THE CARDIAC OUTPUT AT REST IN LAENNEC'S CIRRHOSIS

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Research Article

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INTRODUCTION

Patients with Laennec's cirrhosis and those with occidental beri-beri frequently have the common background of consumption of alcoholic beverages and inadequate diet of long duration. A short circulation time which may be found in occidental beri-beri (1) and in Laennec's cirrhosis (2, 3) suggests an elevated cardiac output. In the case of beri-beri, this has been verified (4, 5, 6, 7), but, to our knowledge, direct measurements of systemic blood flow have not been reported in chronic liver disease. Increased flow of blood to the periphery in patients with Laennec's cirrhosis is suggested by the frequent occurrence of warm extremities, cutaneous vascular spiders, wide pulse pressure, and capillary pulsations in the nail beds.

The present study reports measurements of the resting cardiac output, blood pressure, and peripheral resistance in patients with chronic alcoholism and disease of the liver.

MATERIALS AND METHODS

Selection of patients

Twenty-two hospitalized patients [3] with clinical and/or laboratory evidence of chronic parenchymal disease of the liver were studied. Only patients without clinical evidence of co-existing heart disease and without evidence of acute gastro-intestinal bleeding were included. All subjects gave a history of excessive intake of alcoholic beverages and an irregular and inadequate diet of long-standing.

Of the 22 patients studied, three had "fatty liver," 11 had Laennec's cirrhosis without fluid retention, and eight had Laennec's cirrhosis with either ascites or peripheral edema or both. Of the 19 patients with Laennec's

cirrhosis, all save one (No. 17) had enlargement of the liver, and all but two (Nos. 11 and 18) had cutaneous vascular spiders. All 22 patients had abnormally high Bromsulfalein retention.

A diagnosis of "fatty liver" was made clinically when there was enlargement of the liver and laboratory evidence of hepatic dysfunction without the following: icterus, cutaneous vascular spiders, ascites, edema, splenomegaly, or prominent abdominal veins.

PROCEDURES

Each patient was studied early in the morning without any premedication, fasting and recumbent. An indwelling needle was inserted into the left brachial artery and a similar needle was placed into a right antecubital vein. The patient then was allowed to rest for at least twenty minutes.

Cardiac output

The cardiac output was determined by the dye-injection method as described by Hamilton and his co-workers (8). Five mg. of a 0.5 per cent solution of Evans blue dye were injected rapidly through the venous needle from a tuberculin syringe previously calibrated by weighing. The dead space of the indwelling needle was known and accounted for in determining the amount of dye injected. Samples of arterial blood were collected from the arterial needle through a short length of polyethylene tubing into heparinized tubes mounted along the rim of a circular lucite disc equipped with funnels arranged so that spillage between tubes was minimized. The disc was rotated about a centrally placed vertical shaft by a variable-speed electric motor. The usual collection time for each tube was two and one-half seconds. Samples of arterial blood were centrifuged for 20 minutes at 3,000 rpm. and the concentration of dye in undiluted plasma was determined in micro-cells of 0.5 cc. capacity at a wave length of 625 mμ. using a Beckmann Model DU spectrophotometer. In most patients duplicate estimations were made.

The cardiac index was calculated from the cardiac output and the body surface area using the height and weight at time of study irrespective of the presence or absence of edema. In subjects with marked obesity and perhaps in those with abnormal fluid retention, the body surface area calculated according to Du Bois and Du Bois (9) might distort the predicted value for cardiac index (10, 11). The cardiac output also was expressed in terms of oxygen consumption as a ratio by the formula:

$$\frac{\text{Cardiac output L./min.} \times 100}{\text{Oxygen consumption cc./min.}}$$

TABLE I

*Cardiac index—"normal" values**

Authors	No. subjects	Method	Mean ±	Standard deviation of sample
			Cardiac index	Cardiac output L./min. × 100 / Oxygen consumption cc./min.
Cournand et al. (J. Clin. Invest., 1945, 24, 106.)	30	Fick	3.31 ± 0.54	. 2.32 ± 0.32
Stead et al. (J. Clin. Invest., 1945, 24, 326.)	18	Fick	3.27 ± 0.57	2.52 ± 0.39
Ebert et al. (J. Clin. Invest., 1949, 28, 1134.)	12	Fick	3.59 ± 0.72	2.64 ± 0.34
Chapman et al. (J. Clin. Invest., 1950, 29, 651.)	7	Fick	3.27 ± 0.62	2.67 ± 0.43
Dexter et al. J. Applied Physiol., 1951, 3, 439.)	7	Fick	3.79 ± 0.83	2.77 ± 0.37
Doyle et al. (J. Clin. Invest., 1951, 30, 345.)	10	Fick Dye	3.52 ± 0.79 2.85 ± 0.40	2.41 ± 0.35 1.97 ± 0.87
Freis et al. (J. Clin. Invest., 1952, 31, 131.)	8	Dye	4.19 ± 0.81	
Present Authors	12	Dye	3.76 ± 0.65	

* Calculated by us from data in sources listed. Subjects with "anxiety" excluded as in individual reports. Two or more observations on the same subject were averaged, and the mean was used in these calculations.

Table I indicates values of cardiac index as reported by others and as determined in this laboratory using the dye-injection method in subjects who were considered essentially normal. Also shown are values for the ratio of cardiac output to oxygen consumption.

Oxygen consumption

Oxygen consumption was determined over a six-minute period by means of a closed circuit water spirometer filled with oxygen, after the cardiac output studies were completed.

Arterial pressure

Phasic and mean arterial pressures were measured directly by means of an electromanometer of the condenser-microphone type and recorded on a direct writing oscillograph.[4]

Peripheral resistance

The formula used was (12):

$$\text{Resistance} = \frac{\text{Mean arterial pressure mm. Hg} \times 1332}{\text{Cardiac output cc./sec.}}$$

[4] Made by Sanborn Company, Cambridge, Massachusetts.

Venous pressure

Venous pressure was estimated by means of a saline manometer attached to the indwelling needle located in the antecubital vein, and referred to a zero point 5 cm. below the angle of Louis.

RESULTS

The data are found in Table II.

Cardiac output (Figure 1)

The mean cardiac index of patients with disease of the liver was 4.26 L. per min. per M², and the standard deviation of the sample was ± 2.73 L. per min. per M². Values below the normal range were not seen, and in seven patients they were above the normal range.

As indicated in Figure 1, elevations of output were noted in one of the three patients with "fatty liver" as well as in patients with cirrhosis, irrespective of the presence or absence of abnormal fluid retention or of jaundice.

TABLE II

Cardiovascular studies in patients with cirrhosis

Subject No.	Age	Sex	B.S.A. M²	Days in hospital at time of study	Icterus index units	B.S.P. ret. 5 mg. Kilo. 45 min. %	Hct. %	Oxygen cons. S.T.P. cc./min.	Heart rate per min.	Cardiac index L./min./M²	Mean	Cardiac output + oxygen cons.	Mean stroke volume cc.	Blood press. Syst./Diast. mm. Hg	Mean mm. Hg	Peripheral resistance dynes $cm. sec.^{-5}$	Transverse cardiac diameter % predicted	K	Venous pressure mm. saline
										"Fatty liver"									
1	45	M	1.78	1	<10		43	289	84	5.07 6.68	5.88	3.62	126	114/68	88	672	90	.438	
2	44	M	1.77	2	10–20	33	43	256	86	6.10 3.54	4.82	3.33	100	140/90	107	1002		.406	30
3	41	M	1.70	1	<10	12	39	269	95	3.46 3.68	3.57	2.27	64	153/85	112	1466	99	.370	40
										Laennec's cirrhosis without edema or ascites									
4	40	F	1.67	77	<10	30	30	191	100	6.05 6.11	6.08	5.33	101	113/60	83	654	108	.463	90
5	42	M	1.79	22	20–30	54	38	292	87	5.70 6.25	5.98	3.66	123	105/60	80	598	112	.425	65
6	49	F	1.92	23	<10	27	29	251	79	4.86 5.47	5.17	3.95	125	93/57	74	596	98	.471	100
7	34	F	1.48	19	>100	45	32	243	80	5.07 4.78	4.93	3.00	91	108/61	80	878	109	.394	90
8	44	M	1.76	24	30–40		38	322	76	4.62	4.62	2.52	107	115/70	85	836	119	.394	
9	40	M	1.87	102	<10	17	43	288	88	4.12	4.12	2.67	87	100/74	83	862	119	.438	10
10	43	M	1.64	28	10–20	48	40	295	100	3.91	3.91	2.17	64	102/82	89	1110	123	.412	
11	51	M	1.63	14	<10	17	34		62	3.33 3.27	3.30		87	130/80	97	1439	102	.400	
12	46	M	1.40	22	10–20	39	44		90	3.04	3.04		47	118/70	86	1617	104		
13	57	M	1.85	1	<10		48	246	73	3.08 2.95	3.02	2.27	76	120/75	90	1289	113	.530	
14	42	M	1.77	1	10–20	55	41	304	98	2.50 3.01	2.76	1.61	50	130/100	120	1965		.411	

TABLE II—*Continued*

Subject* No.	Age	Sex	B.S.A. M²	Days in hospital at time of study	Icterus index units	B.S.P. ret. 5 mg. Kilo. 45 min. %	Hct. %	Oxygen cons. S.T.P. cc./min.	Heart rate per min.	Cardiac index L./min./M²		Cardiac‡ output + oxygen cons.	Mean stroke volume cc.	Blood press. Syst./Diast. mm.Hg	Mean	Peripheral resistance dynes cm.sec.⁻⁵	Transverse§ cardiac diameter % predicted	K‖	Venous pressure mm. saline
											Mean								
Laennec's cirrhosis with edema and/or ascites																			
15	42	M	2.15	27	<10	47	32	257	105	11.2	11.2	9.40	233	125/105	111	367	114	.430	
16	59	M	1.77	2	20–30	45	40	332	94	6.33 5.76	6.05	3.23	114	111/69	88	658	111	.446	80
17	51	F	1.94	1	40–60	45	30		117	5.32 4.84	5.08		84	100/67	76	618	102	.431	30
18	64	M	2.06	37	10–20	39	33	253	74	5.39 4.31	4.85	3.98	136	100/55	68	542		.422	90
19	38	F	1.65	4	<10	38	27	200	97	4.37 4.11	4.24	3.50	72	78/56	66	754	102	.428	50
20	39	M	1.85	3	30–40	38	21	238	120	4.61 3.46	4.04	3.13	62	104/66	76	814	135	.459	110
21	42	M	1.88	25	20–30	34	38	270	76	3.97	3.97	2.76	98	97/72	80	854	113	.390	
22	62	M	2.04	15	<10	61	31		93	3.04 3.34 3.34	3.24		71	160/95	117	1408		.479	

* Vitamin B₁ therapy: Subject 4, 20 mg. I.M., 30 days; Subject 5, 10 mg. I.M., 22 days; Subject 19, 100 mg. I.M., 4 days; Subject 21, 100 mg. p.o., 21 days. Subjects 4, 5, 12, and 21 were given a daily multivitamin supplement which contained thiamine hydrochloride 10 mg., riboflavin 6 mg., niacinamide 80 mg., pyrodoxine HCl 6 mg., calcium pantothenate 6 mg., and ascorbic acid 100 mg.

† Icterus index, less than 10 considered normal.
‡ Cardiac output L./min. × 100 / Oxygen consumption cc./min.
§ Criteria of Ungerleider, H. E., and Gubner, R., Am. Heart J., 1942, 24, 494.
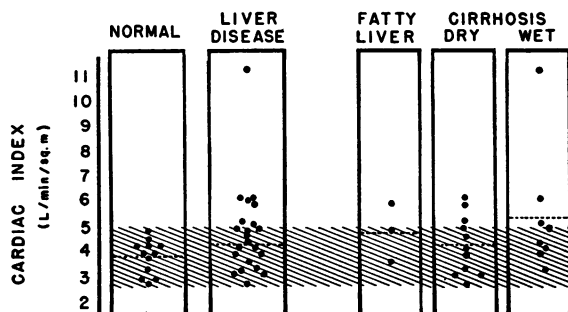‖ Constant for Q-T interval corrected by the formula of Bazett.

FIG. 1. SCATTER OF CARDIAC INDEX

The second column represents all patients with liver disease. The third, fourth, and fifth are subdivisions of column two. The mean for each group is indicated by the dotted line. The shaded area represents the normal mean ± two standard deviations of the sample.

Although one patient (No. 15) had a very high cardiac index, 11.2 L. per min. per M², this apparently did not unduly influence the mean of 4.76 since the median value for the series lay between 4.62 and 4.24 L. per min. per M². (This individual was restudied six weeks later at which time his cardiac index was 16.3 L. per min. per M² and his oxygen consumption was 263 cc. per min.)

The mean value of the ratio,

$$\frac{\text{cardiac output L./min.} \times 100}{\text{oxygen consumption cc./min.}},$$

in the patients with liver disease was 3.47 and ranged from 1.61 to 9.4. In contrast the mean values of this ratio in normal subjects (Table I) range from 1.97 to 2.77. Elevated ratios were found in patients with cirrhosis with and without fluid retention and in patients with "fatty liver."

Figure 2 is a plot of cardiac index against the cardiac output-oxygen consumption ratio. Those patients with the highest value of cardiac index had the highest ratios, suggesting that where the cardiac output is elevated such elevations are not accompanied by parallel increases in oxygen consumption.

Arterial pressure

Values for mean arterial pressure ranged from 66 to 120 mm. Hg. Patients with the higher pressures generally had normal outputs with one exception (No. 15), whose mean pressure was 111 mm. Hg at a time when his cardiac index was 11.2 L. per min. per M².

Peripheral resistance

Values ranged from 367 to 1965 dynes-cm.-seconds^{-5} with a mean of 955, a value within accepted normal standards (13). Peripheral resistance was inversely related to cardiac output as seen in Figure 3. The mean resistance of the seven patients with high cardiac outputs was 596, a low value.

Venous pressure

Antecubital venous pressures where measured were within normal limits. Neck veins were not distended in recumbency in any patients.
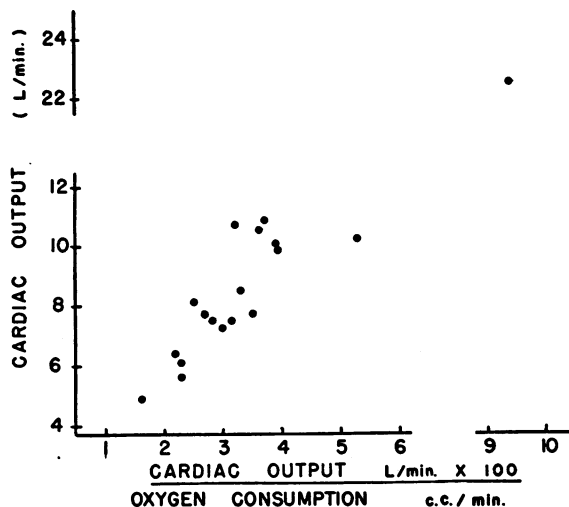

FIG. 2. RELATION OF CARDIAC OUTPUT TO OXYGEN CONSUMPTION AT DIFFERENT LEVELS OF CARDIAC OUTPUT

Heart rate and stroke volume (Figure 4)

A slight elevation of resting heart rate was a feature of most patients with liver disease. Although the patients with the highest outputs tended to have faster rates, there was no consistent association between output and rate. Elevations of stroke volume as opposed to tachycardia were the immediate mechanism which produced the elevations in output.

Heart size

With the exception of two individuals (Nos. 17 and 22), all patients were examined by fluoroscopy. No chamber enlargement was noted. Unusually vigorous cardiac pulsations were conspicuous in
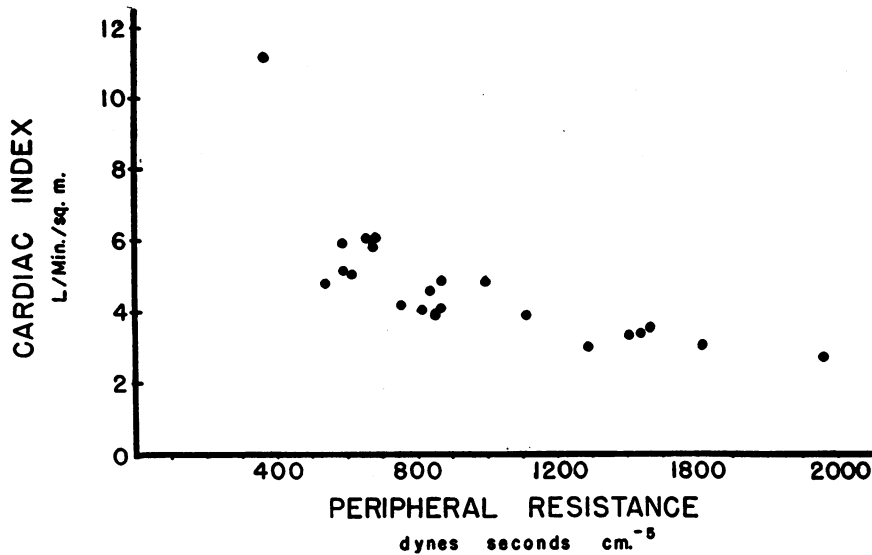
Fig. 3. Relation of Total Peripheral Vascular Resistance to Cardiac Index

some patients and frequently were associated with large stroke volumes.

The transverse diameter of the heart measured from teleoroentgenograms averaged 110 per cent of predicted values. (Normal range = 90 per cent to 110 per cent.) The mean transverse diameter in the seven patients with elevated outputs averaged 105 per cent of predicted values. Heart size, then, was not abnormal.

Electrocardiograms

The Q-T interval was prolonged in eight patients using the criteria of Shipley and Hallaran

Fig. 4. Relation of Stroke Volume to Cardiac Output

(14). Four of the eight had a high cardiac output. All electrocardiograms otherwise were within normal limits.

DISCUSSION

The data indicate that the cardiac output determined at rest and in recumbency may be normal or distinctly elevated in patients with chronic alcoholism and parenchymal disease of the liver.

When the output is increased, it is out of proportion to the oxygen consumption or, by implication from the Fick formula (C.O. = oxygen consumption/arterio-venous oxygen difference), the arterio-venous oxygen difference must be decreased. The increase in blood flow is mainly accomplished by a larger output per beat. Since the arterial pressures are essentially normal, the increased blood flow is associated with decreased total vascular resistance. The hemodynamic picture in these subjects with elevated outputs resembles the high output state as seen in beri-beri heart disease (4, 5, 6, 7) and in the "shunt circulation" of arterio-venous fistulae (15, 16) or Paget's disease (17).

Several factors might be involved in producing the elevated outputs seen in one-third of the present series:

Anxiety, which may elevate the cardiac output (13, 18, 19), does not appear responsible for the increase in blood flow since the subjects were relaxed, indifferent, and without overt resentment.
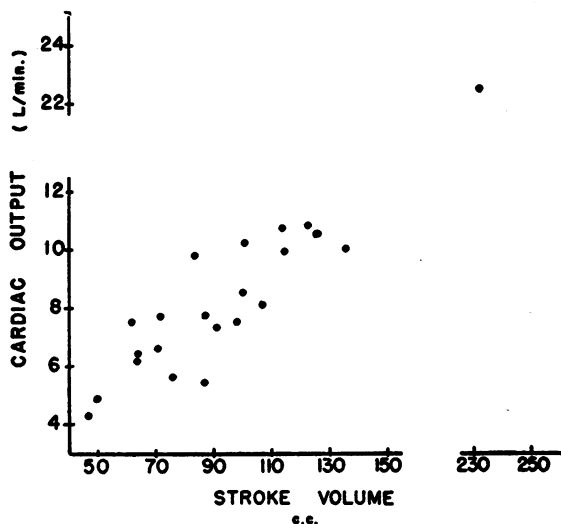
Anemia, a frequent feature of parenchymal disease of the liver, is associated with an elevation of cardiac output when the hemoglobin falls to about 7 Gm. per 100 cc. or the hematocrit to about 20 per cent (20). Anemia of such degree was not seen in these patients, and since high values for cardiac output were seen in subjects with normal or near normal hematocrits, anemia does not adequately explain the elevated output.

All subjects gave a history of longstanding consumption of alcohol combined with a poor dietary intake. This background is similar to that of patients with occidental beri-beri as reported by Weiss and Wilkins (1) and by Blankenhorn (21). However, in our patients, clinical evidence of thiamine deficiency, such as neuritis, was absent, venous pressure was not elevated, cardiac enlargement was not evident, and heart failure was not seen. Four of the seven subjects with elevated outputs (Nos. 4, 5, 6, and 15) had been hospitalized 22 days or longer before study, and during this time they consumed nutritious diets under supervision. Two of these four patients (Nos. 42 and 5), in addition, were given supplementary thiamine chloride parenterally (Table II). In view of these facts, occidental beri-beri seems unlikely as an explanation of the elevated outputs seen in some patients.

Elevated concentrations of blood pyruvic and lactic acid have been noted in some patients with cirrhosis (22, 23, 24). This raises the possibility of impaired utilization of thiamine even in the presence of adequate amounts of the vitamin.

The high output state noted in some patients may be related to a deficiency state other than beri-beri. However, Howarth (25) studied the resting cardiac output in 20 severely malnourished individuals with hunger edema, and without evidence of vitamin deficiencies. The outputs were normal or low. The nutritional heart disease described in association with liver disease in the South African Bantu (26) also appears associated with normal or low cardiac outputs at least at the stage of the disease observed.

The existence of arterio-venous communications in normal as well as in cirrhotic livers has been demonstrated by Herrick, by Prinzmetal and his co-workers, and by Dock (27, 28, 29). The role of these communications in producing elevations of cardiac output would not seem great since estimates of hepatic blood flow and splanchnic arterio-venous oxygen difference (30, 31) suggest the former is decreased and the latter increased in subjects with cirrhosis.

The site of the increased blood flow thus would seem to lie in the periphery of the body, and we fall back on the concept suggested by Weiss and Wilkins (1) in explanation of the circulatory changes in beri-beri, namely that there exists generalized peripheral arteriolar dilatation, acting in effect like multiple arterio-venous shunts in parallel.

Shorr, Zweifach, Furchtgott, and Baez (32) have demonstrated that a vasodilator material, VDM, is produced by the liver under anaerobic conditions, and that it is inactivated by normal but not by anoxic liver tissue. Moreover, VDM was not inactivated under aerobic conditions by the livers of cirrhotic rats (33). It is thus conceivable that in human cirrhosis VDM is increased, or there is an imbalance in the VDM-VEM system in favor of VDM. This, then, could be a mechanism involved in the production of peripheral vaso-dilatation.

In the final analysis, we do not know whether the elevated outputs are related specifically to hepatic disease, or to a form of chronic malnutrition, or even whether they may represent the circulatory response of certain patients with chronic alcoholism to the laboratory situation.

The high incidence of prolongation of the Q-T interval is of interest in relation to similar electrocardiographic findings observed in occidental beri-beri (1), and in general deficiency states not related to thiamine deficiency (34). Prolongation of the Q-T interval has been noted by other workers in cirrhosis (35, 36).

SUMMARY

Observations made in 22 patients with a history of alcoholism, and inadequate diet, and cirrhosis of the liver indicate that the resting cardiac output was elevated in one-third of the patients and was associated with a large stroke volume, normal blood pressure, and low peripheral vascular resistance. Where the cardiac output was high, it was elevated out of proportion to the oxygen consumption, indicating a decreased arterio-venous oxygen difference.

It is suggested that dilatation of the peripheral vascular bed is responsible for the increased blood flow.

ACKNOWLEDGMENTS

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