Circulatory Changes in Chronic Liver Disease*

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A HYPERKINETIC circulatory state may be associated with chronic disease of the liver [*1*]. Evidence of increased peripheral flow is shown by warm, flushed extremities, bounding pulses and capillary pulsations, and an increased cardiac output by tachycardia, an active precordial impulse and frequently an ejection systolic murmur. There are few laboratory observations in support of these clinical features. Kowalski and Abelmann noted an elevated resting cardiac index in approximately one-third of patients with Laennec's cirrhosis and chronic alcoholism; these patients also had a low peripheral vascular resistance and a calculated decrease in arteriovenous oxygen difference [*2*]. An increased peripheral flow was demonstrated in a small number of patients with liver disease [*3*] and confirmed in a larger series of cirrhotic patients by Martini and Hageman [*4*].

Another abnormal circulatory finding in chronic liver disease is arterial unsaturation, possibly due to a shift in the oxygen dissociation curve [*5*] or to shunting of systemic venous blood through pulmonary arteriovenous anastomoses [*6*]. Also, an increased plasma volume or total blood volume has been reported and correlated with the portal-systemic collateral circulation [*7,8*], arterial desaturation [*8*] and a "hypervolemic" anemia (*9*).

The following report describes the circulatory changes in twenty-four patients with chronic portal cirrhosis and six patients with chronic biliary cirrhosis. In addition, six patients with extrahepatic portal vein obstruction were investigated to determine the circulatory effects of a portal-systemic circulation with a normally functioning liver. These three groups were compared with fourteen control subjects.

MATERIALS AND METHODS

Selection of Patients. All twenty-four patients with portal cirrhosis had histological proof of the diagnosis. The disease followed infectious hepatitis in five cases and was associated with chronic alcoholism in three subjects. One subject had hemochromatosis, one patient had Wilson's disease. No definite etiology could be found in fourteen patients. Seven patients had had a surgical portacaval anastomosis at least six months prior to study.

There were four cases of primary biliary cirrhosis, one patient with common duct stricture and one patient with chlorpromazine jaundice of eighteen months' duration. These patients were all icteric.

Six patients with extra-hepatic portal vein obstruction had surgical or portal venographic [*10*] evidence of portal vein obstruction with an extensive collateral circulation, normal liver function and a histologically normal liver. One patient had had a portacaval anastomosis.

Twenty-seven of the thirty-six patients studied had venographic, surgical or autopsy estimation of the presence and magnitude of a portal-systemic venous collateral circulation. In nine patients, assessment was made on clinical grounds and by radiological examination of the esophagus. The portal-systemic collateral circulation was graded zero (absent), one plus (moderate) or two plus (extensive).

The fourteen control subjects were ward patients or laboratory staff.

Procedures. All studies were made on resting, fasting subjects. Cardiac output was determined by the dye dilution method and calculated from the Hamilton formula [*11*]. The technic used to

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measure cardiac output with Evans blue dye and an ear oximeter has been reported in detail from this laboratory [*12*]. In twelve patients dye was injected into the right atrium or pulmonary artery at the time of cardiac or hepatic vein catheterization; all other patients had intravenous injections. Surface area estimation used in calculating cardiac index was obtained from the Du Bois formula using the patient's height and weight when free of ascites and edema.

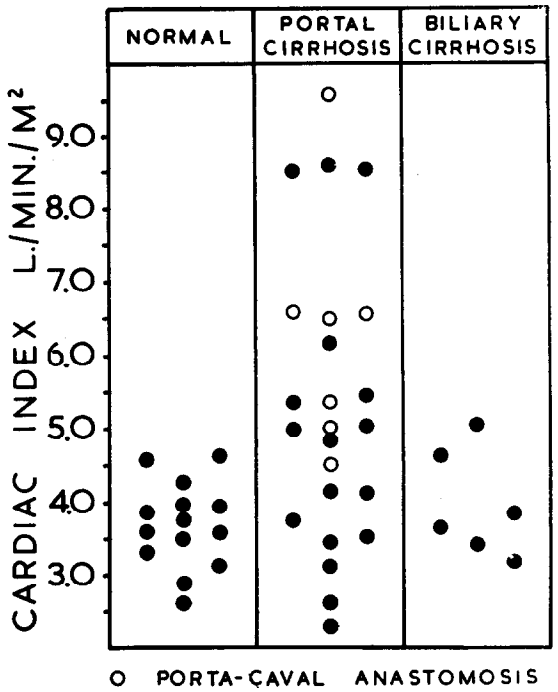

FIG. 1. The range of cardiac indices in normal adult subjects and in patients with portal cirrhosis and biliary cirrhosis. Normal = 3.68 ± 0.6 L./minute/Sq. M. Hollow circles represent patients with portacaval anastomosis.

Plasma volume was determined from the Evans blue dye concentration obtained by a modified extraction method [*13*] in a blood sample drawn ten minutes after the dye injection [*14*]. Peripheral venous or arterial hematocrits used in the calculation of total blood volume and cardiac output were corrected for trapped plasma and total body hematocrit as described by Mollison [*15*].

Phasic arterial pressure was measured with an indwelling arterial needle and a Statham strain gauge (P-23A); the mean pressure was determined by planimetry. Peripheral vascular resistance was determined by the formula:

$$R = \frac{\text{mean arterial pressure (mm. Hg)} \times 1{,}332}{\text{cardiac output (ml./second)}}$$

Arterial oxygen saturation was determined by a modified Haldane [*16*] method and the per cent saturation calculated.

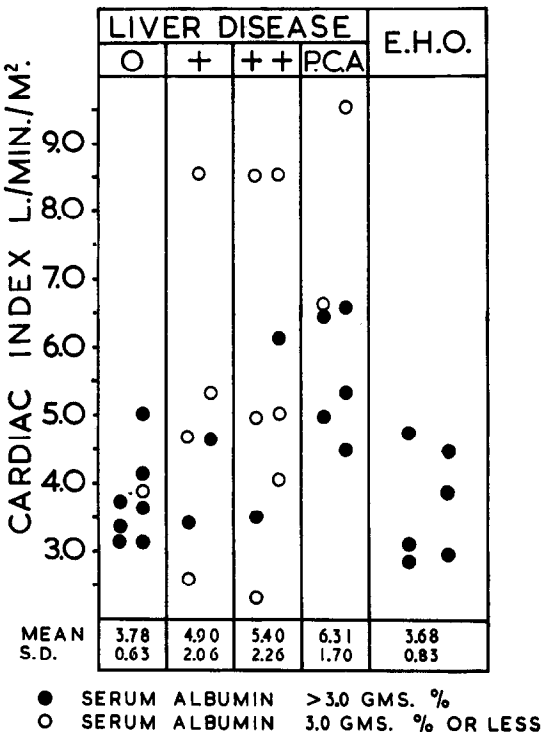

FIG. 2. The range of cardiac indices in patients with liver disease and extrahepatic obstruction (E.H.O.). The portal-systemic collateral circulation is graded zero (absent), one plus (moderate), two plus (marked) and P.C.A. (surgical portacaval anastomosis).

RESULTS

Cardiac Output. The mean cardiac index of the control group was 3.68 ± 0.60 L./minute/sq. M. This value closely approximates the means of several normal series obtained by the Fick and dye methods [*2*]. In portal cirrhosis, the mean cardiac index was 5.36 ± 1.98 L./minute/sq. M. The range was wide but approximately one-half the results were above the upper limit of normal. (Fig. 1.) There was a significant difference ($p < 0.01$) between the cardiac indices of the normal subjects and the group with portal cirrhosis. In contrast, in biliary cirrhosis the mean cardiac index of 3.97 ± 0.75 L./minute/sq. M. did not differ significantly from the normal group ($0.4 < p < 0.5$).

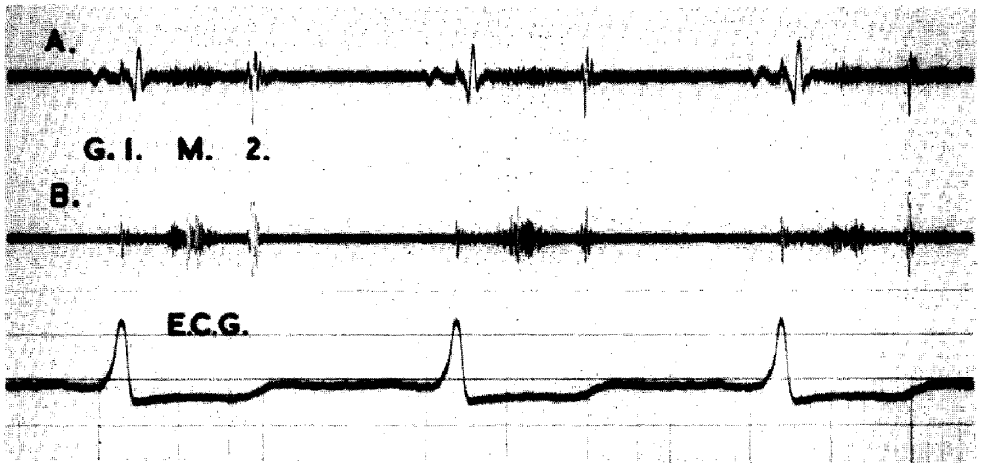

FIG. 3. Phonocardiogram from a patient with high cardiac output and portal cirrhosis. A, low frequency record; B, high frequency record; E.C.G., (electrocardiogram) lead II—showing: 1, first heart sound; 2, second heart sound; M, ejection type systolic murmur; and G, presystolic gallop.

A partial correlation [17] of cardiac index, hematocrit and serum albumin was made. This showed no significant correlation between cardiac index and hematocrit after correcting for the effect of serum albumin alterations ($r = -0.27$); only three patients had hematocrits less than 30 per cent. A better correlation was found between cardiac output and serum albumin after correcting for hematocrit changes ($L = -0.36$); this is not statistically significant ($0.1 < p < 0.2$) but may indicate a trend.

In the patients with liver disease, a statistically significant ($p < 0.05$) correlation was found between the cardiac index and the presence and magnitude of a portal-systemic collateral circulation. (Fig. 2.) However, the cardiac output of six patients with extrahepatic portal vein obstruction and an extensive portal-systemic vascular bed did not differ from the controls. Although all patients with portal cirrhosis and an elevated cardiac output had an increased portal systemic collateral circulation or a portacaval anastomosis, a similar collateral network without liver disease was not associated with a raised cardiac output.

In general, patients with portal cirrhosis and a high cardiac output had ejection systolic murmurs, often associated with a diastolic gallop (Fig. 3), wide pulse pressure, low mean arterial pressure and low peripheral vascular resistance. (Table I.) Clubbing was noted in seven patients with portal cirrhosis and all but one had a cardiac index greater than the upper limit of normal (4.87 L./minute/sq. M.). On the other hand, clubbing was found in four of six patients with biliary cirrhosis, all with a normal cardiac output.

In all patients with liver disease the cardiac index was significantly greater in patients with angiomas compared to patients without nevi ($p < 0.05$). (Fig. 4.) No significant difference was noted when only the patients with portal cirrhosis with and without angiomas were compared ($0.3 < p < 0.4$); however only four patients with portal cirrhosis were free of angiomas. There was no difference in the cardiac indices between patients with one to five angiomas (one plus) and subjects with six or more spider nevi (two plus); many of the "two plus" patients had florid large pulsating angiomas. A similar lack of correlation was found between liver palms and cardiac output.

In spite of the frequently abnormal circulatory state in patients with portal cirrhosis, only two patients had cardiac enlargement by roentgenography (Cases 17 and 38). Electrocardiograms revealed a left ventricular hypertrophy pattern in two patients (Cases 29 and 44), right ventricular enlargement in one instance (Case 17) and an old myocardial infarction in the oldest patient of the group (Case 28).

Blood Volume. The mean blood volume in patients with portal cirrhosis was significantly elevated compared to the control subjects ($0.01 < p < 0.05$). Most of the increase was in the plasma volume fraction with slight change in the red cell mass. (Table II.) In contrast, the blood volume of the patients with chronic biliary

TABLE I

SUMMARY OF CLINICAL AND LABORATORY FINDINGS

(NUMBERS WITHIN PARENTHESES INDICATE RANGE OF FINDING)

Case No.	Age	Sex	Duration of Symptoms	Surface Area (M^2)	Vascular "Spiders" (0–2)	Clubbing	Heart Murmurs (0–4)	Palpable Spleen (0–2)	Ascites (0–2)	Edema (0–2)	Portal-Systemic Collaterals (0–2)	Hematocrit (%)	Cardiac Index (L./m./M^2)	Blood volume (L./M^2)	Arterial Oxygen (% saturation)	Blood Pressure
1	51	M	12 mo.	1.76	1	0	3	1	2	2	2†	30.0	8.5	4.1	94.0	180/80
2	45	F	18 mo.	1.62	2	0	2	0	0	1	2†	31.5	8.5	3.5	94.6	120/70‡
3	41	M	6 mo.	1.91	2	0	1	2	0	0	1†	43.5	3.4	3.3	99.0	143/73
4*	45	M	11 yr.	1.84	0	0	0	1	0	0	0†	45.0	3.8	2.2	99.0	128/80
5	38	M	3 yr.	1.80	1	0	3	1	1	0	1†	42.7	4.8	3.6	93.2	110/58
6	69	F	18 mo.	1.41	2	1	2	2	1	2	2†	40.0	4.1	2.6	93.2	135/64
7	65	M	6 yr.	2.32	2	0	1	0	0	0	1†	41.0	2.6	2.8	....	99/52
8	36	M	3 yr.	1.71	2	1	1	0	0	1	1†	43.2	5.3	3.9	98.2	98/52
9	16	F	5 mo.	1.64	1	0	0	0	1	1	0	34.5	4.2	2.8	97.5	105/74
10	14	F	4 yr.	1.74	2	0	2	2	0	0	1	36.0	8.6	3.3	97.0	133/71
11	52	F	4 yr.	1.43	1	0	0	1	2	1	0	41.4	3.2	2.6	96.4	138/75
12	48	F	6 yr.	1.54	2	0	1	1	0	0	2†	36.2	6.2	2.4	....	130/80‡
13	70	F	4 yr.	1.08	0	0	1	0	0	1	2	37.5	2.3	2.7	96.3	106/46
14	40	M	11 yr.	1.85	0	1	3	2	0	1	2†	34.7	5.1	3.2	96.5	110/52
15	52	F	4 yr.	1.59	1	0	2	1	1	1	2†	33.6	3.5	3.6	95.1	109/65
16	51	M	2 yr.	1.65	2	1	2	0	0	2	2†	35.8	5.0	3.2	94.7	115/58
17	25	M	9 yr.	1.76	1	1	0	0	0	0	..	51.0	5.5	4.1	84.1	120/80
Portal Cirrhosis with Portacaval Anastomosis																
18§	17	F	.....	1.65	0	0	3	1	0	0	..	39.0	6.5	2.8	97.7	110/57
19	57	F	3½ yr.	1.49	2	0	0	1	0	0	..	39.8	5.0	2.6	97.6	125/76
20	47	F	2 yr.	1.72	1	1	2	1	0	1	..	39.0	6.6	3.5	96.3	123/69
21	39	M	5 yr.	1.86	2	0	2	1	0	1	..	34.4	6.7	3.5	95.7	119/61
22	47	M	4 yr.	1.91	2	0	2	1	0	1	..	39.9	4.5	2.9	92.4	134/76
23	56	F	2½ yr.	1.37	2	1	3	1	0	1	..	31.8	5.4	2.7	95.5	104/51
24	49	M	4 yr.	1.90	1	1	2	0	0	0	..	24.2	9.7	3.2	94.6	138/68
Biliary Cirrhosis																
25	63	M	5 yr.	1.52	0	2	0	2	0	0	0	39.5	3.3	3.1	95.6	143/72
26	50	F	4 yr.	1.62	0	0	0	1	0	0	0	39.3	3.2	3.0	98.1	149/89
27	54	F	3 yr.	1.44	0	1	1	1	0	0	0	29.6	3.7	2.6	95.1	160/80
28	71	F	12 yr.	1.27	0	1	0	1	0	0	0	33.8	3.9	2.9	96.7	149/69
29‖	29	F	18 mo.	1.52	0	0	0	2	0	0	0	31.2	5.1	2.8	96.4	130/80‡
30	53	F	6 yr.	1.43	1	1	2	2	0	0	1†	36.5	4.8	3.2	98.1	147/69

* Hemochromatosis.
† Confirmed by surgery, splenogram or autopsy.
‡ Sphygmomanometer reading.
§ Wilson's disease.
‖ Chlorpromazine jaundice.

cirrhosis and extrahepatic portal vein obstruction did not significantly differ from the normal group. (Fig. 5.)

In general, elevated blood volumes were found in portal cirrhosis patients having: (1) an elevated cardiac output, (2) an extensive portal

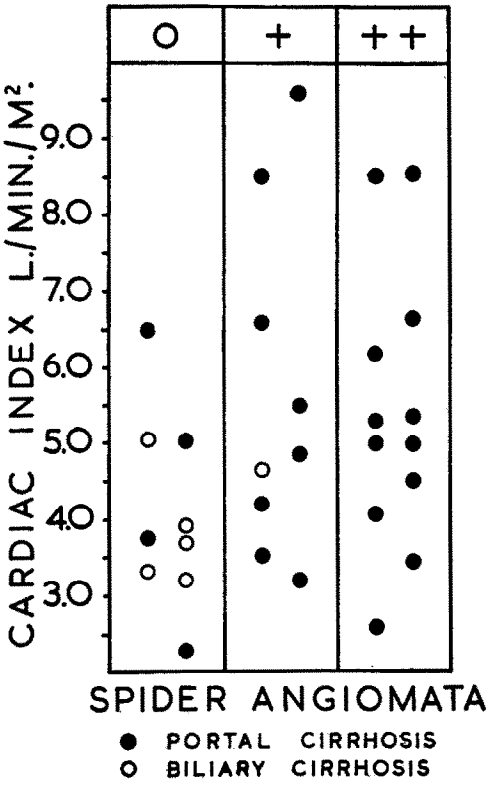

FIG. 4. Correlation of cardiac index and spider angiomas in all patients with liver disease; no spider angioma (zero), one to five angiomas (one plus) and six or more angiomas (two plus).

collateral circulation, (3) arterial desaturation, and (4) decreased serum albumin levels. Patients with an elevated cardiac index had a significantly increased blood volume when compared to the normal group ($p < 0.01$), but this was only of borderline significance ($0.05 < p < 0.1$) when compared to the remaining patients with portal cirrhosis and a normal output.

Patients with liver disease and a demonstrable portal-systemic collateral circulation (Fig. 6) had a significantly greater blood volume ($0.02 < p < 0.05$) than patients with liver disease without a portal-systemic shunt. The presence of the collateral network itself is not responsible for the increased blood volume because the patients with extrahepatic portal vein obstruction had blood volumes mainly within the normal range. This observation does not support the view that the increased volume of the venous collateral bed is largely responsible for the elevated total blood volume found in patients with Laennec's cir-

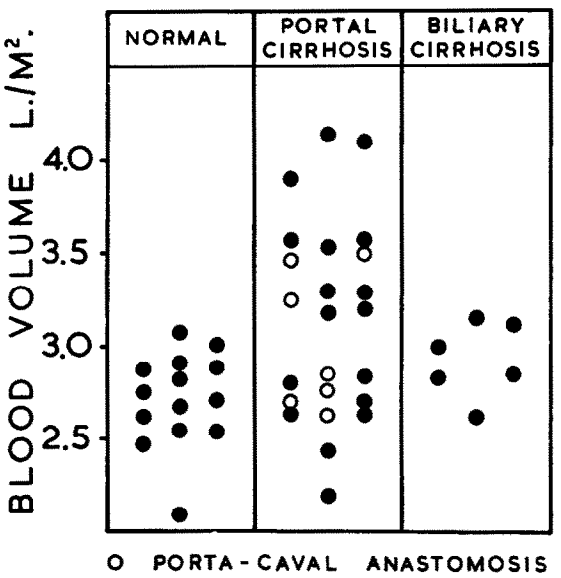

FIG. 5. The range of blood volume in normal adult subjects and in patients with portal cirrhosis and biliary cirrhosis. Normal = 2.72 ± 0.25 L./Sq. M. Hollow circles represent patients with portacaval anastomosis.

rhosis [7,18]. Portacaval anastomosis decreased the collateral network yet the blood volume is increased; this is further evidence against an increased volume of the splanchnic venous system being the main cause of the elevated total blood volume.

There was no statistical difference between the blood volume of portal cirrhotic patients with and without fluid retention ($0.3 < p < 0.5$). A similar lack of correlation between blood volume and ascites or edema in cirrhosis has been noted by Eisenberg [8] and Hiller, Huffman and Levey [18].

Low serum albumin levels are generally found in patients with high blood volumes (Fig. 6); this may represent, in part, dilution of a normal amount of circulating albumin. A similar dilution mechanism accounted for approximately 50 per cent of the low serum albumin levels in patients with cirrhosis studied by Hiller et al. [18].

Arterial Oxygen Saturation. Four of the twenty-four patients with portal cirrhosis had an arterial

oxygen saturation below the lower limit of normal (94 per cent saturated) and in the three patients studied further, the arterial blood did not become fully saturated after breathing 100 per cent oxygen for fifteen minutes. (Table III.) This favors a systemic venous to arterial shunt [*19*].

TABLE II
THE BLOOD VOLUME IN PATIENTS WITH LIVER DISEASE AND EXTRAHEPATIC PORTAL OBSTRUCTION (E.H.O.)

	Normal	Portal Cirrhosis	Biliary Cirrhosis	E.H.O.
Total Blood Volume L./M²				
Mean	2.72	3.13	2.93	2.89
S.D.	0.25	0.52	0.21	0.39
No. of patients	14	24	6	6
Plasma Volume L./M²				
Mean	1.69	2.08	2.00	1.83
Standard Deviation	0.11	0.49	0.08	0.25
Red Cell Mass L./M²				
Mean	1.03	1.05	0.93	1.06
Standard Deviation	0.22	0.26	0.16	0.17

TABLE III
THE HEMATOCRIT AND RED CELL MASS OF THREE PATIENTS WITH HEPATIC CIRRHOSIS AND ARTERIAL OXYGEN DESATURATION

Patients	Arterial Oxygen Saturation (%)		Hematocrit (%)	Red Cell Mass L./M²
	Resting	After Oxygen*		
11	93.2	96.6	42.7	1.41
17	84.7	94.2	51.0	1.84
49	92.4	96.9	49.8	1.24
Normal	97.0	100.0	45.0	1.03

* Saline manometer.

Evans blue dye curves performed during catheterization [*20*] in two patients showed no evidence of an intracardiac right to left shunt. It seems likely that these patients had a pulmonary arteriovenous shunt. Wilson and coworkers [*21*] calculated small pulmonary arteriovenous shunts of unknown variety in patients with cirrhosis. Rydell and Hoffbauer have described a patient with cirrhosis and multiple pulmonary arteriovenous fistulas [*6*]. We have studied a similar patient reported in detail in the next section.

The red cell mass was increased in three of the four patients with arterial desaturation. Two of four patients with low arterial oxygen saturation and portal cirrhosis had clubbing of the fingers. The frequent association of digital clubbing with biliary cirrhosis was not related to peripheral arterial desaturation although many of the patients appeared cyanotic.

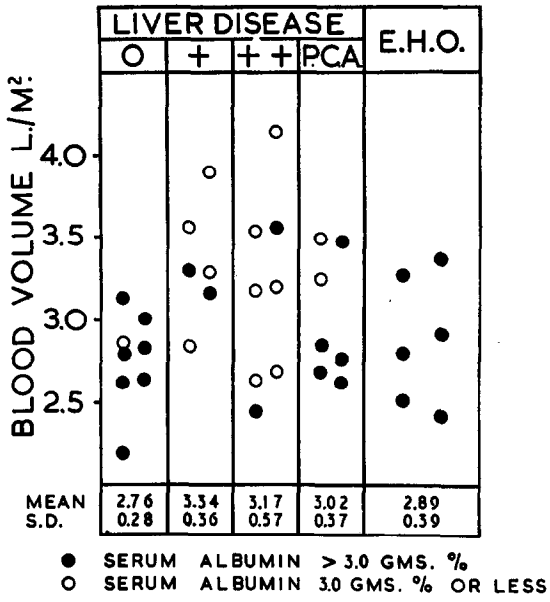

FIG. 6. The range of blood volumes in patients with liver disease and extrahepatic obstruction (E.H.O.). The portal-systemic collateral circulation is graded as in Figure 2.

CASE REPORTS

Two cases are reported as extreme examples of heart disease associated with portal cirrhosis.

CASE 1. *Portal cirrhosis with hyperkinetic circulation and congestive heart failure:* This fifty-one year old white man had been a chronic alcoholic for many years. Congestive cardiac failure had been present for eight months and had progressed in spite of dietary therapy and intramuscular administration of thiamin.

He was admitted to Hammersmith Hospital markedly orthopneic and in frank congestive failure. He was mildly icteric without cyanosis or clubbing. The hands were warm and moist and the peripheral pulses were full and bounding, with a blood pressure 170/80 mm. Hg and pulse rate of 120 per minute. He had a single angioma on his lip. The jugular veins showed a prominent A wave and were distended to the mandible with the patient sitting upright. An active apex impulse was felt 1 to 2 cm. to the left of the mid-clavicular line in the 5th intercostal space. A loud blowing systolic murmur was heard in the tricuspid and pulmonary areas; in addition there was a loud protodiastolic gallop. Massive ascites and lower extremity and sacral edema were present.

Urinalysis showed only a trace of protein. Investigations showed hemoglobin 9.3 gm. per cent, hematocrit 28.0 per cent, leukocytes 19,000 per cu. mm., serum albumin 2.5 gm. per cent, serum globulin 3.5 gm. per cent and serum bilirubin 2.3 mg. per cent. The electrocardiogram was normal and the roentgenogram of the chest revealed questionable cardiac enlargement and marked pulmonary congestion.

TABLE IV
THE BLOOD VOLUME AND CARDIAC OUTPUT OF PATIENT BEFORE AND AFTER TREATMENT

Date	Cardiac Output (L./min.)	Peripheral Resistance (Dynes sec. cm.$^{-5}$)	Mean Arterial Pressure (mm. Hg)	Blood Volume (L./M.^{2})	Central Venous Pressure (mm. Hg)
March 7, 1956.	15.0	610	115	4.14	32/−1
March 12, 1956	9.7	910	110	3.38	13.2*

* Saline manometer.

Five days later limited cardiac catheterization showed the right atrial pressure to be 32/−1 mm. Hg (mean 14 mm. Hg), the cardiac output 15.0 L./minute, the mean arterial pressure 115 mm. Hg, and the calculated peripheral resistance 610 dynes second cm.$^{-5}$. Digitalis, mercurials and a low salt diet were administered with marked improvement and a 9 pound weight loss due to diuresis. Subsequent study when the patient had improved clinically revealed a considerable fall in cardiac output and blood volume, an increase in peripheral resistance and a fall in the central venous pressure. (Table IV.)

The congestive failure improved over the next six weeks although he continued to show evidence of a hyperdynamic circulation. However, his liver function suddenly failed and he died following a gastrointestinal hemorrhage.

Postmortem examination confirmed the presence of chronic portal cirrhosis and esophageal varices. The heart weighed 425 gm. There was slight dilatation and moderate increase in thickness of the left ventricular wall (19 mm.). All valves were normal and the coronary arteries and aorta showed minimal atherosclerosis. Histologically the myocardial fibers were slightly increased in size but showed no other abnormality; no fibrosis or infiltration was seen.

This patient was the only one seen with congestive heart failure. No cause for heart failure could be adduced other than the high output state associated with chronic liver disease.

CASE 17. *Portal cirrhosis and multiple pulmonary arteriovenous fistulas:* This twenty-five year old white man had prolonged fever and jaundice (infectious hepatitis) at the age of four. He was well and active until fourteen years of age when he noted gradual onset of weakness and exertional dyspnea. Since the age of sixteen, multiple episodes of hematemesis or melena had occurred, requiring transfusions on two occasions, and at the age of sixteen he underwent splenectomy for splenomegaly with anemia and thrombocytopenic purpura. At operation the liver was nodular, and biopsy showed portal cirrhosis. For the past year exercise tolerance had become increasingly limited and he has been unable to work. He has had no nocturnal dyspnea, orthopnea, chest pain or ankle swelling.

Physical examination showed a young man with slightly clubbed fingers, cyanotic mucous membranes and nail beds, and a few spider angiomas. Blood pressure (120/70 mm. Hg) and venous pressure were normal. The thorax was enlarged in the A-P diameter. The heart appeared slightly enlarged. The second heart sound in the pulmonary area was slightly split and accentuated. No murmurs or abnormal sounds were heard over the heart or lungs. The liver was not palpable. The peripheral pulses were full and bounding and the extremities were warm.

Laboratory studies revealed the following: hematocrit 51 per cent, hemoglobin 14.2 gm. per cent, serum albumin 3.3 gm. per cent and globulin 3.6 gm. per cent. The electrocardiogram showed right ventricular hypertrophy and roentgenograms of the chest revealed normal lung fields, right ventricular enlargement and dilatation of the main pulmonary artery. No esophageal varices were found on barium swallow.

On cardiac catheterization, the femoral arterial oxygen saturation was 84.1 per cent rising to 94.2 per cent after breathing 100 per cent oxygen. The cardiac index was 4.93 L./minute/sq. M. Analysis of oxygen content of samples obtained from the vena cavae, right atrium, right ventricle and pulmonary artery showed no evidence of a left to right shunt. Evans blue dye studies from the pulmonary artery, right atrium and superior vena cava gave no indication of an intracardiac right to left shunt. The main pulmonary artery pressure was 44/26 (mean 34) mm. Hg. The calculated total pulmonary vascular resistance was 655 dynes second cm.$^{-5}$. Subsequent angiocardiography failed to show an intracardiac shunt or to localize a pulmonary arteriovenous anastomosis. Pulmonary function studies were normal. The plasma volume was 3,958 ml. and the total blood volume 7,196 ml.

This young man with posthepatitis cirrhosis suffered from multiple small gastrointestinal hemorrhages and more recently from an increasingly limited exercise capacity. Cardiac catheterization and pulmonary function data strongly suggested that the arterial desaturation was due to a right to left shunt at the pulmonary arterial level, probably from multiple pulmonary arteriovenous anastomoses. The cause of his modest pulmonary hypertension and increased pulmonary vascular resistance remains unknown. Right ventricular hypertrophy was also noted in a

similar patient described by Rydell and Hoffbauer [6].

COMMENTS

The patients studied are not representative of all cases of portal cirrhosis. Patients were deliberately selected with hyperkinetic circulatory states, extensive collateral circulation, clubbing or cyanosis. The results obtained cannot be applied to liver disease as a whole and the frequency of circulatory changes is unknown. However, certain conclusions can be drawn.

The presence of a high cardiac output in chronic portal cirrhosis has been confirmed. Previous reports have dealt with cirrhosis in alcoholic patients [2,22]; we have observed in cirrhosis of other etiologies a hyperkinetic circulation that could not be related to anemia or nutritional deficiencies.

It is difficult to separate the features involved in the production of a hyperdynamic circulation. The mild liver damage and jaundice of biliary cirrhosis without demonstrable portal collateral circulation, and extrahepatic portal vein obstruction with normal liver function did not lead to a hyperkinetic state. A high cardiac output has been noted in a patient with subacute hepatitis and liver failure who showed no portal collateral circulation at autopsy [23]. We have observed a similar patient with fulminating hepatitis who, without a change of blood pH, had a cardiac output of 15.0 L./minute with a normal blood volume and markedly lowered peripheral resistance. These findings suggest that some degree of liver failure is the essential factor but extrahepatic portal-systemic shunting of blood can be contributory. Further studies before and after portacaval anastomosis are indicated to clarify this point.

The elevated cardiac output with an increased total blood volume (mainly a raised plasma volume with a normal red cell mass) found in portal cirrhosis closely resembles that found with a systemic arteriovenous fistula [24,26], or the generalized vasodilatation of acute beriberi [27,28]. The opening up of a large number of normally present but functionally inactive arteriovenous anastomoses by a vasodilator substance is theoretically equivalent to the effects of a single arteriovenous fistula. Shorr has demonstrated the production of a vasodilator material by the diseased liver [29]. The failure of the diseased liver to metabolize a vasodilator substance produced elsewhere in the body or absorbed from the gut is an alternative explanation to Shorr's hypothesis.

The association of increased cardiac output and a portal-systemic collateral circulation may represent merely two independent aspects of a progressive, chronic disease; or they may be more causally related, due to the shunting away from the liver of some vasodilator substance normally metabolized by the parenchymal cells. An analogous situation accounts in part for the decreased ammonium tolerance found in chronic liver disease [30].

Plethysmography [3] and calorimetric measurements [4] show an increased peripheral blood flow in chronic liver disease. Increased peripheral venous oxygen saturation in cirrhosis and hepatitis has also been presented as evidence of shunting of blood through arteriovenous anastomoses [31]. Whether or not the total increase in cardiac output is distributed to the periphery is unknown. If a vasodilator substance is present it might act generally and the increased flow be more apparent in the upper extremities due to the greater number of arteriovenous anastomoses in hands and forearms. A slight increase in splanchnic flow might therefore be expected. Although the hepatic blood flow is decreased in chronic liver disease [32] the volume and flow through the total splanchnic bed, including collaterals, remains unknown. A generalized vasodilation would accommodate the increased blood volume in the portal cirrhotic group. Neither of these is found in the patients with extrahepatic obstruction and, since a similar degree of collateral circulation is common to both groups, an additional factor is needed to explain the increased blood volume of the former group.

Multiple pulmonary arteriovenous fistulas associated with portal cirrhosis have been clearly demonstrated by Rydell and Hoffbauer [6] and our Case 17 is probably similar. The presence of pulmonary arteriovenous shunts adequately explains the initial arterial oxygen desaturation and failure to reach 100 per cent saturation following inhalation of 100 per cent oxygen in two other patients in this series. This phenomenon may also result from a vasodilator material acting particularly upon preformed pulmonary arteriovenous anastomoses.

In general, patients with an elevated cardiac output due to portal cirrhosis have a normal response to exercise [22] and tolerate the added circulatory burden without decompensation.

No reports were found in the literature similar to our Case 1 who had heart failure due to liver disease without associated thiamin deficiency. It is probable that most patients die of liver failure before congestive heart failure has had time to develop. It is known that a small to moderate sized systemic arteriovenous fistula may be present for many years before causing signs of congestive heart failure.

No specific therapy is indicated for patients with a hyperdynamic circulation unless decompensation is present. Observations in nine cases have shown that as liver function improves in the hospital the cardiac output returns toward normal. Therapy should be directed to improving the underlying liver disease.

SUMMARY

The circulatory findings in twenty-four patients with portal cirrhosis were compared with results in six patients with biliary cirrhosis, six patients with extrahepatic portal vein obstruction and fourteen normal subjects.

Half the patients with portal cirrhosis had a cardiac index above the upper limit of normal. Clinically, these patients had evidence of increased peripheral blood flow and ejection systolic murmurs. Roentgenographic or electrocardiographic changes were uncommon. Patients with biliary cirrhosis and portal vein obstruction had normal cardiac indices.

An increased total blood volume, mainly plasma volume, was found in patients with portal cirrhosis who had an increased cardiac index, a large portal-systemic collateral circulation, arterial oxygen desaturation and low serum albumin levels. The increased portal venous network did not account for the increased blood volume in portal cirrhosis as patients with extrahepatic portal vein obstruction had virtually normal blood volumes. The low serum albumin levels may in part represent the dilution of a normal amount of circulating albumin by an increased plasma volume.

Four patients had low arterial oxygen saturation. Cardiac catheterization data in one patient and studies in two others suggest that the arterial desaturation may be due to the shunting of blood through pulmonary arteriovenous anastomoses. One of these cases is presented in detail.

In most patients with portal cirrhosis the increased cardiac output was tolerated without evidence of decomposition. Congestive heart failure was present in one patient reported in detail. As liver function and the clinical status of patients with portal cirrhosis improved, the cardiac output returned toward normal.

The mechanism of production of the hyperdynamic circulatory state in portal cirrhosis is unknown. There is profound vasodilatation and the mechanism of this is discussed.

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