Hepatic Circulation in Cirrhosis of the Liver

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The hepatic blood flow (EHBF) was estimated by the bromsulfalein method in 39 cirrhotic patients. In 91 normal subjects hepatic blood flow averaged 1530 ml. per minute, and in the cirrhotics, hepatic blood flow averaged 1090 ml. per minute. In association with this highly significant reduction in blood flow, hepatic arteriovenous oxygen difference increased and bromsulfalein extraction fell. These findings indicate that hepatic blood flow tends to decrease more than oxidative metabolism of residual functional cells, so that relative ischemia and hypoxia of active liver tissue develop in cirrhotic disease.

THE HEPATIC vasculature is strikingly transformed by the structural changes that occur in cirrhotic disease. The destruction of parenchymal tissue, reparative hyperplasia of liver cells, and overgrowth of fibrous tissue bring about an attenuation of blood vessels and a reduction in the complexity of the vascular network.[1–3] This process appears to affect preponderantly the branches of the portal vein. Thus, portal venous hypertension and the development of collateral venous drainage may be attributed to the structural obstruction in the liver to the inflow of portal venous blood. It has been claimed that hepatic arterial inflow may actually increase in this situation and that total hepatic blood flow may be augmented in cirrhotic disease. This view has found support in studies by Herrick[4] and Dock[5] of the postmortem perfusibility of the hepatic circuit in the cirrhotic liver. There is little anatomic evidence, however, of diminished resistance to arterial inflow, and it seems probable that any structural change that affects the hepatic vasculature at the level of the sinusoids would affect both arterial and venous perfusion. The development of venous catheterization technics by Cournand and his associates[6] has provided a direct means of examining the behavior of the hepatic circulation in patients with cirrhosis of the liver.

Methods

The hepatic blood flow has been estimated by the bromsulfalein (BSP) clearance technic in 39 patients with cirrhotic disease. In 29 subjects a diagnosis of Laennec's cirrhosis (17 had a history of chronic alcoholism and 12 did not) was made on the basis of prolonged clinical study. Measurements were also made in patients with cirrhosis due to schistosomiasis (four), syphilis (one) and chronic periportal inflammation (biliary cirrhosis, one). Four subjects with Banti's syndrome due to extrahepatic portal venous obstruction are included in this series. Determination of hepatic oxygen extraction was made in 29 of these subjects and in 12 additional persons with cirrhosis (seven with a history of chronic alcoholism and four without) and extrahepatic block (one). The diagnosis was confirmed by biopsy or at necropsy in 46 of the 51 individuals comprising the total series. None of these individuals was jaundiced or in frank cholemia, but all presented clear-cut evidence of portal venous hypertension. Hepatic blood flow was also estimated in 91 "normal" subjects and hepatic oxygen extraction was measured in 27. Data obtained in studies of 14 cirrhotic subjects and of 25 normal individuals included in this paper have been reported previously in preliminary form.[7, 8]

All subjects were selected from patients on the wards of the Presbyterian Hospital in New York City and the Evans Memorial Hospital in Boston, and were studied under comparable conditions of quiet recumbency in the fasting state. An infusion of bromsulfalein (from 200 to 400 mg. per 100 ml. in isotonic saline or glucose) was administered intravenously at a constant rate of about 4 ml. per minute, after a "priming" dose of 150 mg. had been given. A calibrated Murphy drip and tunnel clamp or a Bowman pump* was used to maintain the rate of infusion as nearly constant as possible. An extra length plastic ureteral catheter was inserted into a medial antecubital vein and passed under fluoroscopic control by way of the superior vena cava, right atrium and inferior vena cava into a right hepatic vein. A glucose infusion containing a small amount of heparin (2 mg. per 100 ml. of infusion) was allowed to flow slowly through the venous

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* Obtained from Process and Instruments Company, Brooklyn, New York.

catheter throughout the procedure. After an appropriate period (about 30 minutes) to permit equilibration of the bromsulfalein concentration in the blood, peripheral venous or arterial blood was sampled and from 5 to 10 minutes thereafter a sample of hepatic venous blood was taken through the catheter after withdrawing 2 or 3 ml. of blood and discarding it in order to avoid admixture of the blood sample with heparin-infusion solution. This procedure was repeated at least two or three times at 10 minute intervals. Whenever possible, arterial and hepatic venous blood was sampled simultaneously under anaerobic conditions in order to determine hepatic oxygen uptake. Bromsulfalein was determined colorimetrically in serum or heparinized plasma using a calibration curve based on bromsulfalein standards made up in plasma half diluted with isotonic saline. A Coleman Jr. colorimeter was used in the vast majority of these studies and readings were made at 580 λ using each plasma or serum sample as its own blank. A reading was made after adding a few drops of 20 per cent potassium hydroxide to the sample. Transmittance curves indicated maximal absorption between 570 and 580 λ when standards were made up in isotonic saline or pooled plasma. Some apparent loss of bromsulfalein occurred when plasma was allowed to stand owing to change in plasma pH toward alkalinity. At high concentrations of bromsulfalein isotonic saline solution was used to dilute the plasma sample in order to avoid clouding or precipitation of protein. Hemolyzed samples could not be used because of a variable and uncontrolled degree of clearing with alkalinization. High concentrations of bilirubin also made accurate determination of bromsulfalein impossible. Oxygen content and capacity of the blood were determined by the method of Van Slyke and Neill.[9] The oxygen concentrations were corrected, when necessary, for inadvertant dilution, on the basis of average arterial oxygen capacities.

The hepatic blood flow (EHBF) was estimated from the hepatic bromsulfalein removal rate and hepatic bromsulfalein arteriovenous difference.[7] Bromsulfalein removal was calculated from the rate of infusion and the rate of change in total plasma content of bromsulfalein, assuming distribution of the protein-bound dye in the plasma alone and calculating plasma volume on the basis of body surface. In general the plasma level remained relatively constant (see tables). An effort was made to keep the plasma concentration below 2 mg. per 100 ml., since saturation of hepatic removal mechanisms occurs at higher levels and bromsulfalein extraction (hepatic bromsulfalein arteriovenous difference divided by arterial bromsulfalein concentration) tends to fall. When bromsulfalein extraction was less than 10 per cent at peripheral arterial or venous concentrations greater than 1 mg. per 100 ml. or less than 15 per cent at values less than 1 mg. per 100 ml., the determinations were considered valueless and discarded because the hepatic arteriovenous difference was too small under these circumstances for accurate measurement.

Validity of the Method for Estimating Hepatic Blood Flow

The method used in this study for estimating hepatic blood flow is based on three major assumptions: (1) that blood obtained from a right hepatic vein is representative of the mixed venous blood draining from the liver as a whole; (2) that the concentration of bromsulfalein in the peripheral arterial or venous blood is equal to the concentration in blood entering the liver; and (3) that bromsulfalein is removed from the blood exclusively by the liver. The situation obtaining in the splanchnic vasculature as a result of portal cirrhosis makes it necessary to examine these points in some detail.

Exploratory sampling of blood from various sites in any single liver has been carried out in eight subjects, two of whom had cirrhosis of the liver.[10] Bromsulfalein extraction differed at the extremes by 26, 20, 14, 13, 10 and 9 per cent in the normal individuals, and by 2 per cent in each of the cirrhotics. These results indicate relatively uniform removal of the dye throughout every part of the hepatic parenchyma. The contribution of nonextractive tissues, such as the capsule, may account for a tendency to reduced extraction in areas close to the periphery of the liver. Samples obtained close to the inferior vena cava also tended to show somewhat lower extraction of bromsulfalein, possibly because regurgitation of blood resulted in contamination of the hepatic venous sample with blood containing a higher concentration of the dye. In view of these observations every effort was made to maintain the position of the tip of the catheter deep in the center of the right hepatic lobe. Since the hepatic veins drain separately into the inferior vena cava it is impossible to sample mixed hepatic venous blood. Hence any inequality of extraction by different parts of the liver cannot be corrected and error is introduced into the measurement of flow. For this reason chiefly the value obtained is referred to as the "estimated hepatic blood flow" (EHBF).

TABLE 1.—*Estimated Hepatic Blood Flow in "Normal" Human Subjects*

Subjects	Sex	Age yrs.	Surface area	P_{BSP}	E_{BSP}	R_{BSP}	Hematocrit	EHBF
			M.²	*mg.%*	*%*	*mg./min.*	*%*	*ml./min.*
A. C.	M	24	1.76	1.83	58.0	5.5	46.0	970
A. P.	F	24	1.65	2.00	53.0	5.4	49.0	1000
E. R.	F	24	1.37	1.43	53.0	4.4	46.0	1060
J. M.	M	25	1.99	1.20	86.0	6.2	45.0	1090
J. Mc.	M	22	1.75	1.52	59.5	5.5	44.5	1090
J. F.	M	28	2.07	2.35	48.0	6.0	51.0	1090
C. M.	M	33	1.90	1.33	72.0	5.7	46.0	1110
R. Mc.	M	37	1.82	1.64	59.5	5.7	48.0	1120
M. H.	F	22	1.40	1.60	37.5	4.3	37.5	1130
E. M.	F	55	1.88	1.52	37.0	3.9	40.0	1140
R. S.	F	20	1.58	1.30	59.0	4.6	48.0	1150
W. S.*	M	51	2.02	1.30	64.0	5.4	44.0	1160
S. J.	M	28	1.60	1.20	48.5	4.3	37.0	1170
P. W.	F	36	1.49	0.90	54.5	3.9	33.0	1190
J. F.	M	23	1.77	1.67	44.0	5.7	36.0	1190
G. H.	M	23	1.69	1.16	73.5	5.2	49.0	1200
A. A.	M	36	1.91	1.29	73.0	5.8	48.5	1200
F. G.	M	21	1.73	0.75	88.0	4.1	49.0	1220
K. Mc.	F	46	1.32	0.70	70.5	4.0	37.0	1240
M. R.	F	26	1.46	1.14	51.0	4.0	45.0	1250
N. P.*	M	60	1.70	1.04	71.0	4.9	48.0	1260
W. R.*	M	33	1.91	1.24	72.0	6.0	47.0	1270
J. S.	M	51	1.78	1.50	50.5	5.0	48.0	1280
H. O.	M	32	1.92	0.95	78.5	5.5	42.5	1280
M. S.	F	40	1.61	0.70	84.5	4.2	45.0	1290
R. V.*	M	37	2.05	1.36	67.5	6.2	48.0	1290
N. O.	F	35	1.60	1.25	49.5	4.6	41.5	1290
D. D.	M	21	1.71	1.45	52.0	5.4	44.5	1300
E. C.	F	27	1.65	1.46	47.5	5.2	43.0	1310
V. B.	F	19	1.53	1.48	46.0	4.9	45.0	1310
C. T.	M	21	1.93	1.22	82.0	6.5	51.0	1320
J. S.	M	23	1.61	0.87	71.0	4.2	48.5	1320
D. C.	M	30	1.50	0.75	75.5	4.9	30.0	1340
C. M.	M	57	1.50	1.13	83.5	7.3	43.0	1350
A. D.*	M	54	1.82	0.92	65.5	4.5	44.0	1350
A. D.	M	20	1.85	1.21	65.0	6.0	42.0	1360
A. B.	F	33	1.61	0.65	91.5	4.7	42.0	1370
D. D.	M	56	1.60	0.90	43.5	3.4	39.0	1450
V. P.	M	27	1.77	1.12	68.0	5.6	49.5	1450
H. T.	M	22	1.81	0.80	81.5	5.2	45.0	1450
L. W.	F	20	1.62	0.97	60.0	5.5	35.0	1480
A. B.	M	41	1.68	1.28	41.0	4.3	45.0	1500
M. T.	M	36	1.55	0.50	88.0	4.1	38.0	1500
M. H.*	M	24	2.06	0.72	87.0	5.4	43.5	1530
J. T.	M	31	1.90	1.42	44.0	5.4	44.0	1530
R. P.	M	20	1.90	0.87	70.0	5.1	45.0	1530
A. S.	M	28	1.78	1.62	37.0	5.6	40.0	1540
P. Mc.*	M	43	1.75	1.34	45.0	5.3	43.0	1540
B. G.	M	51	1.71	1.00	47.0	4.4	40.0	1550
M. B.	M	21	1.68	0.77	72.0	5.0	44.0	1550
W. H.*	F	63	1.54	0.60	66.5	4.0	36.0	1560
J. D.	M	49	1.75	1.47	35.0	4.1	50.0	1590
J. T.	M	29	2.09	1.10	70.5	6.3	49.0	1600
J. W.*	M	48	1.73	0.85	61.5	4.4	48.5	1620
R. B.	M	47	1.90	1.00	45.0	4.9	34.0	1630
L. C.	M	22	1.78	0.65	84.0	5.3	40.0	1630
A. E.	M	39	1.70	0.94	56.5	5.4	38.5	1640
W. T.	M	39	1.85	0.85	64.0	4.8	43.0	1650
S. D.	M	33	1.94	1.05	47.0	3.9	52.5	1660
K. H.	M	52	1.76	0.74	60.0	5.1	31.5	1670
C. H.	M	29	1.74	1.08	47.0	4.8	44.0	1670
F. B.	M	26	1.70	0.85	54.0	4.0	48.5	1680
M. B.	F	40	1.33	1.22	34.0	4.1	41.5	1700
R. C.	M	21	1.85	1.02	57.0	5.3	46.5	1720
J. B.	M	47	1.99	0.72	65.0	4.3	48.0	1730
L. S.	M	50	1.70	2.04	27.0	5.1	47.0	1730
A. S.	M	24	1.86	0.60	75.0	4.3	44.0	1730
J. A.	F	24	1.75	1.08	52.0	5.6	44.0	1770
E. W.	F	33	1.65	0.84	41.0	4.1	34.5	1790
J. S.	M	25	1.98	1.35	49.5	6.3	47.0	1790
J. P.	M	37	1.60	0.72	54.0	4.1	41.5	1810
F. C.	M	21	1.94	0.73	91.0	5.6	53.5	1810
L. K.	M	30	2.06	0.94	73.5	5.7	54.0	1820
S. F.	M	43	1.93	0.90	52.0	4.7	45.0	1820
T. B.	M	35	2.03	1.07	60.0	5.6	52.0	1830
F. P.*	M	36	1.87	0.80	62.5	5.6	40.0	1860
J. E.	M	49	1.84	0.66	58.5	4.0	44.0	1860
J. B.	M	33	1.69	0.90	49.5	5.1	39.5	1880
S. G.	M	29	1.93	1.20	34.5	5.0	36.0	1900
J. Ed.	M	47	1.81	0.68	43.0	3.2	43.0	1920
C. M.*	M	43	2.21	1.57	41.5	6.7	46.5	1930
C. N.	M	25	1.86	1.05	50.0	5.5	45.5	1940
J. C.	M	22	1.77	1.34	47.0	6.7	48.0	2030
V. C.	M	23	1.94	0.70	71.0	6.0	41.0	2050
J. L.	M	20	2.15	0.69	87.0	5.8	52.5	2060
J. B.	M	31	2.03	0.60	58.5	3.7	49.0	2060
B. B.	M	45	1.66	0.70	39.0	3.2	46.0	2080
J. B.	M	22	1.98	0.50	90.0	5.3	45.0	2110
D. O'B.	M	20	1.68	0.66	54.0	4.6	40.0	2150
F. D.	M	30	1.96	1.17	46.0	6.0	48.0	2160
O. G.	M	24	1.78	1.05	42.0	5.4	49.0	2370

All values were obtained at bromsulfalein plasma levels changing no more than 0.005 mg. per cent per minute, and were rounded off after calculation was completed.

P_{BSP} = plasma concentration of BSP

E_{BSP} = hepatic extraction of BSP

R_{BSP} = hepatic BSP removal rate

EHBF = estimated hepatic blood flow

* Subjects in whom uncomplicated hypertensive vascular disease was demonstrable.

TABLE 2.—*Estimated Hepatic Blood Flow in Hepatic Cirrhosis*

Subjects	Sex	Age	Surface area	P_{BSP}	ΔP	E_{BSP}	R_{BSP}	Hematocrit	EHBF
Laennec's Cirrhosis—History of Chronic Alcoholism									
		yrs.	M^2	*mg.%*	*mg.%/min.*	%	*mg./min.*	%	*ml./min.*
W. P.	M	49	1.82	1.31	+0.005	24.0	1.3	44.0	750
G. G.	M	39	1.87	1.03	+0.002	39.5	2.0	37.0	790
I. C.	F	46	1.54	2.64	000	17.5	2.4	37.0	810
C. S.	F	48	1.54	2.43	+0.020	20.5	2.3	43.0	820
H. D.	M	51	1.79	3.18	−0.010	13.5	2.4	36.0	860
R. W.	M	54	1.84	2.53	−0.005	19.0	2.2	50.0	930
J. E.	M	39	1.94	2.88	+0.005	19.0	3.7	29.0	960
E. Mc.	F	67	1.80	2.15	+0.005	16.0	1.9	44.0	980
R. B.	M	40	1.66	1.32	+0.006	36.0	2.8	42.0	990
N. F.	M	31	1.91	0.54	−0.002	52.0	1.7	42.0	1050
E. G.	M	39	1.96	0.85	−0.006	33.0	2.0	44.0	1280
J. C.	M	61	1.93	1.48	+0.005	21.5	2.7	34.5	1320
H. D.	M	33	1.68	1.67	+0.005	25.5	3.5	49.0	1600
F. F.	M	43	1.59	0.50	−0.003	44.5	1.9	47.0	1600
E. K.	M	55	1.74	0.77	+0.030	25.0	1.8	47.0	1780
D. C.	F	38	1.82	1.55	+0.010	10.0	1.9	36.0	1910
O. H.	M	38	1.65	1.09	000	23.0	2.5	49.0	1990
Laennec's Cirrhosis—Without History of Chronic Alcoholism									
I. N.	F	19	1.86	1.87	−0.005	24.0	2.3	30.0	730
N. W.	F	47	1.43	4.30	+0.010	12.0	2.4	41.0	780
S. G.	M	47	1.81	0.69	−0.003	20.0	0.7	36.0	780
A. R.	M	54	1.67	1.28	+0.005	26.0	2.0	36.0	940
P. P.	M	22	1.72	1.49	000	11.5	1.1	35.0	960
K. N.	F	38	1.52	1.85	+0.030	12.0	1.4	40.0	1030
P. Mc.	M	22	1.59	1.32	+0.002	32.0	2.5	42.0	1030
P. N.	M	20	1.78	1.50	+0.040	11.0	1.3	36.0	1220
N. D.	M	32	2.03	1.33	+0.005	34.0	3.4	44.0	1310
S. W.	M	28	1.57	0.83	+0.001	26.0	1.7	41.0	1330
H. C.	M	24	1.82	0.63	+0.001	45.0	2.3	39.0	1340
T. K.	M	24	1.90	0.83	+0.010	42.0	3.5	41.0	1720
Biliary Cirrhosis									
F. G.	F	52	1.62	1.90	+0.010	12.0	1.5	37.0	1030
Syphilitic Cirrhosis									
J. L.	M	49	1.64	3.00	000	18.5	1.7	37.0	490
Schistosomiasis									
V. Q.	F	46	1.53	2.00	−0.005	36.5	2.4	33.0	480
M. D.	M	34	1.44	0.72	000	59.5	2.0	44.0	840
H. R.	M	23	1.65	1.03	000	65.5	4.5	44.0	1190
A. O.	M	32	1.60	1.08	+0.002	45.5	3.8	40.0	1280
Banti's Syndrome									
L. H.	M	17	1.67	1.04	−0.005	72.0	2.7	36.0	560
P. J.	M	32	1.73	1.36	+0.010	56.5	2.9	42.0	640
M. H.	F	23	1.74	0.77	−0.001	67.5	3.8	35.0	1120
J. J.	M	34	1.78	0.70	000	47.0	2.9	37.0	1380

All values were taken at points where bromsulfalein (BSP) plasma concentrations were changing least. Change in BSP concentration is noted under ΔP as mg. % per minute, and direction of the change is shown by the signs. All other abbreviations are as in table 1. Data obtained when E_{BSP} was less than 10 per cent above BSP plasma concentrations of 1 per cent and less than 15 per cent below levels of 1 mg. per cent have been excluded.

TABLE 3.—*Splanchnic Oxygen Metabolism*

Subjects	Sex	Age	Arterial		Hepatic venous		Splanchnic oxygen A–V difference	Splanchnic oxygen uptake	Splanchnic oxygen uptake per M.² body surface
			Oxygen content	Oxygen capacity	Oxygen content	Oxygen saturation			
In Normal Men									
		yrs.	*ml.%*	*ml.%*	*ml.%*	%	*ml.%*	*ml./min.*	*ml./min./M.²*
M. G.	F	36	18.8	19.9	16.5	83.0	2.3	—	—
D. O'B.	M	20	15.4	16.1	12.8	79.5	2.6	46.6	27.8
M. G.	F	28	15.5	16.5	12.9	78.2	2.6	—	—
J. E.	M	49	17.4	18.1	14.7	81.4	2.7	51.6	28.0
H. N.	M	30	13.0	13.7	10.2	74.5	2.8	—	—
G. N.	M	26	16.7	21.0	13.7	65.2	3.0	—	—
K. Mc.	F	46	14.4	14.4	11.3	76.0	3.1	38.4	29.1
A. S.	M	24	18.2	19.1	15.1	79.0	3.1	53.6	28.8
J. P.	M	37	15.7	16.2	12.4	76.5	3.3	59.7	37.3
A. B.	M	41	17.7	18.7	14.4	77.0	3.3	49.5	28.4
A. W.	M	43	15.8	16.6	12.3	74.0	3.5	—	—
T. P.	M	29	19.4	20.0	15.7	78.5	3.7	—	—
J. D.	M	49	18.7	19.9	15.0	75.4	3.7	58.8	33.6
R. L.	M	26	15.1	15.8	11.4	72.2	3.7	—	—
M. G.	M	40	16.1	17.6	12.3	70.0	3.8	—	—
E. W.	F	33	12.7	13.7	8.9	65.0	3.8	68.0	41.2
L. C.	M	41	17.8	18.5	12.9	69.7	3.9	—	—
S. F.	M	43	18.1	19.0	14.0	73.6	4.1	74.5	38.6
T. D.	F	38	13.4	14.1	9.3	66.0	4.1	—	—
M. H.	M	24	17.9	18.6	13.8	74.3	4.1	62.7	30.4
S. D.	F	36	15.3	16.6	11.0	66.3	4.3	—	—
J. B.	M	31	19.0	19.7	14.7	74.6	4.3	88.6	41.2
D. P.	M	43	17.4	17.6	13.0	74.0	4.4	—	—
T. B.	M	35	18.5	19.9	14.0	70.5	4.5	82.4	40.6
J. W.	M	39	11.2	12.5	7.0	56.0	5.5	—	—
L. S.	M	50	18.2	19.1	12.5	65.5	5.7	98.5	58.0
I. T.	M	49	19.5	21.5	13.8	64.2	5.7	—	—
In Hepatic Cirrhosis									
Laennec's Cirrhosis—History of Chronic Alcoholism									
J. E.	M	39	10.8	11.2	17.7	68.7	3.1	29.8	15.3
L. R.	M	65	16.0	17.6	12.9	73.3	3.1	—	—
K. C.	F	50	15.4	17.2	11.9	69.7	3.5	—	—
N. F.	M	31	17.8	18.5	14.2	76.8	3.6	37.8	19.8
L. W.	F	33	16.3	17.7	12.6	71.3	3.7	—	—
H. D.	M	33	18.2	19.1	14.0	73.3	4.2	67.2	40.0
P. M.	M	63	15.8	16.6	11.2	68.8	4.6	—	—
E. K.	M	55	18.5	20.6	13.8	67.0	4.7	83.6	48.1
D. C.	F	38	14.6	15.3	9.5	62.0	5.1	97.4	53.5
F. F.	M	43	17.4	18.5	12.0	64.8	5.4	86.4	54.3
R. W.	M	54	19.4	20.7	13.9	67.1	5.5	51.2	27.8
S. G.	M	47	11.9	13.1	6.4	48.9	5.5	—	—
L. A.	M	60	13.9	15.8	8.3	52.5	5.6	—	—
E. G.	M	39	15.9	17.5	10.2	58.2	5.7	—	—
C. S.	F	48	16.0	17.5	9.3	53.3	6.7	55.0	35.7
G. G.	M	39	14.3	15.3	6.4	42.7	7.9	62.4	33.4

TABLE 3—*Continued*

Subjects	Sex	Age	Arterial		Hepatic venous		Splanchnic oxygen A–V difference	Splanchnic oxygen uptake	Splanchnic oxygen uptake per M.² body surface
			Oxygen content	Oxygen capacity	Oxygen content	Oxygen saturation			
Laennec's Cirrhosis—Without History of Chronic Alcoholism									
		yrs.	*ml.%*	*ml.%*	*ml.%*	%	*ml.%*	*ml./min.*	*ml./min./M.²*
S. W.	M	28	17.9	19.6	15.0	77.0	2.9	38.6	24.6
H. C.	M	24	14.2	15.2	10.9	71.8	3.3	44.2	24.3
K. N.	F	38	15.9	17.2	12.5	72.6	3.4	35.0	23.0
C. M.	M	42	14.5	15.8	10.8	68.5	3.7	—	—
T. K.	M	24	14.7	15.2	11.0	72.5	3.7	63.7	33.5
I. N.	F	19	13.1	13.6	9.3	68.5	3.8	27.7	14.9
A. R.	M	54	15.2	15.9	11.0	69.2	4.2	39.5	23.6
P. N.	M	20	15.6	16.5	11.4	69.0	4.2	51.2	28.8
N. W.	F	47	16.4	17.3	12.1	70.0	4.3	33.6	23.4
N. D.	M	32	18.6	19.6	14.1	72.0	4.5	59.0	29.0
P. Mc.	M	22	15.5	16.3	10.9	67.0	4.6	47.4	29.8
P. P.	M	22	13.3	14.1	8.4	59.5	4.9	47.0	27.4
K. O'D.	F	20	16.5	17.6	11.4	64.8	5.1	—	—
R. Mc.	M	30	16.2	17.1	11.0	64.5	5.2	—	—
B. M.	M	46	11.8	12.0	6.6	55.0	5.2	—	—
Schistosomiasis									
H. R.	M	23	18.8	19.4	15.1	77.8	3.7	44.0	26.7
V. Q.	F	46	12.2	13.0	5.7	43.3	6.5	31.2	20.4
M. D.	M	34	14.8	15.6	7.8	50.0	7.0	58.8	40.8
Biliary Cirrhosis									
F. G.	F	52	15.6	16.4	10.8	65.9	4.8	49.5	30.5
Syphilitic Cirrhosis									
J. L.	M	50	14.3	15.1	8.6	56.9	5.7	27.9	17.0
Banti's Syndrome									
J. D.	M	33	6.6	7.7	2.7	33.8	3.9	—	—
M. H.	F	23	13.3	13.8	9.3	67.8	4.0	44.8	25.8
L. H.	M	17	13.9	14.8	9.0	60.7	4.9	27.4	16.4
P. J.	M	32	16.9	17.0	11.0	64.7	5.9	37.8	21.8
J. J.	M	34	14.7	15.6	8.6	55.0	6.1	84.2	47.3

Splanchnic oxygen consumption was calculated as the product of hepatic blood flow and splanchnic oxygen arteriovenous difference.

In normal persons removal of bromsulfalein in the splanchnic bed outside the liver is of no importance because the portal venous blood is returned to the heart almost entirely by way of the hepatic veins. This is no longer true in cirrhosis where an elaborate collateral venous system has been established. However, determination of the bromsulfalein content of portal and peripheral venous blood obtained simultaneously at operation in two patients with cirrhotic disease failed to disclose any significant difference. The possibility of enterohepatic circulation of bromsulfalein likewise has no practical importance in normal subjects because the hepatic venous bromsulfalein concentration in these and other studies has always been lower than the peripheral venous or arterial concentrations. In the presence of cirrhosis, this becomes a matter of great importance because direct return of dye from the

intestine to the systemic circuit by way of the portal venous collaterals would be equivalent to administration of a second bromsulfalein infusion of unaccountable size. As a result, estimations of bromsulfalein removal would be erroneously low. However, oral administration of large doses of bromsulfalein (500 mg.) to four patients with large functioning portocaval anastomoses failed to produce detectable concentrations of bromsulfalein in the peripheral blood within 45 minutes. Lorber and Shay[11] have reported observations of low concentrations of dye in the blood of normal individuals 30 minutes after introducing doses of from 2 to 5 mg. per Kg. of body weight into the duodenum, but they state that amounts equivalent to an intravenous dose of 2 mg. bromsulfalein per Kg. of body weight does not result in significant enterohepatic circulation. Since subjects with cirrhosis excrete the dye slowly and in small amounts it is probable that little of it is available for enterohepatic circulation during the measurement of hepatic blood flow. The priming dose is usually no more than 2 mg. per Kg. of body weight and the plasma concentration is maintained at a relatively low level. Finally, as noted above, the portal venous bromsulfalein concentration does not appear to differ from peripheral venous concentration. Hence, it seems most unlikely that enterohepatic circulation introduces a significant error into the calculation of hepatic blood flow in cirrhotic patients.

The problem of extrahepatic removal of bromsulfalein becomes a matter of major concern in evaluating the measurement of hepatic blood flow in cirrhosis because the hepatic removal is greatly reduced, whereas extrahepatic extraction probably remains unchanged, thus contributing more importantly to the total removal of dye than in the normal. It has been recognized from the outset[7] that extrahepatic removal of bromsulfalein from the blood must occur, but it has been considered insignificant because most of the injected dye is excreted in the bile. Cohn and his co-workers[12, 13] have shown that the extrahepatic bromsulfalein removal may be quite large in absolute terms

TABLE 4.—*Statistical Analysis of Data in Tables 1 to 3*

	Normal			Cirrhosis		
	Male	Female	Total	Male	Female	Total
Estimated Hepatic Blood Flow						
No. of observations	73	18	91	29	10	39
Mean (ml./min.)	1580	1340	1530	1140	970	1090
Range (ml./min.)	970–2370	1000–1790	970–2370	490–1990	480–1910	480–1990
σ	±280	±200	±300	±350	±360	±380
σ_m	±325	± 46.6	± 31.5	± 65	±114	± 60.8
Hepatic Bromsulfalein Extraction						
No. of observations	73	18	91	29	10	39
Mean (%)	61	55	60	34	23	31
Range (%)	27–91	37–91.5	27–91.5	11–72	10–67.5	10–72
σ	±15.3	±15.3	±15.6	±16.2	±16.7	±17.3
σ_m	±1.8	±3.6	±1.6	±3.0	±5.3	±2.8
Hepatic Oxygen Arteriovenous Difference						
No. of observations	21	6	27	30	11	41
Mean (ml.%)	3.87	3.36	3.76	4.75	4.63	4.71
Range (ml.%)	2.8–5.8	2.3–4.3	2.3–5.8	2.9–7.9	3.4–6.7	2.9–7.9
σ	±0.76	±0.78	±0.71	±1.15	±1.08	±1.17
σ_m	±0.16	±0.34	±0.15	±0.21	±0.33	±0.18

but they have worked with high plasma concentrations of bromsulfalein. When the plasma bromsulfalein level was maintained between 1 and 2 mg. per 100 ml. in dogs before and after evisceration, extrahepatic removal (determined after evisceration) was found to be less than 5 per cent of the total preoperative removal rate at the same blood level.[10] It is evident, therefore, that the error introduced by extrahepatic removal is less than that introduced by other factors such as failure to sample mixed hepatic venous blood. It has seemed reasonable to accept the hepatic removal rate determined on the basis of the infusion rate at a more or less constant plasma bromsulfalein concentration of less than 3 mg. per 100 ml. as sufficiently accurate for the purposes of this study.

Results

An evaluation of the hepatic circulation can only be made against the background provided by an analysis of values obtained in a similar but "normal" population, that is, "normal" with respect to hepatic function and circulation. Table 1 contains values for hepatic blood flow measured in 91 individuals free of hepatic and cardiovascular disorders with the exception of 11 who had uncomplicated hypertensive vascular disease. Since the group with hypertensive disease did not differ in any statistically significant manner from the remainder, the figures are considered as a whole. Estimated hepatic blood flow averaged 1530 ml. per minute with a standard deviation of ±300 ml. per minute, ranging from 970 to 2370 ml. per minute (table 4). Analysis of variance failed to reveal any consistent or statistically significant difference between groups studied in sequence that could be attributed to change in technic, the hospital population, method of selection, or to other causes. Hence the figures are arranged in all the tables in ascending order with respect to hepatic blood flow or arteriovenous oxygen difference. It may be seen that they are rather symmetrically distributed about the mean of 1530 in table 1. The tendency for the figures in females to fall below the total mean is evidence of a significant sex difference. The mean figures for hepatic blood flow in 18 females was 1340 ml. per minute and in 73 males 1580 per minute (table 4). The difference between these two groups was highly significant, amounting to more than four times the standard error of the difference (relative deviate, $dev/\sigma = 4.0$). The figures for hepatic blood flow were not significantly correlated with body surface (S.A.) and consequently have not been adjusted for variation in body surface.

Inspection of the figures for plasma concentration of bromsulfalein (P_{BSP}) at the time of hepatic blood flow (EHBF) measurement suggests that higher values of hepatic blood flow are frequently associated with low plasma levels of bromsulfalein. Sherlock[14] has found a good negative correlation between plasma concentration of bromsulfalein and hepatic blood flow in her studies of normal subjects, and she suggests that the higher values obtained for hepatic blood flow when the plasma concentration of bromsulfalein is less than 1 mg. per 100 ml. may be erroneous because of augmented extrahepatic bromsulfalein uptake at low plasma concentrations. There is no direct evidence in favor of this contention and statistical analysis of the values in table 1 fails to lend it support. A slight but statistically significant negative correlation obtains between all figures for plasma concentration of bromsulfalein and hepatic blood flow ($r = .49$) but no correlation ($r = -.03$) was demonstrable between these values at bromsulfalein concentrations equal to or less than 1 mg. per 100 ml. The negative correlation for the group as a whole is best explained on technical grounds. The rate of bromsulfalein infusion does not vary greatly from subject to subject and in consequence higher bromsulfalein concentrations tend to occur in individuals with low hepatic blood flow than in those with high flow at equilibrium. Although bromsulfalein extraction is to some extent a function of the concentration in the plasma, it ranged much more widely than the concentration. Bromsulfalein extraction was less on the average in females (55 per cent) than in males (61 per cent) but the difference was not significant ($dev/\sigma = 1.4$). Mean bromsulfalein extraction for the total group was 60.0 ± 15.6 per 100 ml. (table 4).

The data obtained in studies of patients with

cirrhotic disease are set forth in table 2 according to cause. Since the values for mean hepatic blood flow in the different groups do not differ significantly and since all these disorders have in common a reduction of portal venous inflow and real or potential cirrhosis all figures have been treated en masse as representative of a population ("cirrhotics") sufficiently homogeneous and distinctive for the purposes of this investigation. Indeed, cirrhotic disease was demonstrable by biopsy or necropsy in nearly all these individuals except in those with Banti's syndrome due to extrahepatic portal venous obstruction. The latter have been included in the group as a whole because the circulatory disturbance resembles that of the others and because cirrhosis ultimately develops in many patients and may have been present in early form undetectable by biopsy or gross appearance. The similarities between the groupings in table 2 indicate that, regardless of cause, cirrhotic disease produces similar hepatic circulatory effects. With expansion of these groups, it is possible, of course, that a more subtle diversification not at present apparent may be demonstrable, but these theoretic dissimilarities are not germane to the broader issues with which this analysis is concerned.

Estimated hepatic blood flow ranged from 480 to 1990 ml. per minute among the "cirrhotics" and averaged 1090 ± 380 ml. per minute (table 4). The difference between the "cirrhotic" and "normal" mean values for hepatic blood flow was highly significant, amounting to 6.4 times the standard error of the difference. As among the normal subjects, a sex difference was apparent, mean hepatic blood flow in women averaging 970 ml. per minute as against 1140 ml. per minute for males, but it was not statistically significant. Mean hepatic bromsulfalein extraction among "cirrhotics" (31.4 ± 17.3 per cent) differed significantly from the normal ($dev/\sigma = 9.0$). Since the plasma concentration of bromsulfalein varied through the same range among these individuals as in the normals, this deviation could not be attributed to a higher bromsulfalein blood level. Women again were found to have lower, but not significantly lower, values for bromsulfalein extraction than men (mean equal to 23.0 per cent in contrast to 34.0 per cent). In summary, then, it may be concluded that hepatic blood flow is significantly reduced in cirrhotic disease in association with diminished hepatocellular ability to remove bromsulfalein from the blood.

The difference in oxygen content between arterial and hepatic venous blood is equal to the amount of oxygen taken up by all the tissues supplied by the arteries feeding the portal venous system. This value is therefore a function of the total splanchnic oxygen consumption which may be estimated by multiplying hepatic blood flow and the hepatic arteriovenous oxygen difference in the normal person. But in the "cirrhotic" an appreciable volume of blood escapes from the portal vein through anastomotic channels and cannot contribute either to calculated hepatic blood flow or to hepatic arteriovenous oxygen difference. Recent studies[15, 16] have revealed that the oxygen content of portal venous blood is high and that the oxygen uptake of splenic and gastrointestinal tissues is slight in resting, fasting individuals. It could be argued, therefore, that the values obtained under the conditions of this study reflect predominantly hepatic oxygen uptake in normals as well as "cirrhotics" and that loss of portal blood through anastomotic channels does not significantly affect the final figure.

Hepatic arteriovenous oxygen differences in normal subjects (table 3) ranged from 2.3 to 5.8 ml. per 100 ml. and averaged 3.76 ± 0.71 ml. per 100 ml. (table 4). Again the figures for women were less but not significantly less than those for men (mean for women equal to 3.36 ml. per 100 ml., and for men 3.87 ml. per 100 ml.). Among "cirrhotics" the hepatic arteriovenous oxygen difference was 4.71 ± 1.17 ml. per 100 ml. on the average, significantly higher than the normal mean ($dev/\sigma = 3.8$). An insignificant sex difference again favoring the males was demonstrable (table 4). In contrast, calculation of "splanchnic oxygen consumption" in 13 normal subjects and 30 cirrhotic patients in whom hepatic blood flow and hepatic oxygen arteriovenous difference were determined simultaneously, revealed dissimilarity between the two groups of borderline significance. These values averaged 64.1 ± 16.8

ml. per minute in the normal subjects and 51.2 ± 19.1 ml. per minute in the cirrhotic patients ($dev/\sigma = 2.2$). When calculated on the basis of body surface area, the deviation was even less marked, 35.6 ± 8.3 ml. oxygen per minute per square meter of body surface in normals and 29.8 ± 10.6 ml. per minute per square meter in "cirrhotics" ($dev/\sigma = 1.9$). The slightly lower value for oxygen consumption observed in "cirrhotics" might be attributable to loss of portal blood through collateral channels.

Comment

The findings of this study indicate that hepatic blood flow is reduced in the presence of any cirrhotic process. The elevation in hepatic arteriovenous oxygen difference in the absence of increased total oxygen consumption suggests that slower perfusion of the liver with prolonged contact between cells and blood may permit more efficient extraction of oxygen. In consequence hepatic venous oxygen content would fall as observed, and the oxygen tension in fluids bathing the cells would be reduced. The fact that bromsulfalein extraction and removal rate were uniformly diminished may be explained by the destruction of extracting cells or by a selective disturbance in the mechanisms of bromsulfalein transfer. Both factors were probably involved. Ample evidence of liver damage was available in nearly every instance. Brauer and his associates[17] has shown that bromsulfalein uptake by liver cells proceeds independently of oxidative activity and since the hemodynamic changes that favored relative enhancement of oxygen extraction should also have improved bromsulfalein uptake it may be inferred that bromsulfalein transport into the bile was selectively depressed. On the other hand oxygen uptake per unit of functioning cell mass must have actually increased since calculated oxygen consumption remained within normal limits despite extensive parenchymal damage.

The relative contributions of the portal venous and hepatic arterial circulations cannot be accurately assessed. It seems unlikely, however, that diminished hepatic arteriolar resistance leads to an absolute increase in arterial inflow at the expense of the portal venous input, since one would expect under these circumstances an elevation, not a reduction, in estimated hepatic blood flow and a fall, not an increase, in hepatic arteriovenous oxygen difference. Though the fraction of arterial blood contributing to hepatic venous outflow probably rose, there is no evidence that it exceeded, or even kept pace with, the tissue demand for oxygen and, presumably, other materials.

Hepatic ischemia and relative tissue hypoxia appear to be characteristic stigmas of cirrhotic disease. Whether these precede or follow the destruction of hepatic cells and the proliferation of connective tissue must remain unsettled. It is tempting to speculate on the possibility that the changes in hepatocellular oxygen metabolism and bromsulfalein transport may reflect some serious derangement of cellular physiology that is ultimately followed by necrobiosis and changes in the tissue structure and vascular architecture of the liver.

The data presented here have been derived from a heterogeneous group of patients with different diseases and in different phases of the same disease. Furthermore, the criteria for selection eliminated from consideration those patients with jaundice or excessive disturbance of bromsulfalein removal. It should be emphasized therefore that the preceding discussion applies to cirrhosis in general. It should not be interpreted as precluding the possibility that hyperemia and diverse changes in oxygen and bromsulfalein extraction might occur in certain types or at certain stages. Additional data are required to permit more particularizing statements regarding the discrete effects of such factors as ascites, recent hemorrhage, biliary obstruction and specific etiologies.

Summary

The hepatic blood flow (EHBF) has been estimated by the bromsulfalein (BSP) clearance method in 91 normal human subjects and in 39 patients with various kinds of cirrhotic disease, including four with Banti's syndrome due to extrahepatic portal venous obstruction. The hepatic arteriovenous oxygen difference was also determined in 27 normal and 41 cirrhotic sub-

jects, in 13 and 30, respectively, of whom hepatic blood flow was measured simultaneously.

Mean hepatic blood flow was 1530 ± 300 ml. per minute in the normal and 1090 ± 380 ml. per minute in the cirrhotic. This reduction in hepatic blood flow was highly significant and it was associated with a marked fall in hepatic bromsulfalein extraction, 60 ± 15.6 per cent, normal, and 31 ± 17.3 per cent, cirrhotic.

The hepatic arteriovenous oxygen difference, on the other hand, rose significantly among the cirrhotics (41 patients) from a normal (27 individuals) mean of 3.76 ± 0.71 ml. per 100 ml. to 4.71 ± 1.17 ml. per 100 ml. as a result of a decrement in hepatic venous oxygen concentration. Calculated hepatic oxygen consumption, however, did not differ much from the normal.

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