LIVER BLOOD FLOW IN PREGNANCY—HEPATIC VEIN CATHETERIZATION [1]

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Numerous liver function tests have been devised and most investigators agree that some disturbance in liver function occurs during the toxemias of pregnancy. These changes are of relatively small magnitude and the clinical use of these tests in pregnancy is not widespread. The technique of venous catheterization with resultant sampling of blood directly leaving the liver offers further opportunities for study of liver function.

METHODS

A method of estimating hepatic blood flow in man based on the "Fick" principle has been described by Bradley and coworkers (1). In their article they point out that "The 'Fick' principle may be applied to any organ provided three facts are known: (*1*) the concentration of some substance, X, in the blood entering the organ, (*2*) the concentration of X in the mixed venous blood leaving the organ, and (*3*) the total amount of X removed from the blood by the organ each minute. Given these data, the blood flow through the organ per minute may be calculated by dividing the total removal rate of X by the amount of X removed from each milliliter of blood as it traverses the organ."

The removal rate of X by the liver cannot be measured directly, but an indirect method is available if X can be given at such a rate that its blood level remains constant. Under these conditions, the infusion rate equals the hepatic removal rate, provided that the extraction of X depends entirely upon hepatic activity. Bromsulfalein (BSP) was used as the test substance since it apparently satisfied these conditions.

The calculation of hepatic blood flow then can be determined by the following formula:

$$EHBF = \frac{R}{0.01\,(P - H)} \times \frac{1}{1 - \text{Hematocrit}}$$

Where $EHBF$ = estimated hepatic blood flow,
R = removal rate or the infusion rate in mgm. per minute,
P = peripheral venous concentration of BSP in mgm. per minute,
H = hepatic venous concentration of BSP in mgm. per minute.

Hematocrit was from anticoagulated blood drawn from the hepatic vein in most cases. Four hematocrits were always taken and the average of the 4 used in the calculations. Occasionally peripheral vein blood would be used for hematocrit determination because of temporary difficulty in obtaining enough hepatic vein blood through the catheter: in Tables I, II, and III these peripheral vein hematocrits are starred (*).

If the concentration of BSP in the peripheral blood is changing, hepatic blood flow may also be estimated if the plasma volume is determined. In this case, R (the removal rate of BSP by the liver) $= I$ (the infusion rate mgm. per minute) plus or minus $\Delta P \times V$ where $\Delta P =$ the rate of change in concentration of BSP in the peripheral blood in mgm. per ml. per minute and $V =$ plasma volume in ml. Plus or minus depends on whether the concentration of BSP in the peripheral blood is rising or falling. If the peripheral concentration is rising, $R = I - (\Delta P \times V)$ since less dye is being removed than is administered. If the peripheral concentration is falling, $R = I + (\Delta P \times V)$ for the converse reason.

Samples of hepatic vein blood are obtained with more or less ease by catheterization of the right hepatic vein with a 100-cm. No. 8 ureteral catheter with a slightly curved through-and-through tip with one eye. The catheter, through which an isotonic saline infusion is running, is inserted in the median basilic vein under local anesthesia. With the patient in the supine position on a fluoroscope table, the catheter is then passed into the subclavian vein, the superior vena cava, the right atrium, the inferior vena cava, and the right hepatic vein. The patient experiences no discomfort during this procedure. The most difficult part of the procedure is to get the tip of the catheter past the right atrium and into the inferior vena cava rather than down into the right auricle and ventricle. In advanced pregnancies this was more difficult than in the non-pregnant cases presumably because of increased angulation of the vena cava at this point due to elevation and deviation of the heart to the left by the upward displacement of the diaphragm and liver. Apprehensive patients with small peripheral veins were occasional failures

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TABLE I

The average EHBF in non-pregnant women with no evidence of liver disease

Subject	Age in years	Diagnosis	Surface area	Average serum concentration BSP		Average extraction percentage $\frac{P-H}{P}$	Total removal rate BSP	Hepatic blood flow	Hepatic blood flow	Average ΔP	Plasma volume	Hematocrit	Blood volume	*EHBF* per cent of total blood volume
				P	*H*									
			*M.*²	*mgm. per cent*		*per cent*	*mgm. per min.*	*ml. per min.*	*ml. per min. per 1.73 M.*²					
R. S.	26	Salpingitis	1.45	.81	.28	69.1	3.92	1402	1674	.0000656	2270	39.60*	3760	37.2
R. L.	23	Salpingitis	1.69	1.03	.58	43.10	4.86	1737	1779	.0000844	2688	36.00	4200	41.3
H. M.	28	No disease	1.68	1.87	.98	45.80	6.79	1270	1307	.0002323	2688	35.70	4180	30.4
R. C.	22	Salpingitis	1.43	2.18	1.30	39.80	6.95	1410	1706	.0001236	2315	37.10	3680	38.3
F. G.	22	Salpingitis	1.58	3.80	3.23	13.95	6.59	1736	1900	.0004564	2435	38.85	4050	42.8
F. J.	32	Salpingitis	1.75	3.53	2.43	28.50	7.65	1192	1177	.0000788	2582	38.80	4220	28.2
E. S.	25	Gonococcal cervicitis	1.52	2.42	1.60	32.80	5.98	1385	1576	.0003530	2315	41.40	3950	35.0
G. P.	29	Post-abortal salpingitis	1.56	1.17	.45	59.50	5.30	1297	1438	.0008445	2635	34.50	4020	32.2
M. F.	33	Psycho-neurosis	1.50	2.74	1.94	30.40	6.30	1313	1515	.0001425	2336	40.10	3900	33.6
P. T.	22	Salpingitis	1.52	1.81	.94	48.10	5.93	1203	1370	.0001000	2380	39.80	3950	30.4
M. L.	35	Bartholin cyst	1.44	1.22	.45	62.10	5.94	1298	1560	.0002770	2360	36.50	3720	34.8
M. L.	25	4 weeks postpartum	1.55	2.27	1.53	32.30	6.20	1264	1410	.0002150	2850	28.90	4000	31.6
L. S.	32	Salpingitis	1.38	1.64	.84	47.40	6.20	1223	1535	.0000534	2400	31.25	3490	35.0
M. W.	21	Salpingitis	1.58	2.74	1.99	26.20	6.76	1547	1695	.0001430	2780	31.40	4050	38.1
M. C.	22	25 days postpartum	1.67	2.21	1.20	45.40	7.68	1517	1573	.0007145	2700	35.50*	4190	36.2
Average									1548					35

* Indicates peripheral vein hematocrit. All others from hepatic vein. (See page 952.)

when peripheral venous spasm rendered the catheter immovable except for withdrawal. Not leaving the catheter in the body for longer than 90 minutes was preferred after 2 patients developed peripheral phlebitis when the catheter had been left in the veins for longer than 2 hours; the phlebitis disappeared rapidly under simple treatment.

The BSP infusion was allowed to run into the same arm through which the catheter was inserted and samples of peripheral blood were withdrawn from the opposite arm. The concentration of BSP in the peripheral blood was considered equavalent to afferent blood to the liver since the liver presumably is the exclusive site of removal of the dye.

In pregnancy it would be necessary to take into account the action of the fetal liver in removing BSP were it not for the fact that bromsulfalein does not cross the placenta. Two patients in the second stage of labor were given bromsulfalein intravenously in quantity sufficient to keep the peripheral concentration high for a period of 20 to 30 minutes prior to delivery of the baby. Immediately after delivery, samples of the blood from the umbilical cord showed no BSP present whereas the mother's peripheral blood concentration was still very high.

For a complete discussion of the method of determining the BSP concentration, of the validity of the method, and of the calculation of the *EHBF*, the reader is referred to Bradley *et al* (1). Our method of BSP determination was essentially the same as theirs. However, we did work with higher blood levels of BSP (*i.e.*, 1.0 mgm. per cent or over for the hepatic blood levels, since these are always lower than the peripheral) because below this level we found an increasing percentage of error in the plasma BSP recoveries. If the plasma concentration was 1.0 mgm. per cent or over, the percentage error was only 2½ to 5 per cent. Since the best plasma recoveries usually showed a 5 per cent loss, all plasma levels were corrected for this loss by dividing by .95.

Whereas in non-pregnant patients the estimated plasma volume could be determined from the surface area by reference to the tables of Gibson and Evans (2), in pregnant patients this could not be done. Hence, in the pregnant patients, it was necessary to measure the plasma volume accurately, using the dye T–1824 or Evans blue. This determination was done immediately following completion of the bromsulfalein part of the experiment according to the technique of Price and Longmire (3) with the following modification. Approximately 5 ml. of Evans blue were loaded in a 5-ml. syringe equipped with a guard to keep the plunger steady and weighed together with the needle. The dye was injected into an infusion tubing just above the hub of the infusion's needle and extreme precautions taken to lose none of the dye by using the smallest possible hypodermic needle (gauge No. 26) for injection with a clamp just behind the site of injection to prevent diffusion of the dye backwards into the infusion tubing. Immediately following injection, the infusion

was allowed to run very rapidly for 3 minutes to insure complete flushing of the dye from the infusion tubing. The needle and syringe together with the residual dye on the walls of the syringe were then weighed again and the difference from the original weight represented the amount of T–1824 injected. Samples were taken according to the method of Gibson and Evelyn (4) at 15-minute intervals and the concentration of the dye in the plasma determined in the Coleman spectrophotometer. A constant (K) for the lot of dye used and for the machine was determined from a calibration curve.

RESULTS

A series of non-pregnant women was first examined in order to provide a standard for comparison. This series is presented in Table I; the *EHBF* varied from 1,177 to 1,900 ml. per minute per 1.73 M^2. of body surface with an average of 1,548 ml. These results are practically the same as those of Bradley and coworkers. It will be noticed that the average ΔP in this series is high. We found it difficult to maintain a constant blood level of the bromsulfalein. Therefore, all our results were dependent on the added determination of plasma volume, and these values were obtained from the tables of Gibson and Evans. The last column in these tables represents the *EHBF* percentage of total blood volume. In these non-pregnant women, it averaged 35 per cent with a range of from 28.2 per cent to 42.8 per cent.

Fifteen normal pregnancies of various periods of gestation were studied and the equivalent hepatic blood flows determined. These data are presented in Table II. The range of *EHBF* was from 1,075 to 2,465 ml. per minute per 1.73 M^2. of body surface area with an average of 1,554 ml.

TABLE II

The average EHBF in normal pregnancy

Subject	Age in years	Diagnosis	Surface area	Average serum concentration BSP		Average extraction percentage $\frac{P-H}{P}$	Total removal rate BSP	Hepatic blood flow	Hepatic blood flow	Average ΔP	Plasma volume	Hematocrit	Blood volume	*EHBF* per cent of total blood volume
				P	*H*									
			M.²	*mgm. per cent*		*per cent*	*mgm. per min.*	*ml. per min.*	*ml. per min. per 1.73 M.²*					
M. W.	23	Para-4 Gravida-5 35 wk. gestation	1.83	2.28	1.63	29.4	5.07	1137	1075	.0006340	4480	31.60	6630	17.1
A. K.	27	Para-0 Gravida-1 40 wk. gestation	1.85	1.50	.70	52.6	6.87	1454	1360	.0000466	3533	37.30*	5760	25.2
R. D.	31	Para-3 Gravida-4 8 wk. gestation	1.45	2.59	2.10	18.1	5.63	2065	2465	.0001360	2850	40.20	4670	44.2
L. W.	34	Para-3 Gravida-4 Thr. abortion 12 wk. gestation	1.75	1.61	.89	50.2	7.10	1287	1273	.0001320	3110	36.40	5200	24.7
D. B.	26	5 mo. gestation	1.52	2.09	1.37	34.1	6.42	1319	1500	.0001030	2900	31.40	4270	30.9
A. W.	18	Para-0 Gravida-1 38 wk. gestation	1.65	2.34	1.48	36.1	6.75	1188	1245	.0001160	3080	32.30	4730	25.1
H. S.	32	Hyperemesis gravidarum 3 mo. gest.	1.58	3.02	2.61	14.1	5.67	1646	1803	.0003070	4700	22.40	6300	26.1
K. D.	23	Para-0 Gravida-1 37 wk. gestation	1.80	1.94	1.29	32.6	7.19	1520	1460	.0000205	4500	34.00	7100	21.4
E. K.	25	Para-3 Gravida-4 37 wk. gestation	1.58	3.01	2.15	28.5	6.90	1092	1196	.0002820	3680	31.10	5540	19.7
M. D.	25	Para-4 Gravida-5 Term gestation	1.73	2.12	1.56	26.1	6.49	1854	1854	.0001690	3950	34.80*	6000	30.9
M. M.	38	Thr. abortion 10 wk. gestation	1.57	3.45	2.65	23.0	6.47	1517	1672	.0002140	2350	43.80*	4200	36.1
M. S.	22	6 mo. gestation Para-0 Gravida-1	1.73	1.58	.73	52.4	7.69	1423	1423	.0000930	3380	30.10	4830	29.4
E. S.	21	Para-0 Gravida-1 7 mo. gestation	1.50	2.57	1.71	33.9	7.16	1200	1385	.0002590	3360	32.13	4950	24.2
A. F.	23	Para-1 Gravida-2 7 mo. gestation	1.70	2.61	1.86	28.1	7.86	1697	1728	.0002720	3240	33.80*	4890	34.7
A. P.	24	Bartholin abscess 6 mo. gestation	1.59	1.79	1.30	30.3	6.49	1726	1878	.0001480	3120	31.10	4520	38.1
Average									1554					28.5

* Indicates peripheral vein hematocrit. All others from hepatic vein. (See page 952.)

TABLE III

*The average EHBF in pregnant women with toxemia**

Subject	Age in years	Diagnosis	Surface area	Average serum concentration BSP		Average extraction percentage $\frac{P-H}{P}$	Total removal rate BSP	Hepatic blood flow	Hepatic blood flow	Average ΔP	Plasma volume	Hematocrit	Blood volume	*EHBF* per cent of total blood volume
				P	*H*									
			*M.*²	*mgm. per cent*		*per cent*	*mgm. per min.*	*ml. per min.*	*ml. per min. per 1.73 M.*²					
L. P.	28	Mild pre-eclampsia	1.6	1.85	0.60	62.9	6.72	1007	1090	.0001010	2788	40.6	4640	21.7
E. Z.	26	Essential hypertension	1.68	1.97	1.00	46.8	6.65	1285	1323	.0000520	3060	34.2	4490	28.6
J. M.	20	Severe pre-eclampsia pre-Caesarean	1.6	2.77	2.27	18.3	6.32	1969	2130	.0001399	2263	34.6**	3460	56.9
		10 days post-Caesarean	1.52	2.44	1.84	24.7	5.75	1736	1973	.0002575	2536	27.9	3520	49.3
A. B.	27	Hypertension with superimposed pre-eclampsia	1.68	2.60	2.28	12.4	5.06	2374	2445	.0004154	3413	34.1	5180	45.8
A. G.	28	Nephritis 3 months pregnant	1.76	1.15	0.48	58.3	6.76	1595	1568	.0000761	2286	34.3**	3480	45.8
M. F.	25	Early pregnancy (3rd) with history of eclampsia and severe pre-eclampsia with previous pregnancies	1.82	2.29	1.88	16.2	7.65	4070	3860	.0001327	2625	39.9	4360	88.0

* Table III shows a few toxemic pregnant patients examined with interesting but inconclusive results since there are so few cases.

Patient L. P. with very mild pre-eclampsia had a normal *EHBF*. Patient E. Z. had essential hypertension and a normal *EHBF*. Patient A. G., examined when 3 months pregnant, had chronic nephritis but went on to term successfully; her *EHBF* was normal.

J. M. had severe pre-eclampsia for which Caesarean section was performed; her *EHBF* was somewhat elevated both before delivery and to a less extent post-operatively. It is interesting also to note the high *EHBF* percentage of total blood volume in her case. The same elevations of *EHBF* and *EHBF* per cent of blood volume were found in patient A. B. who had hypertension with superimposed pre-eclampsia, developing premature separation of the placenta and delivering a 6 lb. 11 oz. stillbirth.

Patient M. F. had a very high *EHBF* per minute, so high, in fact, it represented 88 per cent of the total blood volume. Two previous pregnancies had been complicated by eclampsia and pre-eclampsia. She was examined at 10 weeks in this, the third, pregnancy at which time her temperature, pulse, blood pressure and urine were normal. The remainder of her pregnancy was perfectly uneventful, with normal labor occurring at term.

While most inconclusive because of the paucity of examined cases, these results suggest some abnormality of liver blood flow in the severe toxemias of pregnancy. Further study in this direction is expected, and certainly necessary before any definite conclusions can be made as to the effect of toxemias on liver blood flow.

** Indicates peripheral vein hematocrit. All others from hepatic vein. (See page 952.)

which is practically identical with the non-pregnant average *EHBF*. Subject R. D. in this series was examined when she was pregnant 4 months. She had had 2 previous normal pregnancies. Although her *EHBF* was high, 2,465, she went on to term with this pregnancy without developing any signs of toxemia.

As would be expected from the fact that the equivalent hepatic blood flow does not change in normal pregnancy, the *EHBF* percentage of total blood volume was somewhat decreased, particularly late in pregnancy when the blood volume is increased. The *EHBF* percentage of total blood volume in this series averaged 28.5 per cent with a range of 17.1 to 44.2 per cent. A physiological increase in blood volume is a known fact in pregnancy. Liver blood flow remains unchanged, however, presumably because of shunting of the excess blood volume through the placenta.

CONCLUSION

Liver blood flow in normal pregnancy does not differ from liver blood flow in non-pregnant patients with normal livers. The average *EHBF* per minute per 1.73 M.² was 1,554 ml. in normal pregnancy and 1,548 ml. in non-pregnant women. The decreased *EHBF* per cent of total blood volume in pregnancy is an obvious corollary to the fact that liver blood flow remains unchanged in the presence of an increased blood volume of pregnancy.

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