Original Communications

The Effect of Ethanol Upon Systemic and Hepatic Blood Flow in Man

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THERE have been conflicting reports concerning the effect of ethanol on the hepatic circulation. Studies by Smythe et al. in the dog showed no significant effect of ethanol administered by gastric gavage on either hepatic or general systemic flow.[1] On the other hand, Mendeloff demonstrated a consistent increase in the estimated hepatic blood flow during infusion of ethanol[2] in a study of young men without liver disease and concluded that the effect on hepatic blood flow was independent of that on systemic flow. More recently Castenfors et al. failed to demonstrate a change in hepatic blood flow in healthy volunteer subjects during infusion of ethanol.[3]

Although several methods of measuring hepatic blood flow have been described, the method most widely employed and most practical for successive measurements has involved the constant intravenous infusion of an indicator such as sulfobromophthalein.[4] The indicator indocyanine green* is particularly suitable in this technic because it is removed almost exclusively by the liver.[5,6]

The present report concerns an investigation of the effects of ethanol on the systemic and the splanchnic circulation in man. Also tested was the efficiency of prolonged infusion of indocyanine green for repeated determination of hepatic blood flow. A preliminary report has been made previously.[7]

METHODS

The subjects were seven male and two female patients who had been hospitalized with acute illnesses. They were all studied during convalescence. Although six of the nine patients were known to have taken alcohol in excessive quantity at some time, all were without clinical or laboratory evidence of liver disease at the time of study.

The subjects were not given any medication before the study. Catheterization of the right hepatic vein was performed by passing a nylon cardiac catheter (Cournand No. 8 or No. 9) through a basilic vein into the inferior vena cava under fluoroscopic guidance. The catheter was advanced into the right hepatic vein to the wedge position and then withdrawn until blood could be sampled freely. In the opposite arm, a needle (Cournand No. 17) was placed into the brachial artery. In this arm also a polyethylene catheter was passed through a needle into a vein and threaded into the axillary vein. Through this catheter indocyanine green in isotonic saline solution was administered by means of a constant infusion pump at a rate of 0.4 to 0.7 mg. per minute. For purposes of administration and calibration the dye was stabilized in a solution contain-

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This work was supported by Grant H-5217 from the National Heart Institute, National Institutes of Health, U. S. Public Health Service, and by grants-in-aid from the Life Insurance Medical Research Fund and the U. S. Army Medical Research and Development Command, Department of the Army, under Contract No. DA-49-193-MD 2013.

* Cardio-green.® Hynson, Westcott, & Dunning, Baltimore, Maryland.

ing 0.2 to 0.5 gm. per 100 ml. of human albumin. After a period of equilibration, usually thirty to forty minutes, the cardiac output was determined by rapidly injecting Evans Blue dye (T-1824), approximately 5 mg. from a calibrated pipette, into the axillary vein, flushing the dye with 10 ml. of saline solution. At the same time blood was sampled continuously with a withdrawal pump from the brachial artery via a cuvette densitometer (Colson).[8,9] Brachial arterial and hepatic venous pressures were measured at this time in most patients by means of strain gauge transducers (Statham), recording on a direct writing oscillograph (Sanborn). The baseline was taken to be 10 cm. above the back of the subject. Hematocrit was corrected for trapped plasma by multiplying by the factor 0.96.

Following the determination of cardiac output, the infusion was changed in six subjects to contain ethanol* in isotonic saline solution, delivering 0.5 to 0.8 gm. per minute at approximately the same rate of infusion as during the control period; infusion without ethanol was continued in three control subjects. Again, following a period of re-equilibration, when samples were taken for dye analysis from both the hepatic vein and the brachial artery at frequent intervals and when ethanol levels were measured in samples taken from the brachial artery, cardiac output and pressures in the artery and in the hepatic vein were measured.

Estimated hepatic blood flow (EHBF) was determined as previously reported.[6] For this purpose determination was made only during a period when arterial dye concentration remained constant, thus avoiding the need to correct for changing concentration. Such corrections are subject to errors in estimating plasma volume.

Cardiac output (CO) in liters per minute was determined from the formula:

$$CO = I/60a$$

when I = injected amount of indicator (mg.), in this case Evans Blue dye, and a = the area of the dilution curve of the initial circulation of the indicator (mg. second per L.).

Plasma dye concentrations were determined spectrophotometrically (Beckman DU), measuring Evans Blue dye concentration at 630 mμ and indocyanine green concentration at 805 mμ, in both instances the peak of the absorption curves for the respective dyes on the spectrophotometer in use. At these wave lengths in either case there is negligible interference by the other dye.

Blood alcohol was determined according to the method of Newman and Newman.[10]

Peripheral vascular resistance (PVR), in dyne second cm.$^{-5}$, was determined according to the formula:

$$PVR = \frac{\overline{BA} \times 80{,}000}{CO}$$

when $\overline{BA}$ = mean arterial pressure (mm. Hg) and CO = cardiac output (ml. per minute).

Splanchnic vascular resistance (SVR), in dyne second cm.$^{-5}$, was determined from the formula:

$$SVR = \frac{(\overline{BA} - \overline{HV}) \times 80{,}000}{EHBF}$$

when $\overline{BA}$ = mean arterial pressure (mm. Hg), $\overline{HV}$ = mean hepatic venous pressure (mm. Hg) and EHBF = estimated hepatic blood flow (ml. per minute).

RESULTS

All pertinent physiologic data are recorded in Table 1. At the time of initial observations, after the period of equilibration, mean hepatic blood flow was 0.92 L. per minute per M^2. Excluding one subject (J. K.), whose cardiac output was not measured, the mean hepatic blood flow was 0.83 L. per minute per M^2. Corresponding determinations of cardiac output had a mean value of 3.38 L. per minute per M^2. The mean fraction of cardiac output distributed to the hepatic bed was 24.0 per cent (standard deviation (S.D.) 1.9).

In three patients infusion was continued as in the control period without ethanol. The results for one of these (C. F.) are demonstrated in Figure 1. In two of these subjects, later measurements of both cardiac output and hepatic flow showed minor changes from the initial measurements; hepatic flow fraction, therefore, remained constant. In one control subject (W. G.) the hepatic flow increased 58 per cent, although cardiac output increased by only 28 per cent; the hepatic fraction, therefore, increased to more than 32 per cent.

During infusion of ethanol cardiac output increased in all four subjects in whom it was measured. In three of these the increase in cardiac output was demonstrable on the first

* Pure ethyl alcohol, U.S.P. and N.F., U. S. Industrial Chemicals Division, National Distillers and Chemical Corporation, Boston, Massachusetts.

TABLE

Measurements and Derived Data Before and

Subject, Age (yr.) and Sex	Body Surface Area (M^2.)	Time of Infusion (min.)	Time of Ethanol Infusion (min.)	Blood (Arterial) Ethanol Concentration (mg./100 ml.)	Hepatic Extraction Ratio	Heart Rate (beats/ min.)	Cardiac Index (L./min./ M^2.)
E. L., 55, F	1.37	55	...	...	0.68	82	2.84
		80	...	...	0.64	85	...
		110	...	...	0.58	82	3.10
C. F., 51, M	1.46	40	...	...	0.83	60	...
		85	...	...	0.72	64	...
		105	...	...	0.67	64	3.51
		135	...	...	0.68	58	3.28
W. G., 59, M	1.47	40	...	...	0.93	64	...
		60	...	...	0.76	72	3.73
		100	...	...	0.46	70	4.78
C. W., 36, M	1.62	25	...	...	0.67	...	...
		40	...	...	0.61	96	3.13
		73	18	33	0.50	100	5.78
		100	45	38	0.49	106	5.31
H. G., 37, M	1.84	45	...	...	0.71	90	4.52
		60	...	...	0.63	84	...
		102	35	40	0.48	86	4.51
		132	65	103	0.47	96	7.16
J. K., 55, M	1.85	20	...	...	0.61	96	...
		50	...	...	0.62	...	...
		80	18	38	0.51	94	...
		107	45	100	0.48	94	4.81
C. P., 53, M	2.08	30	...	...	0.78	...	...
		40	...	...	0.82	70	2.15
		80	25	48	0.47	85	3.12
		115	60	78	...	90	2.81
R. D., 35, M	1.71	35	...	...	0.70	84	3.95
		85	25	47	0.55	...	...
F. H., 58, M	1.82	35	...	...	0.74	75	3.18
		75	30	75	0.54	78	4.08

measurement within twenty to thirty minutes following the beginning of infusion. In one subject (H. G.) the initial measurement of flow during this period was identical with that before ethanol infusion, but thirty minutes later cardiac output had increased by 58 per cent. In the group of four subjects the initial measurement of cardiac output during infusion of ethanol showed a mean increase of 35 per cent. Among the six subjects in whom hepatic flow was measured both before and during infusion of ethanol, four showed a distinct increase, one (R. D.) showed a small increase and one subject (J. K.) a small decrease. For the group of six the mean increase in hepatic flow was 21 per cent.

For the subjects in whom both hepatic flow and cardiac output were measured during infusion of ethanol, the mean hepatic flow at the time of first measurement following equilibration was 1.10 L. per minute per M^2., the simultaneous mean cardiac output 4.46 L. per minute per M^2. and the mean hepatic flow fraction 24.6 per cent (S.D. 5.4). Two of the subjects (C. W. and H. G.) showed marked changes in the hepatic flow fraction during the initial period of ethanol infusion. In one of these (C. W.) cardiac output increased out of proportion to the increase in hepatic flow, and consequently the hepatic flow fraction fell. In the other subject (H. G.) the hepatic flow increased before demonstrable change in cardiac output was obtained. At the time of later measurement, however, cardiac output had increased significantly in this subject, and the hepatic flow fraction had actually become less than during the control period. In two subjects (J.

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During Infusion of Ethanol in Nine Subjects

Hepatic Flow Index (L./min./M².)	Hepatic Flow: Cardiac Output	Brachial Artery Pressure (mm. Hg)		Peripheral Vascular Resistance (dyne sec. cm⁻⁵.)	Mean Hepatic Vein Pressure (mm. Hg)	Splanchnic Vascular Resistance (dyne sec. cm⁻⁵.)
		Mean	Systolic/ Diastolic			
0.68	0.240	100	152/84	2,055	4	8,260
0.67	...	...	...	...	...	...
0.725	0.233	104	145/80	1,960	4	8,080
0.80	...	...	...	...	...	...
0.76	...	...	...	...	...	...
0.81	0.230	98	132/82	1,530	7	6,145
0.745	0.228	95	128/76	1,590	7	6,470
...	...	...	...	...	...	...
0.98	0.264	60	92/40	875	2	3,210
1.55	0.324	60	92/40	685	3	2,000
0.725	...	...	...	...	...	...
0.75	0.240	93	122/74	1,470	5	5,795
1.10	0.191	92	125/73	785	5	3,900
1.055	0.200	90	123/74	835	5	3,980
1.12	0.248	86	120/68	830	7	3,065
1.24	...	...	...	...	...	...
1.495	0.337	83	120/70	800	8	2,180
1.515	0.212	85	105/78	515	8	2,210
1.68	...	75	116/56	...	12	1,625
1.26	...	...	...	...	...	...
1.205	...	...	...	...	...	...
1.115	0.232	65	88/50	585	10	2,135
0.48	...	...	...	...	...	...
0.445	0.208	75	112/65	1,340	8	5,790
0.76	0.243	88	123/80	1,085	8	4,060
...	...	73	98/65	1,000	...	...
1.05	0.265	105	145/85	1,240	5	4,445
1.075	...	95	130/75	...	6	3,870
0.725	0.228	...	...	...	...	...
0.93	0.228	...	...	...	...	...

K. and R. D.) studies were incomplete. In one of these subjects (J. K.) cardiac output was not measured during the control period, but the hepatic flow fraction during ethanol infusion was 23.2 per cent, similar to the mean value for the group. In the other subject (R. D.) cardiac output was not measured during ethanol infusion. In this subject, who had a normal hepatic flow fraction during the control period, no increase in hepatic flow was demonstrated during the brief period of ethanol infusion.

There was no consistent change in mean arterial or mean hepatic venous pressure during ethanol infusion and, therefore, because both cardiac output and hepatic flow increased in most subjects during ethanol infusion, resistances in both the general systemic vascular bed and in the splanchnic vascular bed almost invariably decreased. During ethanol infusion the mean decrease in peripheral vascular resistance for the three subjects in whom measurements were made was 22 per cent. The mean decrease in hepatic vascular resistance for five subjects was 27 per cent.

During infusion of ethanol, four of the six subjects demonstrated distinct euphoria and increased motor activity.

COMMENTS

Indocyanine green may be expected to be a particularly satisfactory substance for use in the constant infusion method of determining hepatic blood flow. Since it appears to be removed exclusively by the liver and since its extraction ratio is high,[6] the accuracy of the method should be somewhat greater than that

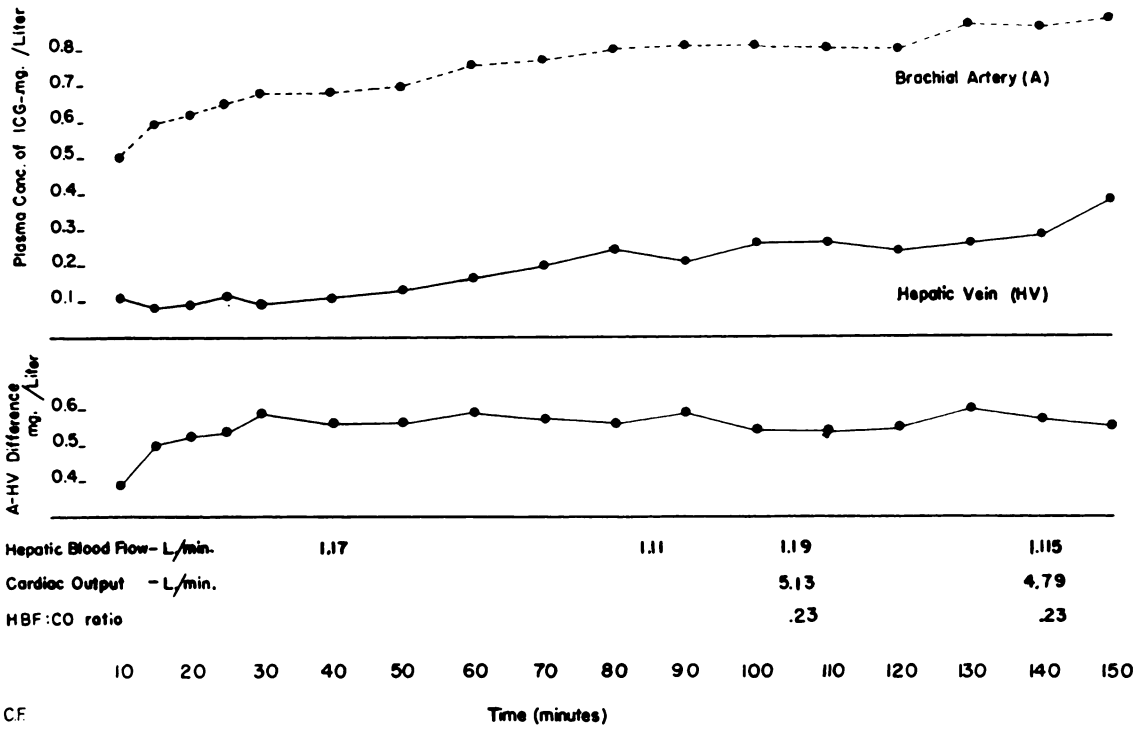

FIG. 1. Determination of hepatic blood flow in Subject C. F. by constant infusion of indocyanine green and periodic sampling for dye concentration in the hepatic vein and a peripheral (brachial) artery.

employing sulfobromophthalein, which is extracted in significant amounts under some circumstances by organs other than the liver.[11,12] Although no direct comparison was made in the present study, indocyanine green infusion could be maintained for periods up to and even beyond two hours for the repeated measurement of hepatic blood flow, as was reported previously.[6] The data from which estimates of hepatic flow were determined for one subject (C. F.) are plotted in Figure 1.

An analysis of simultaneous measurements prior to infusion of ethanol reveals a mean hepatic blood flow of 0.83 L. per minute per M^2. and a mean cardiac output of 3.38 L. per minute per M^2. indicating a hepatic flow fraction of 0.240. These figures agree closely with those reported by others. In dogs, Reynell et al. found hepatic flow to average 24 per cent of cardiac output but with considerable variability within the series.[13] Myers and Hickam demonstrated that in normal human beings 20 per cent of cardiac output went to the liver and in patients with congestive heart failure and reduced cardiac output 24 per cent.[14] In the series of Bradley[4] and Bondy,[15] both studying healthy human subjects, mean hepatic flows were 0.865 and 0.850 L. per minute per M^2. Total systemic flow was not measured in either of these studies. If these results are combined and a normal cardiac index, 3.5 L. per minute per M^2.,[16] is assumed, the hepatic flow fraction in their combined studies can be calculated to be 0.245. This figure agrees well with the fraction actually determined in the present study both before and during infusion of ethanol.

Although the present study demonstrated a rather consistent increase in hepatic flow under the influence of ethanol, this increase in local circulation corresponded, on the average, to a similar increase in total cardiac output, giving a net effect of no change in the hepatic flow fraction. The increased individual variability in the hepatic blood flow during infusion of ethanol may be partly a function of the duration of the study period.

Infusion of ethanol was associated with

lowering of resistance in both the splanchnic and systemic vascular beds. In the absence of any change in venous pressure this suggests that ethanol acts either as a vasodilator or that it increases the number of blood vessels perfused. There is no evidence of any specific or distinctive effect of ethanol upon the splanchnic or hepatic vascular bed. It should be pointed out, however, that the peripheral and splanchnic vascular resistances, as calculated, represent the resultants of the resistances of many vascular beds in series and in parallel. For the splanchnic vascular bed, this includes the stomach and intestines, the spleen and the liver, the latter receiving both arterial blood and, through the portal circulation, venous blood which has already passed through other viscera. The effect of an agent such as ethanol need not be uniform throughout the splanchnic system. Indeed there is evidence that changes in hepatic arterial flow and portal venous flow may occur independently of each other.[17]

The mechanism of the vasodilator effect of ethanol, suggested by this study, is not known. It has been demonstrated by Mendeloff[2] and by Lieber et al.[18] that infusion of ethanol produces elevation in circulating lactate levels. There is also evidence that an increase in serum lactate levels is associated with vasodilatation, increased cardiac output and possibly increased liver blood flow.[19,20] Also, indirect vascular effects of ethanol may result from excitation or depression of the central nervous system.

The discrepancies between this and other studies[1–3] are not explainable at this time. It is possible that the amount, rate or route of administration of ethanol may play a role. The rate of administration and the ethanol levels reached in the present study approximated or exceeded those attained in the studies of Mendeloff[2] and of Castenfors et al.[3] The method of administration in these studies was similar, however. In a recently reported study,[21] administration of ethanol was associated with a small but significant decrease in hepatic blood flow, but it should be noted that the amount of ethanol administered and the blood levels achieved were much smaller than those in the present study and in the other studies reported herein.

The present results suggest that the net effect of ethanol administration on the hepatic circulation is proportional to that on the systemic circulation. There was no evidence of any specific or differential effect of ethanol upon the splanchnic or hepatic vascular beds.

SUMMARY

The use of indocyanine green in the constant infusion method of estimating hepatic blood flow is described. In nine subjects under control conditions, the mean hepatic blood flow was found to be 0.92 L. per minute per M^2. In eight subjects in whom cardiac output was determined simultaneously, the mean hepatic flow was 0.83 L. per minute per M^2. and the corresponding mean cardiac output 3.38 L. per minute per M^2. The mean hepatic flow fraction in these eight subjects was 0.240.

During infusion of ethanol at a rate of 0.5 to 0.8 gm. per minute the mean hepatic blood flow rose to 1.09 L. per minute per M^2. and the corresponding total cardiac output to 4.46 L. per minute per M^2. The hepatic flow fraction remained essentially constant at 0.246.

Ethanol had no significant effect on systemic arterial or hepatic venous pressures. Changes in calculated peripheral and splanchnic vascular resistance were inversely proportional to the effects upon flow.

These results suggest that the net effect of ethanol upon the hepatic circulation is proportional to that upon the systemic circulation.

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