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THE EFFECT OF ADRENALINE AND NORADRENALINE ON HEPATIC BLOOD FLOW AND SPLANCHNIC CARBOHYDRATE METABOLISM IN MAN

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The action of adrenaline and noradrenaline on the heart and peripheral circulation in man has been studied (Goldenberg, Pines, Baldwin, Greene & Roh, 1948; Barcroft & Konzett, 1949), but their effects on the hepatic circulation are uncertain. Bradley (1946), using the hepatic vein catheterization technique, described, in a preliminary communication, an increase in hepatic blood flow with adrenaline. Grayson & Swan (1950) used changes in the temperature of the human colon as a qualitative index of blood flow and noted colonic vasoconstriction with both adrenaline and noradrenaline.

In the present study not only have the effects of adrenaline and noradrenaline on the hepatic blood flow been determined but also simultaneous changes in splanchnic carbohydrate metabolism.

METHODS

The twenty-two subjects studied had no known hepatic dysfunction and were rested in bed and without food for 12 hr. Sodium amytal 0·2 g. was given by mouth 30 min. before the observations began.

A radio-opaque catheter was passed into an antecubital vein, and under fluoroscopic control introduced into one of the hepatic veins. After a priming dose of bromsulphalein (B.S.P.) had been given, an intravenous infusion of B.S.P. of suitable strength at a constant rate was started (Sherlock, Bearn, Billing & Paterson, 1950). Assuming that the liver is the only organ removing B.S.P. from the peripheral blood and that the concentration of B.S.P. in the peripheral venous blood does not change, then the rate of the infusion is equal to the rate of removal of the dye by the liver. By application of the Fick principle the hepatic blood flow can be calculated (Bradley, Ingelfinger, Bradley & Curry, 1945).

Twenty minutes after the infusion had begun blood samples were taken from the hepatic vein catheter and through an indwelling needle in an antecubital vein. At the same time 0·2 ml. capillary blood was withdrawn from the ear. The level of B.S.P. in the peripheral venous blood was estimated to ensure that it was greater than 1·0 mg./100 ml. plasma; two further sets of control samples were taken at 10 min. intervals. Adrenaline or noradrenaline were then added to the B.S.P. infusion so that the subject received the test substance at a constant rate for 30 min.

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Bromsulphalein without the test substance was then infused and the observations were continued for a further hour, at the end of which the position of the hepatic vein catheter was checked fluoroscopically. Blood was taken from the three sampling sites at intervals of 5, 10, 15, 30, 45, 60, 75 and 90 min. from the beginning of the adrenaline or noradrenaline infusion. Brachial blood pressure (auscultatory) and pulse rate were determined frequently. In most instances blood from the brachial artery was obtained at the conclusion of the observations; it was assumed that the oxygen content of the arterial blood did not change during the experiment.

Preparation and administration of adrenaline and noradrenaline. The same batch of adrenaline hydrochloride was used throughout (Allen & Hanbury, 1:1000) and was stored in 0·5 ml. ampoules in the dark at 4° C. This preparation does not contain noradrenaline. Immediately before use the adrenaline was diluted with 40 ml. B.S.P. infusion and about 250 mg. ascorbic acid added to prevent oxidation.

L-Noradrenaline bitartrate was dissolved in N/100-HCl (prepared from pyrogen-free water) under sterile conditions, to give a 1:1000 solution of noradrenaline. This solution was stored in the dark at 4° C, and was diluted immediately before use with 40 ml. of the B.S.P. infusion. Adrenaline was given at the rate of 0·10 μg./kg./min. (nine subjects); noradrenaline was given at the rate of 0·10 μg./kg./min. (four subjects); 0·15 μg./kg./min. (three subjects); and 0·20 μg./kg./min. (six subjects).

Analytical methods. All analyses were carried out on the same day as the observations. The hepatic and peripheral venous blood samples were taken into heparinized tubes and analysed for blood glucose (King, Haslewood, Delory & Beall, 1942), blood lactic acid (Barker & Summerson, 1941) and plasma B.S.P. (Sherlock *et al.* 1950), using 0·2, 1 and 2 ml. samples respectively. 0·2 ml. capillary blood was taken direct into 3·5 ml. copper sulphate reagent and the glucose content determined; this was assumed to be the same as that in arterial blood (Somogyi, 1948). Hepatic venous blood and brachial arterial blood were collected in oiled syringes under liquid paraffin into oxalated containers, and the oxygen unsaturation was immediately estimated on 5 ml. samples using the Haldane blood-gas apparatus. The plasma volume was calculated from the tables of Gibson & Evans (1937).

Calculations. The estimated hepatic blood flow (E.H.B.F.) was calculated as previously described (Sherlock *et al.* 1950) and expressed in ml./sq.m./min. Where necessary, correction was made for changing peripheral venous B.S.P. levels (Bradley *et al.* 1945). No allowance has been made for changes in the vascular capacity of the splanchnic area, since such changes, if they occur, would only exert a transitory effect on the calculated hepatic blood flow.

Samples of blood from the hepatic artery and portal vein cannot be obtained in man except by surgical means. It has, therefore, been necessary to assume that the concentration of a substance in capillary or peripheral venous blood is identical with that in the portal vein blood (Bondy, James & Farrar, 1949). If the difference in concentration of a substance in the hepatic venous blood and peripheral venous or arterial blood is multiplied by the hepatic blood flow, the result gives the amount of that substance being produced or removed by the liver, or, more precisely, the splanchnic area.

$$\text{Hepatic glucose output (mg./sq.m./min.} = \frac{H_{Gl} - C_{Gl}}{100} \times \text{E.H.B.F.},$$

$$\text{Splanchnic oxygen consumption (ml./sq.m./min.)} = \frac{V_{O_2} - A_{O_2}}{1000} \times \text{E.H.B.F.},$$

$$\text{Splanchnic vascular resistance} = \frac{\text{Mean blood pressure (mm. Hg)}}{\text{E.H.B.F. (ml./min.)}},$$

where H_{Gl} = hepatic venous glucose concentration (mg./100 ml.),
C_{Gl} = capillary glucose concentration (mg./100 ml.),
V_{O_2} = hepatic venous oxygen unsaturation (ml./l.),
A_{O_2} = arterial oxygen unsaturation (ml./l.).

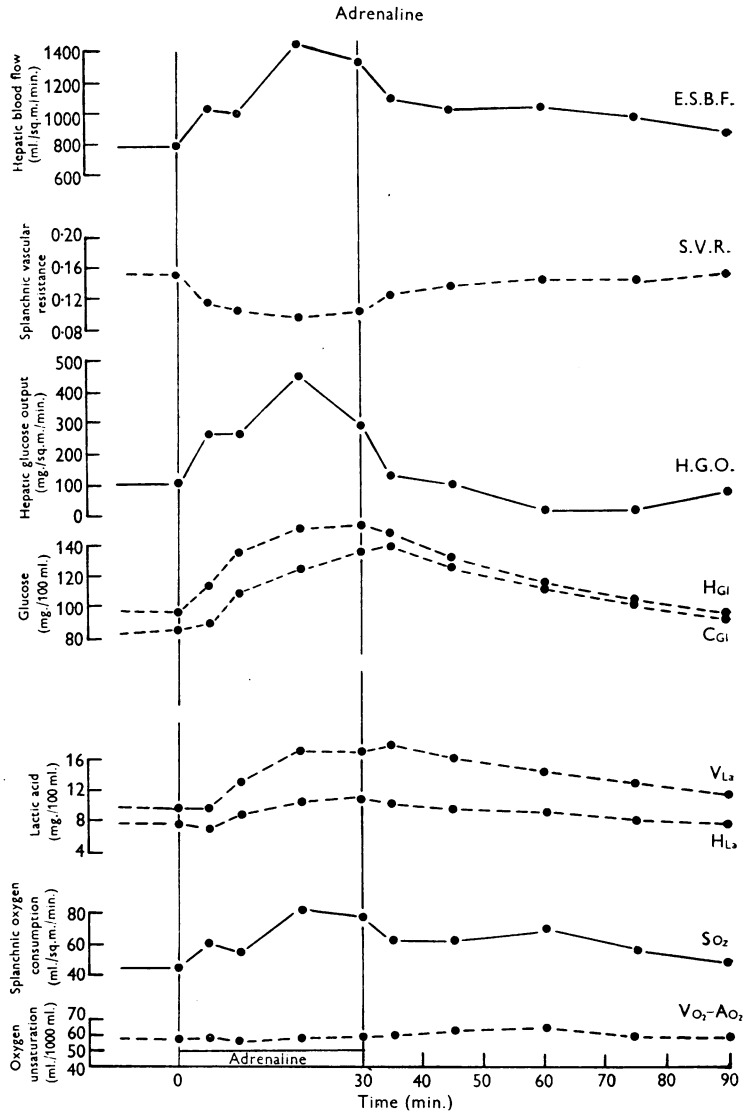

Fig. 1*a*.

Fig. 1. The effects of intravenous adrenaline and noradrenaline on hepatic blood flow (E.H.B.F.), splanchnic vascular resistance (S.V.R.), hepatic glucose output (H.G.O.), hepatic venous glucose concentration (H_{Gl}), capillary glucose concentration (C_{Gl}), peripheral venous lactic acid concentration (V_{La}), hepatic venous lactic concentration (H_{La}), splanchnic oxygen consumption (S_{O_2}), and hepatic venous–arterial oxygen difference ($V_{O_2} - A_{O_2}$). Mean results for adrenaline 0·10 μg./kg./min. (nine observations) and noradrenaline 0·20 μg./kg./min. (six observations).

RESULTS

The results obtained have been recorded in Figs. 1–6 and Table 1, and summarized in Table 2. Fig. 1 was constructed from the mean values obtained by giving 0·10 μg./kg./min. adrenaline to nine subjects and 0·20 μg./kg./min. noradrenaline to six subjects.

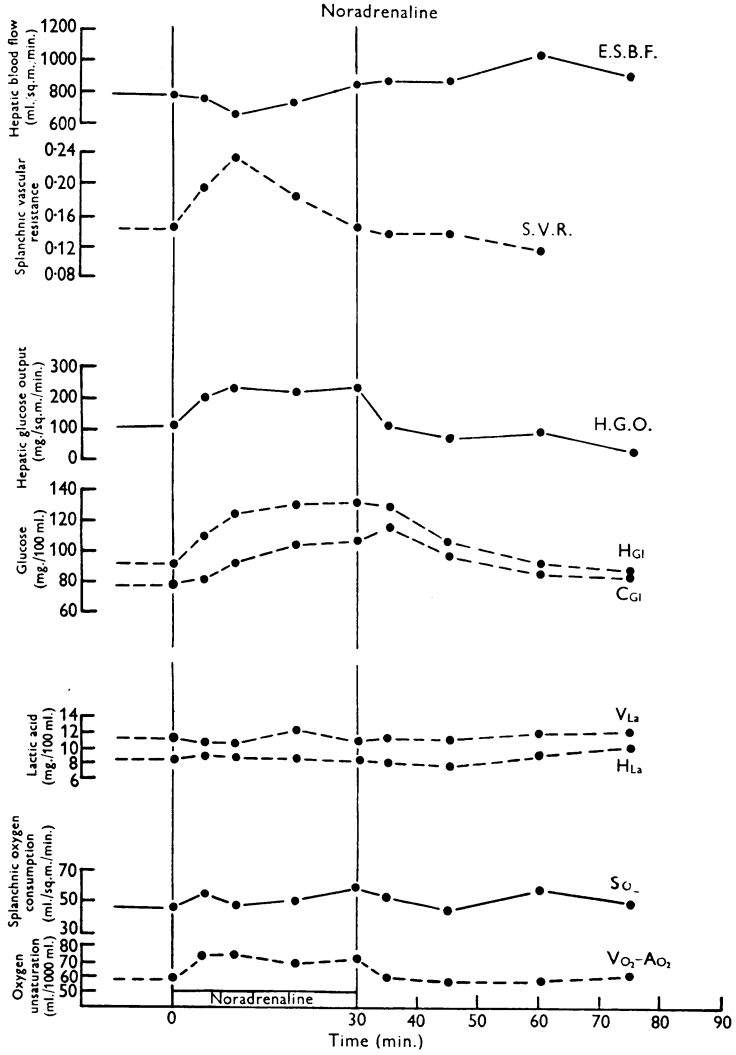

Fig. 1*b*. For legend see p. 432.

General effects. Symptomatic changes were few; in some subjects, however, the adrenaline infusions caused a slight headache. Facial pallor was observed in all subjects receiving adrenaline, but with noradrenaline this was slight

and occurred only with the larger doses. There was a facial flush after the cessation of both the adrenaline and noradrenaline infusions. Muscle twitchings were observed only once.

Adrenaline caused a rise in the systolic blood pressure (0–54 mm. Hg) and a fall in diastolic blood pressure (6–26 mm. Hg). The pulse rate also increased (16–56 beats/min.).

Noradrenaline caused a rise in systolic blood pressure (24–100 mm. Hg) and diastolic blood pressure (20–70 mm. Hg) with a rise in pulse pressure (4–44 mm. Hg). The pulse rate decreased during the infusion (6–24 beats/min.), but during the recovery period there was slight tachycardia.

Estimated hepatic blood flow and splanchnic vascular resistance. In all subjects adrenaline caused a rise in hepatic blood flow and a fall in splanchnic vascular resistance (Fig. 2), indicating vasodilatation. The averaged results are shown in Fig. 1 and Table 1.

TABLE 1. Mean results of the effect of adrenaline and noradrenaline on hepatic blood flow, hepatic glucose output, capillary blood-glucose concentration, peripheral venous lactic acid concentration, and splanchnic oxygen consumption.

Infusion mixture	Rate of infusion (μg./kg./min.)	No. of observations	E.H.B.F. (ml./sq.m./min.)		Hepatic glucose output (mg./sq.m./min.)		Capillary glucose (mg./100 ml.)		Peripheral venous lactic acid (mg./100 ml.)		Splanchnic oxygen consumption (ml./sq.m./min.)	
			Initial	Maximum change	Initial	Maximum change	Initial	Maximum change	Initial	Maximum change	Initial	Maximum change
Adrenaline	0·10	9	779	+830	95	+640	84	+56	9·5	+10·3	43	+50
Noradrenaline	0·10	4	1090	−349	87	+116	89	+11	10·5	+1·7	60	+10
Noradrenaline	0·15	3	703	−169	101	+352	78	+30	10·2	+1·9	37	+17
Noradrenaline	0·20	6	767	−200	102	+361	77	+39	11·0	+2·1	48	+20

Noradrenaline caused a small fall in hepatic blood flow (Fig. 2), except in one case where there was no change. In the present small series of observations increasing the dose of noradrenaline did not appear to increase the flow reduction (Table 1). This fall in hepatic blood flow was usually observed within 10 min. and occurred simultaneously with a rise in the mean blood pressure, so that the calculated splanchnic vascular resistance increased, indicating vasoconstriction (Fig. 2). With the exception of four observations, the values for hepatic blood flow returned to normal before the end of the noradrenaline infusion. In some instances there was slight splanchnic vasodilatation after the noradrenaline infusion ceased.

Hepatic glucose output. Both adrenaline and noradrenaline caused an increase in the concentration of capillary glucose in all subjects (Fig. 3). The concentration of glucose in the hepatic venous blood rose at a greater rate than in the capillary blood (Fig. 1), indicating a release of glucose from the liver into the general circulation. This increased glucose output from the liver was observed with noradrenaline, in spite of a diminished hepatic blood flow, but it was not as great as that resulting from adrenaline (Table 1). Maximum readings for

hepatic glucose output occurred before the maximum readings for capillary glucose concentration (Fig. 1). Capillary–peripheral venous blood glucose differences were not appreciably altered.

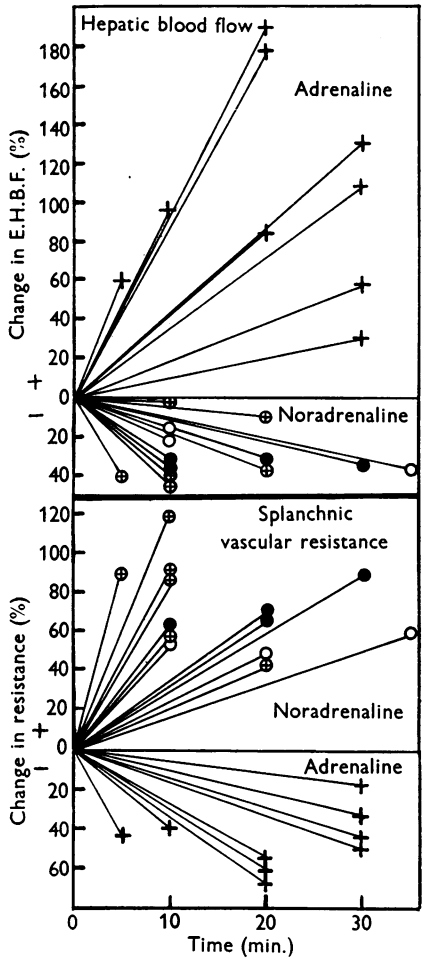

Fig. 2. Maximum changes in hepatic blood flow and splanchnic vascular resistance. In this and subsequent figures, time 0 refers to the beginning of the infusion and the rate of infusion is indicated by: +——+ adrenaline 0·10 μg./kg./min; ●——● noradrenaline 0·10 μg./kg./min; ○——○ noradrenaline 0·15 μg./kg./min.; ⊕——⊕ noradrenaline 0·20 μg./kg./min.

The glycaemic action of noradrenaline was about one-sixth that of adrenaline, given at a similar rate. Fig. 4 shows that the glycaemic effects of noradrenaline depend on the rate of the infusion.

Lactic acid uptake. The concentration of lactic acid in the peripheral venous blood was at all times greater than in the hepatic venous blood, thus indicating

that under basal conditions lactic acid was being continually removed from the circulation (Fig. 1). Adrenaline caused a considerable increase in the lactic acid content of the peripheral venous blood. The level in the hepatic venous blood also rose but at a slower rate, so that the values for the peripheral-

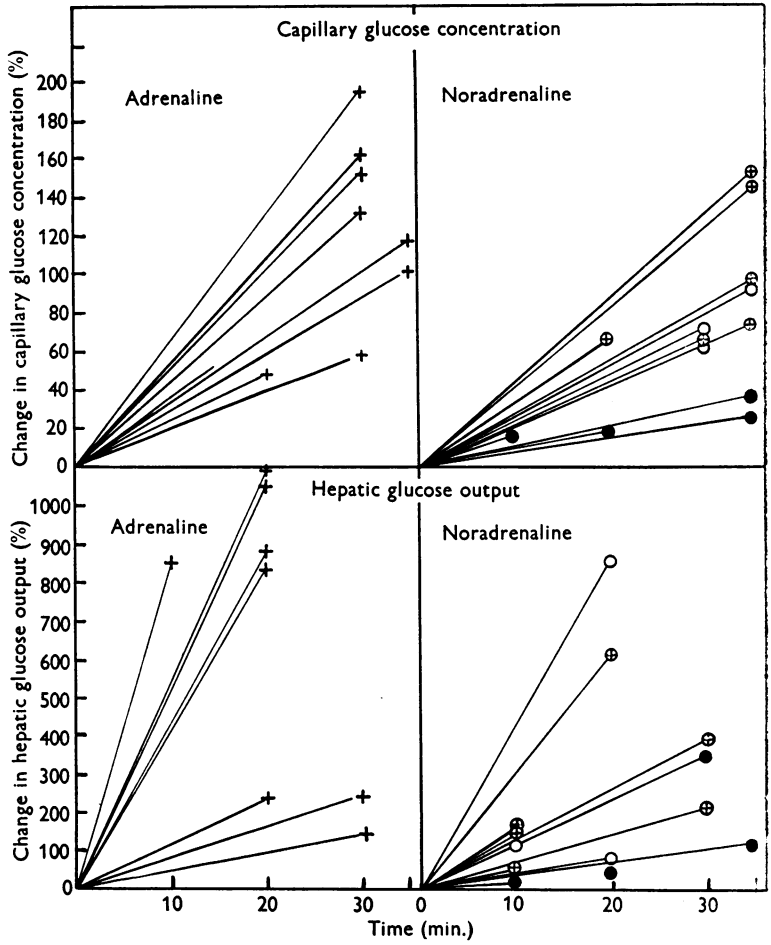

Fig. 3. Maximum changes in capillary glucose concentration and hepatic glucose output.

hepatic venous lactic acid difference (V_{La}–H_{La}) increased, and even an hour after the infusion had not returned to the control values. Noradrenaline, however, had little effect on lactic acid production whatever the rate of the infusion. A maximum rise of 4 mg.% was observed in one subject, but in the majority was considerably less. There was also little change in the concentration of lactic acid in the hepatic venous blood.

Splanchnic oxygen consumption. Adrenaline caused a marked increase in splanchnic oxygen consumption. This calculated increase was derived almost

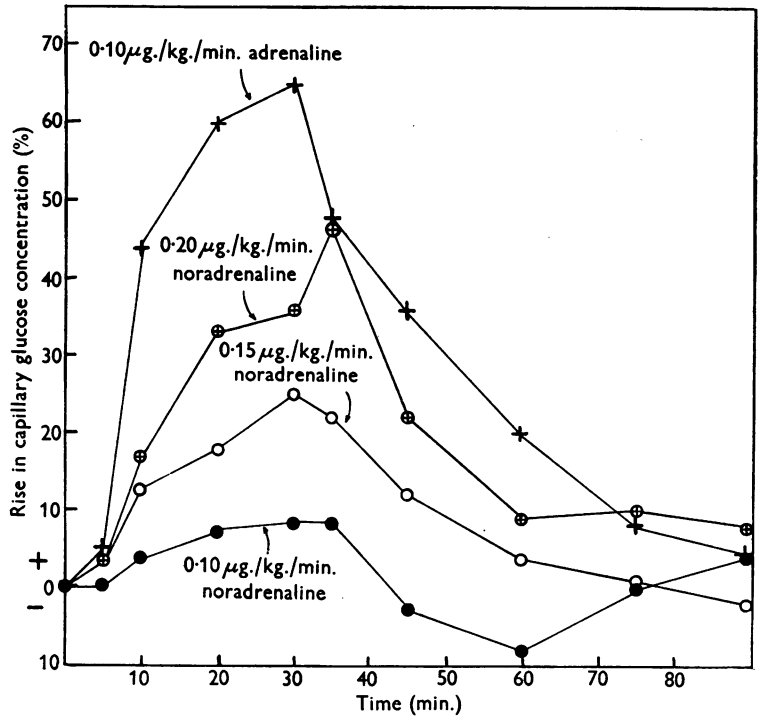

Fig. 4. Changes in mean values of capillary glucose concentration.

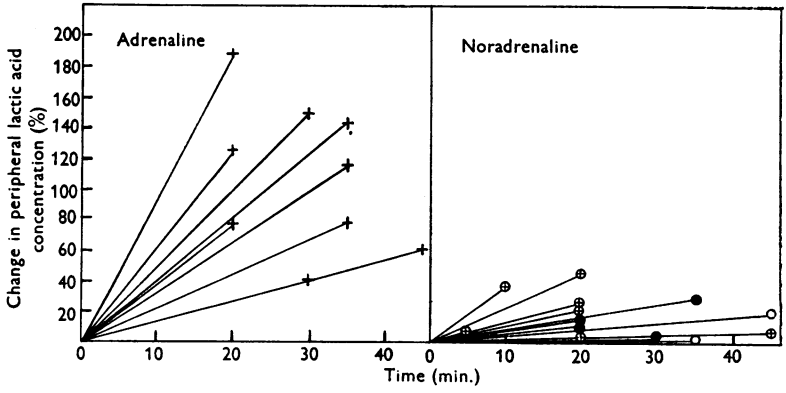

Fig. 5. Maximum changes in peripheral venous lactic acid concentration.

entirely from the increased hepatic blood flow, since the values for V_{O_2}–A_{O_2} remained remarkably constant (Fig. 1). Noradrenaline had only a small effect on splanchnic oxygen consumption. The oxygen content of the hepatic venous

blood decreased during the period of reduced hepatic blood flow, so that the normal splanchnic oxygen consumption was maintained throughout the observations and in some subjects increased slightly (Fig. 6).

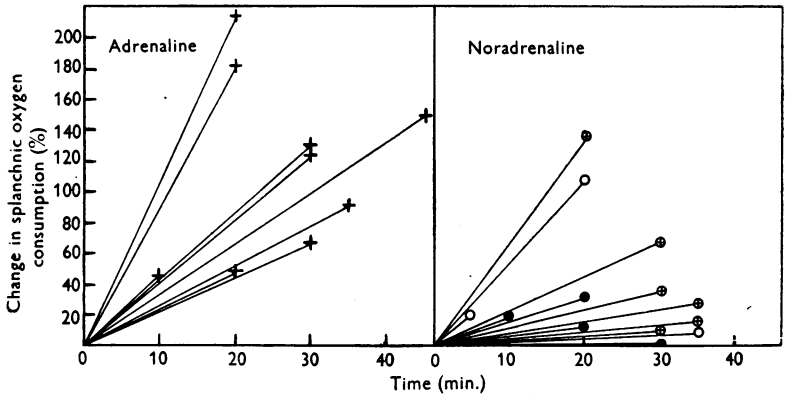

Fig. 6. Maximum changes in splanchnic oxygen consumption.

DISCUSSION

The hepatic vein catheterization technique has enabled some of the actions of adrenaline and noradrenaline on the liver in man to be studied without the complications of surgical trauma or anaesthesia. Adrenaline was given at a constant rate of 0·10 μg./kg./min., since this was known to cause only slight symptoms and to be considerably less than that believed to be liberated by the body in moments of stress (Cannon & Rapport, 1921). Noradrenaline was given in a similar dose; the metabolic effects were, however, so small that the rate of administration was increased to 0·15 and 0·20 μg./kg./min. to see if a greater response could be obtained.

This work has shown that adrenaline caused marked increases in hepatic blood flow, which were considerably greater than the normal variations found during a 2 hr. control period (Sherlock *et al.* 1950). These findings are in agreement with those reported by Bradley (1946) using a similar technique. Grayson & Swan (1950) concluded from changes in colonic temperature that adrenaline constricted colonic vessels. Goldenberg, Aranow, Smith & Faber (1950) have given adrenaline in larger doses (0·3–0·9 μg./kg./min.) to patients with phaeochromocytomas, and have observed overall vasoconstriction. Animal experiments, using large single doses of adrenaline, have also shown that adrenaline can cause a reduction in hepatic blood flow (Clarke, 1928; McMichael, 1932). The effect of adrenaline appears, therefore, to be related to the dose given.

It is possible that adrenaline causes initial splanchnic vasoconstriction, which is then followed by vasodilatation as we have described. Such a vasoconstriction, if it occurs, must be very transient, as our results 5 min. after

the commencement of the infusion already show increases in hepatic blood flow. The overall vasoconstrictor action of noradrenaline (Goldenberg *et al.* 1948) has been shown to include the liver, since in all subjects except one there was a slight diminution in hepatic blood flow. Grayson & Swan (1950) reported that noradrenaline causes vasoconstriction in the exposed colon in man.

The hyperglycaemic action of adrenaline is well known and results from mobilization of liver glycogen without subsequent increased carbohydrate utilization (Cori, Cori & Buchwald, 1930). In the present work the hepatic glycogenolytic action of adrenaline has been clearly demonstrated by the rise in hepatic venous glucose concentration in spite of the increase in hepatic blood flow. The resulting increased output of glucose from the liver was responsible for the rise in the capillary blood-glucose concentration, although no close relation could be found between the two. This poor correlation may well be explained by changes in the peripheral utilization of glucose.

Noradrenaline given at a rate of 0·10 μg./kg./min. produced a glycaemic response one-sixth as great as that obtained with a similar dose of adrenaline. When the rate of noradrenaline administration was increased to 0·20 μg./kg./min. the rise in capillary blood-glucose concentration was still only about one-half of that obtained with adrenaline (0·10 μg./kg./min.). Observations in man (Goldenberg & Aranow, 1950, unpublished), and in rabbits (Sahyun, 1933) have also stressed the relatively poor glycaemic action of noradrenaline. It is of interest to note that the increases in hepatic venous–capillary glucose concentration difference during infusions of noradrenaline (0·20 μg./kg./min.) were of the same order as those found with adrenaline, although the actual glucose output was less, due to the reduced hepatic blood flow.

Adrenaline is known to diminish muscle-glycogen concentration in man (Hildes, Sherlock & Walshe, 1949) and to increase the concentration of lactic acid in the blood. The effect of noradrenaline on muscle glycogen in man is not known, but the resulting lactacidaemia is so small that one would expect any diminution to be slight. This is true of the rabbit, on whom it has been shown that noradrenaline has little effect on muscle glycogen (Sahyun & Webster, 1933).

Adrenaline causes an increase in the total oxygen consumption in man (Cori & Buchwald, 1930). Lundholm (1949) has shown that in cats the increased oxygen consumption caused by adrenaline is, in part, an index of the amount of lactic acid which has been synthesized to glycogen. Since glycogen resynthesis takes place in the liver, it was to be expected that the period of increased splanchnic oxygen consumption would coincide with the period of maximum lactic acid uptake (Fig. 1), as it is probable that the liver is the chief organ removing lactic acid from the circulation.

The increase in splanchnic oxygen consumption resulting from noradrenaline was considerably less than that caused by adrenaline. This finding is in keeping

both with the work of Reale, Kappert, Skoglund & Sutton (1950), who showed that noradrenaline causes no appreciable change in total oxygen consumption, and with our observation that its lactacidaemic action is slight.

Recent work by von Euler (1946) has shown that noradrenaline is liberated in greater amounts than adrenaline from the endings of the sympathetic nerves and is of considerable physiological importance. It is of interest, therefore, that these amines have opposite actions on the hepatic circulation and that, compared with adrenaline, noradrenaline has such a small effect on splanchnic carbohydrate metabolism.

TABLE 2. Summary of results

		Adrenaline	Noradrenaline
Circulatory	Pulse rate	Increase	Decrease
	Blood pressure: systolic	Increase	Increase
	diastolic	Decrease	Increase
	Estimated hepatic blood flow	Great increase	Slight decrease
	Splanchnic vascular resistance	Decrease	Increase
Metabolic	Hepatic glucose output	Great increase	Slight increase
	Capillary glucose concentration	Great increase	Slight increase
	Peripheral venous lactic acid concentration	Increase	Little change
	Splanchnic oxygen consumption	Increase	Slight increase

SUMMARY

1. Adrenaline was administered intravenously at a rate of 0·10 μg./kg./min. to nine normal subjects for 30 min. Noradrenaline, at rates of 0·10–0·20 μg./kg./min., was similarly administered to thirteen normal subjects.

2. The hepatic vein catheterization technique was used to determine the changes in estimated hepatic blood flow and in the concentrations of glucose, lactic acid and oxygen in the hepatic venous blood. Capillary blood glucose and peripheral venous blood lactic acid concentrations were simultaneously determined.

3. Adrenaline caused an increase in estimated hepatic blood flow, while noradrenaline administration resulted in a slight decrease.

4. Adrenaline increased the output of glucose from the liver and the capillary blood-glucose concentration rose. Noradrenaline had a small effect on hepatic glycogenolysis, and the increase in capillary blood-glucose concentration was about one-sixth of that observed with a similar dose of adrenaline.

5. Adrenaline increased the peripheral venous lactic acid concentration, while noradrenaline was shown to have little effect.

6. Adrenaline increased splanchnic oxygen consumption; this was not observed with noradrenaline.

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