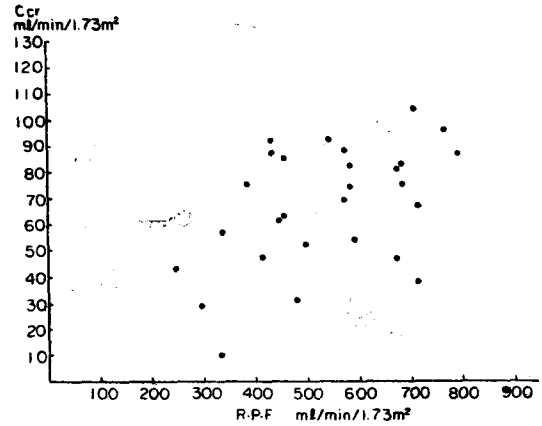

Fig. 8. RPF vs Ccr

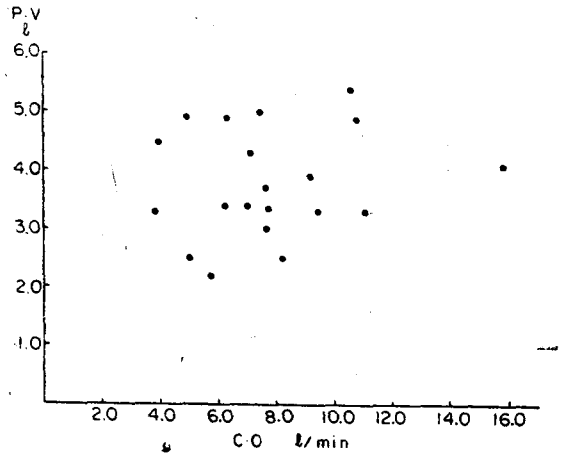

Fig. 5. PV vs CO

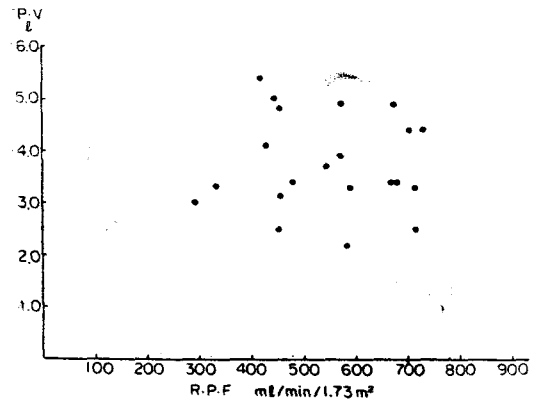

Fig. 6. PV vs RPF

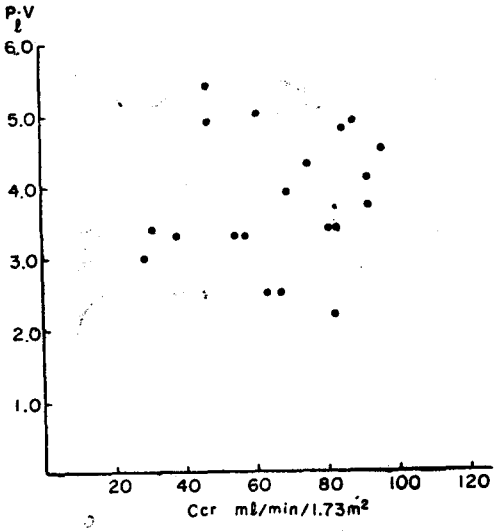

Fig. 9. PV vs Ccr

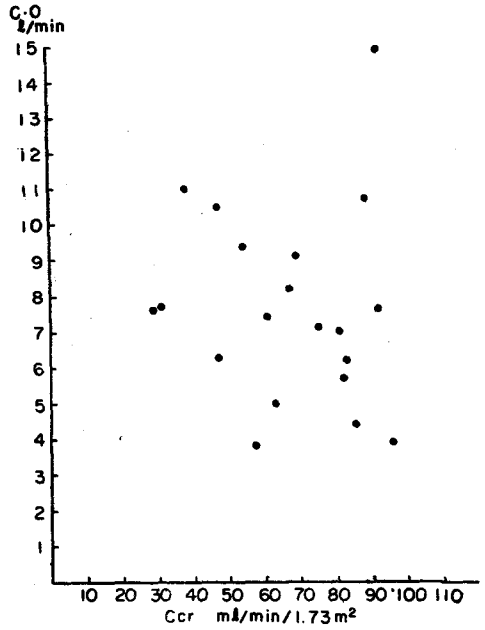

Fig. 10. CO vs Ccr

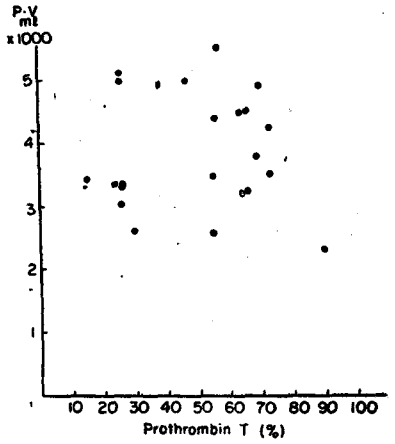

Fig. 12. PV vs prothrombin time

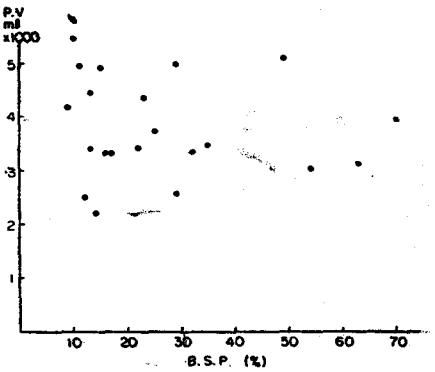

Fig. 13. PV vs BSP

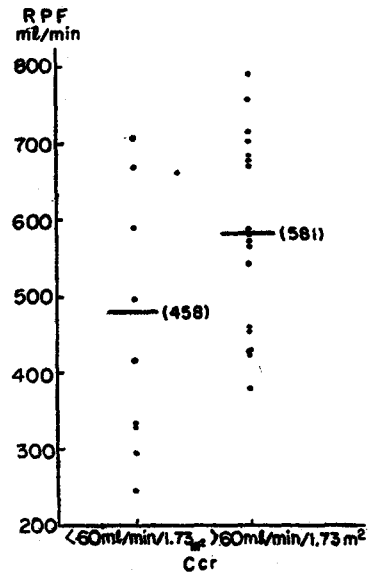

Fig. 11. RPF vs Ccr in 2 groups

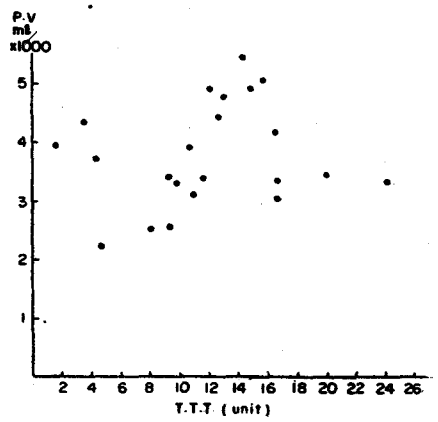

Fig. 14. PV vs TTT

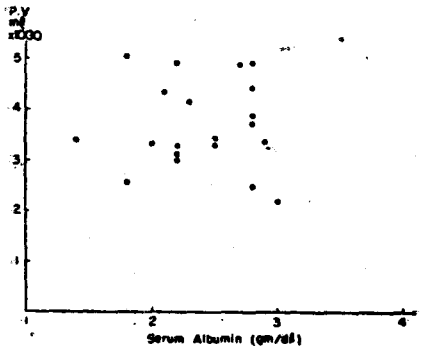

Fig. 15. PV vs serum albumin

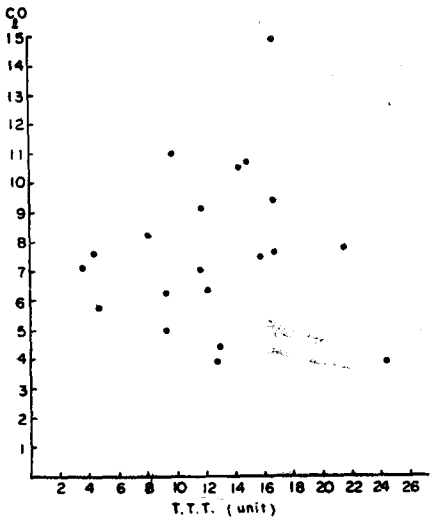

Fig. 18. CO vs TTT

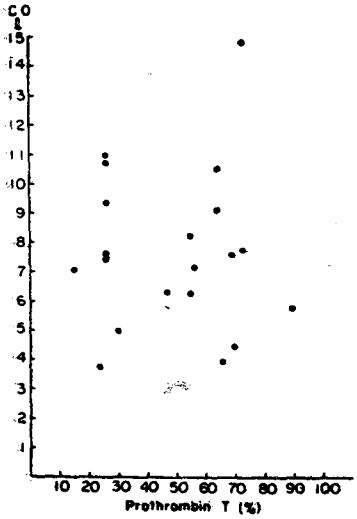

Fig. 16. COvs prothrombin time

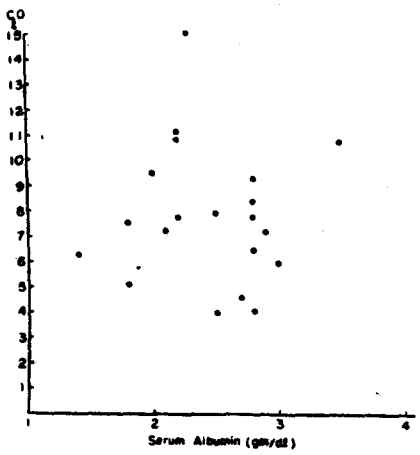

Fig. 19. CO vs serum albumin

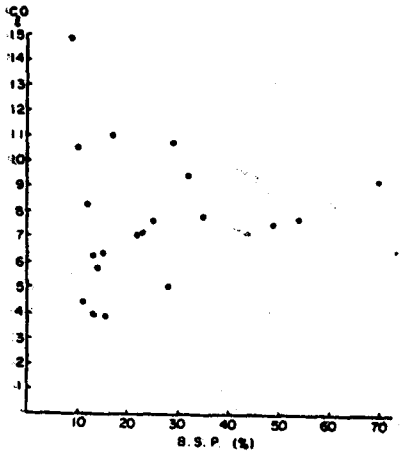

Fig. 17. CO vs BSP

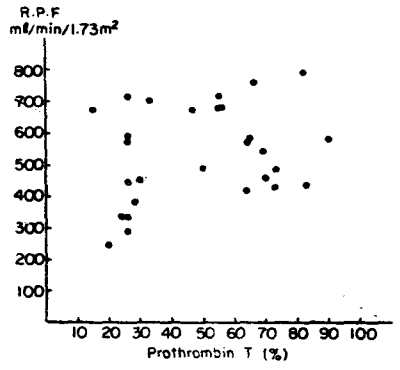

Fig. 20. RPF vs prothrombin time

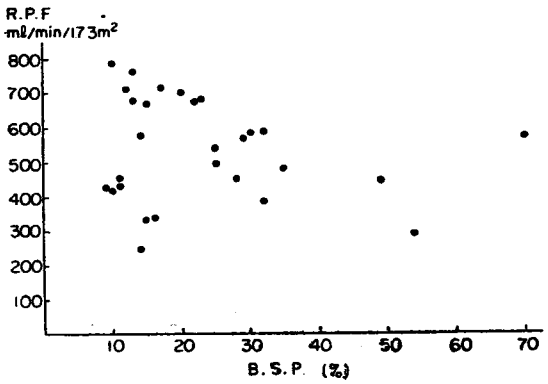

Fig. 21. RPF vs BSP

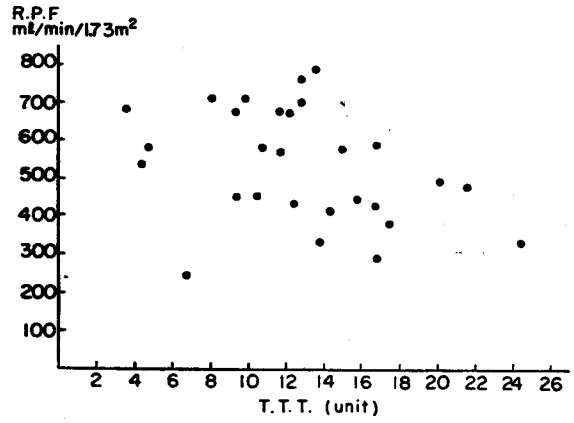

Fig. 22. RPF vs TTT

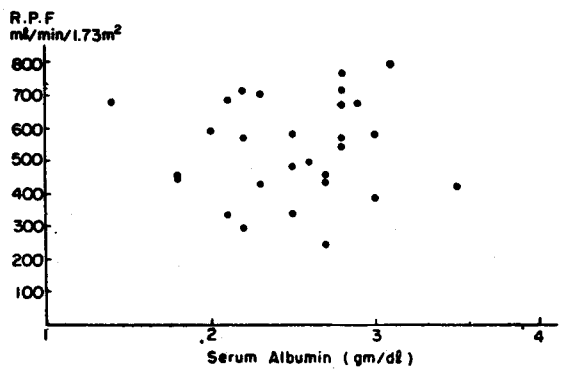

Fig. 23. RPF vs serum albumin

DISCUSSION

Plasma volume has been known to be increased in patients with liver cirrhosis.[2,3,4,5,6] Increase in total blood volume in cirrhosis of the liver is primarily the results of expanded plasma volume with red cell mass remaining unchanged.[15]

Increased plasma volume and normal red cell mass were confirmed in our study. However, plasma volume calculated by body weight showed only incressing tendency and this might reflect additive effect of ascites to lean body weight, although Maddrey et al concluded both values were valid when plasma volume was calculated by either actual or ideal body weight.[6]

Clinical findings including response of ascites to treatment had no correlation, nor liver function, in regards to plasma volume in cirrhosis in the present observation. On the other hand, splenomegaly, collaterals on the abdominal walls and esophagel varices,[2] cyanosis and esophageal varices,[3] varix alone,[16] portal hypertension with splenomegaly,[17] low serum, albumin[7] and evidence of portal hypertension,[6] were assumed to be associated with increased plasma volume.

Precise mechanisms for the elevated plasma volume were not known, but several factors have been suggested. Portal vein obstructions and the increased size of the collateral vascular bed required to handle the portal circulation with splanchnic and splenic sequestration of fluid were primarily responsible for the elevated plasma volume.[2,16,6] Existence of a correlation between wedged hepatic venous pressure and the plasma volume have been found,[16] while the pressure was normal in some other observation.[6] Elevated splenic pressure is more constant findings comparable to expanded plasma volume in cirrhosis than elevated wedged hepatic venous pressure.[6] Splenomegaly associated with portal hypertension was found to correlate with plasma expansion.[6,17] while Kimber reported no correlation between these findings.[18]

Following the removal of enlarged spleen in patients with liver cirrhosis, decrease in plasma volume resulted.[17] It has been postulated that an abnormal protein

or macr omolecule produced by the spleen is responsible for increased plasma volume.[19] Recent observations suggested that portal hypertension is a main factor for elevated plasma volume seen in liver cirrhosis and a direct mechanical effect of portal venous flow is responsible for the elevation. They also found that a definite fall in plasma volume in eight out of twelve patients with portal hypertension studied before and after a portacaval shunt.[6]

Arteriovenous shunt may be involved in plasma volume elevation[7] or renal sodium retention with resultant increase of extracellular fluid is a possible cause of plasma volume expansion in cirrhosis.[6] Generalized abnormal vasodilation of the vessels of the body is considered as another possible mechanism.[8]

Cardiac otput as well as cardiac index is increased in most patients with cirrhosis of the liver.[7,8,15] Presence of high cardiac output in cirrhosis is confirmed in our study.

Total vascular peripheral resistance is decreased in cirrhosis because of low mean blood pressure,[20] which is similar to our results.

No correlation between increased cardiac output and ascites, jaundice or edema have been found.[7,20] Cardiac output tends to be higher when patients are more severely ill,[10] and it returns to normal after clinical improvement.[7] Thus, liver failure is an essential factor in high cardiac output.

Clinical findings including response of ascites to treatment and liver function had no correlation with cardiac output except that esophageal varices were present in patients with high cardiac output in our observation.

Exact mechanism for elevated cardiac output in cirrhosis is unclear. Functional peripheral vascular shunting,[7] and peripheral vasodilatation by vasoactive substance,[15] were suggested. Increased cardiac output is also seen in chronic anemia, however in this situation, hematocrit is usually below 20 percent[21] and hemoglobin below 7 gm per dl.[22] Nutritional defeciency, especially of thiamine, is thought to be related with high cardiac output in cirrhosis.[7]

Many investigators demonstrated the development of spontaneous renal failure in patients with advanced liver cirrhosis. No known specific renal lesions which correlate with functional impairment of the kidneys are described.[23,24,25] Ascites, water and electrolyte disturbance with associated renal circulatory dysfunction are invariable signs of the cirrhotics in terminal stage.

The causes of renal failure in cirrhosis have been sought by many investigators. Disturbed renal perfusion,[9] increased renal vascular resistance,[26] autonomic interrelationship between hepatic and renal circulation,[27] artrio-venous shunting,[28] and toxic substances elaborated or incompletely metabolized by injured liver,[5] were suggested for explanation. All of these varied opinions suggest functional, rather than organic, nature of the disorder. Recently, it has been shown that survival and functional activity of isolated rat kidney is prolonged when it is perfused with an isolated liver, suggesting that normal liver function may be essential to maintain normal kidney function.[29] Moreover, Koppel et al proved that renal failure in cirrhosis is functional and potentially reversible.[1] They transplanted kidneys from cirrhotic patients with renal failure into patients with end-stage kidney disease with success. And it was concluded that the transplanted kidneys regain normal function either because they are removed from the deleterious environment of hepatic failure or because an essential biologic requirement for normal renal function is provided by the normal liver of the recipients.

Studies by many authors have shown a reduction in renal plasma flow in patients with advanced cirrhosis accompanied by renal failure.[5,9,26,28,30]

In our study, renal plasma flow is either normal or reduced. It was defintely decreased in those patients with signs of azotemia, namely, increased blood urea nitrogen level and decreased endogenous creatinine clearances.

Exact mechanism of reduced renal circulation is unknown. Several possible causes of decrease of renal plasma flow have been suggested. Increased renal vascular resistance[9] may be an etiological factor, particularly that of afferent arterioles, with redistribution of blood within the kidney[28] Reduced renal extraction of PAH[26], increased renal vein pressure due to ascites[23], arterial hypotension, which is seen only in the terminal phase of cirrhosis,[25] and reflex

renal vasoconstriction,[27] have been suggested. Recently Barnardo et al found that infusion of dopamine caused increase in renal plasma flow, possibly due to lowering of renal vascular resistance.[32]

Recent observations postulated that renal ischemia is secondary to renal cortical vasoconstirction with increased medullary blood flow evidenced by reduction in renal extraction of PAH.[33] This, at least, is not caused by increased sympathertic nervous system activity, since infusion of phentolamine into renal artery causes no alteration in renal hemodynamics.[30]

Plasma renin levels are higher in group with renal failure[41] and increased plasma renin activity is the result, rather than cause, of renal failure in cirrhosis.[42]

Endogenous creatinine clearance is usually decreased in liver cirrhosis,[23,25,28,34] as confirmed in present study.

Filtration fraction in our patients revealed variable, but slightly lowered value. It is low, especially in the cases with low glomerular filtration rate in cirrhotics,[28] consitent with our results. On the other hand, it has been reported as elevated,[26] and variable but not always elevated.[9]

Renal tubular function is observed as intact by many authors.[25,28,35] In our series phenolsulfonphthalein excretion in most cases appeared to be normal.

Correlations of clinical findings and liver function, except for ascites, to renal plasma flow are not consistent in present observation.

It has been noted that reduced renal plasma flow is seen mostly in the patients with ascites not responding to diuretics,[9] and that renal clearances are usually normal in many cases without ascites or with responsive ascites.[36] And severe hepatic dysfunction and resistant ascites again are thought to be related to reduced renal circulation.[26]

Recent observation by Klingler et al emphasized discrepancies between renal function and clinical features.[10]

Renal plasma flow in resistant ascites group is definitely decreased in our study suggesting response of ascites to treatment to consider as an important Parameter in evaluating renal function of cirrhotic patients.

Urinary findings and elecrolytes are not remarkable in present study, although hyponatremia and hyperkalemia[25,26,28] are associated with renal dysfunction in cirrhosis.

Elevated blood urea nitrogen in our series was accompanied by low creatinine clearance, disturbed PSP excretion and inconsistent changes in renal plasma flow. And there was no significant correlation of renal plasma flow to endogenous creatinine clearance in author's observation.

From the clinical studies by several authors of renal failure in cirrhotics, several important findings have been pointed out. Renal failure developes rapidly, and bears grave prognosis.[23,25] Oiguria is usually seen only at the terminal stage.[23] Renal failure is imminent and it supervenes prior to the onset of azotemia[28] or renal insufficiency.[25] Recovery from renal failure is clearly related to improvement in hepatic function.[23,26]

Decreased effective blood volume is responsible for reduced renal plasma flow,[4] and this is supported by the fact that when a large amount of fluid is removed, renal failure developes often in cirrhosis. However, expansion of plasma volume does not result in improvement of glomerular filtration or renal plasma flow,[5] and there is no correlation between plasma volume and renal circulatory function., although in some instances' plasma volume expansion results in transient ameriolation of renal hemodynamics.[31,37]

Diversion of greater than normal portion of cardiac output to sites other than kidneys suggested by reduced renal fraction of cardiac output.[8,26] Consistent with this observation are diminished peripheral vascular resistance,[7] and increased blood flow to skin and muscle.[8] Elevated cardiac output is observed in cirrhosis with normal,[15] increased,[38] or reduced[39] renal plasma flow. Thus, there is no correlation between cardiac output and renal plasma flow as well as glomerular filtration rate[10]

Cardiac output is increased in cirrhotics mainly with elevated plasma volume.[7]

In our present observation, there are no definite correlation between renal hemodynamics and plasma volume or cardiac output, although relative decrease in renal fraction of cardiac output and increased fractional cardiac index were seen.

As to our present observation it is suggested that

impairment of hemodynamics, systemic and renal, exists in the presence of apparently normal renal function and hepatic reserve. And changes in renal hemodynamics are at least not directly related to systemic hemodynamic alterations.

SUMMARY

Cardiac output, plasma volume and renal plasma flow were determined to evaluate hemodynamic changes in 29 patients with cirrhosis of the liver.

The results obtained were as follows.

1. The mean plasma volume was 3793+895 ml and it was significantly higher than the normal controls. The mean blood volume (5266±1222 ml) and blood volume per kg body weight (95.7±23.41 ml) were also increased significantly. The mean plasma volume per kg body weight (69.1±19.1 ml) showed increased tendency and the mean difference between blood volume and plasma volume per kg body weight (26.4±7.05 ml) was in lower limit of normal range.

2. The mean cardiac output was 7708±2652 ml/min and it was significantly increased. The mean cardiac index (4924±1998 ml/min/M^2), stroke volume (95.2±34.2 ml/beat), stroke index (62.3±27.34 ml/beat/M^2) and fractional cardiac index (1.54±0.577) were also increased significantly. The mean total peripheral resistance was 1664±753.8 dynes sec cm^{-5} M^2 and it was significantly lower than the normal controls.

3. The mean renal plasma flow was 537±146.8 ml/min/1.73 M^2 and it was normal to decreased tendency. The mean endogenous creatinine clearance (66.7±23.0 ml/min/1.73 M^2) was significantly decreased. Filtration fraction was variable, but it was slightly lower than normal in most cases. The mean renal fraction of cardiac output (11.4±6.27%) was relatively decreased.

4. Although renal plasma flow was normal or decreased in general, it was definitely diminished in patients with creatinine clearance less than 60 ml/min/1.73 M^2, resistant ascites, and signs of azotemia (elevated BUN and serum creatinine).

5. Diminished glomrular filtration rate with low filtration fraction and decreased renal fraction of cardiac output observed strongly supported increased renal afferent arteriolar resistance.

6. Renal circulatory impairment preceded azotemia or oroliguria in cirrhosis.

7. Clinical findigns and liver function were not correlated with hemodynamic changes, except for esophageal varices associated with high cardiac output obsedved.

8. No definite correlation of renal hemodynamics with plasma volume or cardiac output was found.

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