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Effects of adrenaline, isoprenaline and histamine on transsinusoidal fluid filtration in the cat liver

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Summary

1. Hepatic volume was recorded by a plethysmographic technique in cats anaesthetized with pentobarbitone. It has been shown previously that during an increase of hepatic venous pressure in this preparation, there is a maintained filtration of fluid from the sinusoids into the plethysmograph. The rate of this filtration is directly proportional to the increase in hepatic venous pressure. Infusions of drugs during this period of steady filtration provide a sensitive measure of the effects of the drugs on transsinusoidal fluid transfer.

2. Infusions of adrenaline, isoprenaline and histamine had no effect on the steady transsinusoidal filtration produced by an increased hepatic venous pressure. It is concluded that these agents do not change sinusoidal hydrostatic pressure by more than 1·5 mmHg (1 mmHg≡1·333 mbar) even though they alter hepatic arterial and portal flows. They do not change sinusoidal surface area by more than 20% and histamine does not change sinusoidal permeability.

3. The data are discussed in the light of current theories on the application of Starling's hypothesis to the liver sinusoids and to muscle capillaries. The postsinusoidal resistance appears to be very low in the liver and it does not increase during contraction of the capacitance vessels. The liver does not have presinusoidal sphincters, and closed sinusoids analogous to closed capillaries in skeletal muscle do not occur. The major factor controlling hepatic transsinusoidal fluid movements in the anaesthetized cat is hepatic venous pressure.

Introduction

In the vascular bed of skeletal muscle, the direction and magnitude of transcapillary fluid movements depend primarily on the balance between hydrostatic and colloidal osmotic pressures in the capillaries and interstitial fluids (Starling's hypothesis). In addition the magnitude of any net fluid movement is influenced by the capillary surface area available for exchange and by the permeability of the capillary wall. These latter factors were embodied in measurements of capillary permeability-surface area product by Renkin (1959) and capillary filtration coefficient by Mellander (1960). Factors which influence or control these variables have been reviewed by Mellander & Johansson (1968). Close arterial infusions of isoprenaline cause vasodilatation and increase capillary filtration coefficient in skeletal muscle and intestine in cats (Johnsson & Oberg, 1968; Diana, 1970; Folkow, Lundgren & Wallentin, 1963). The inhibition of precapillary sphincter activity results in an increased capillary surface area due to opening of previously closed capillaries. Histamine causes vasodilatation and an increased capillary permeability which result

in fluid filtration from the capillaries (Kjellmer & Odelram, 1965; Appelgren, Jacobsson & Kjellmer, 1966; Dietzel, Massion & Hinshaw, 1969).

In the hepatic vascular bed, the quantitative aspects of transsinusoidal fluid transfer are less well understood. The discontinuous endothelium of the sinusoids is permeable to proteins (Mayerson, Wolfram, Shirley & Wasserman, 1960) and the transsinusoidal colloid osmotic pressure is low. Sinusoidal hydrostatic pressure is correspondingly low and fluid filtration across the sinusoids is remarkably sensitive to small increases in hepatic venous pressure (Greenway & Lautt, 1970; Greenway & Stark, 1971). It is not known whether sinusoidal surface area can be varied by the activity of presinusoidal sphincters. To study this situation further, we examined the effects of drugs which modify hepatic arterial or portal blood flows and which are known to modify capillary surface area and permeability in skeletal muscle, namely adrenaline, isoprenaline and histamine. In the previous paper (Greenway & Lautt, 1972), we showed that adrenaline but not histamine or isoprenaline causes an initial effect on hepatic blood volume. After this initial capacitance effect, none of the three drugs caused any progressive change in hepatic volume. This suggested that these agents did not cause net fluid exchange in the liver but we wished to test this under more critical conditions. The method used in skeletal muscle to determine capillary filtration coefficient (Mellander, 1960) is not as satisfactory in the liver due to the prolonged delayed compliance of the venous bed (Greenway & Lautt, 1970). However, a rise in hepatic venous pressure causes a transsinusoidal fluid filtration which continues at a steady rate for several hours. We have examined whether infusions of adrenaline, isoprenaline or histamine modify this steady filtration during the increased venous pressure.

Methods

Cats were anaesthetized with sodium pentobarbitone and prepared as described in the previous paper (Greenway & Lautt, 1972). Arterial and portal pressures and hepatic volume were recorded. In addition, control of hepatic venous pressure was obtained by a long-circuit technique which has been described and evaluated previously (Greenway & Lautt, 1970). Briefly, the inferior vena cava was ligated below the liver and the hepatic outflow was drained from a cannula in the thoracic inferior vena cava. Blood entering the inferior vena cava below the occlusion drained from cannulae in the femoral veins. The blood was returned from a reservoir through cannulae in the external jugular veins. Hepatic venous pressure was controlled by raising or lowering the outlet of the hepatic venous cannula.

The transsinusoidal filtration rate ((ml/min)/100 g) was calculated from the slope (in ml/min) of the steady increase in hepatic volume during the period the hepatic venous pressure was raised to 7 mmHg (1 mmHg≡1·333 mbar). It was standardized to 100 g liver. The times at which the slope was measured during control and experimental periods are described in the section on experimental procedure in **Results** and are shown in Fig. 1.

Results

Control values

Ten cats (mean weight 2·5 kg; mean liver weight 96 g) were used. After the preparation was set up and the measured parameters were stable, hepatic venous

pressure was increased by 7 mmHg. Mean arterial pressure was 134 ± 12 mmHg (mean ± S.E.) before and 130 ± 11 mmHg after, mean portal pressure was 7·3 ± 0·7 mmHg before and 10·8 ± 0·6 mmHg after, and mean total hepatic flow was (98 ± 5·4 ml/min)/100 g before and (91 ± 4·6 ml/min)/100 g after hepatic venous pressure was raised. The mean steady-state transsinusoidal filtration during the raised venous pressure was (0·33 ± 0·06 ml/min)/100 g.

Experimental procedure

To clarify the experimental procedure, the results obtained in one cat in which adrenaline was infused are shown in Fig. 1. These data are taken directly from the record which could not be shown owing to its length. After a control period, hepatic venous pressure was increased by 7 mmHg. Hepatic volume increased rapidly at first, then after 15–20 min the volume increased at a steady rate (slope A). We have previously shown that the initial rapid increase is due to passive distension

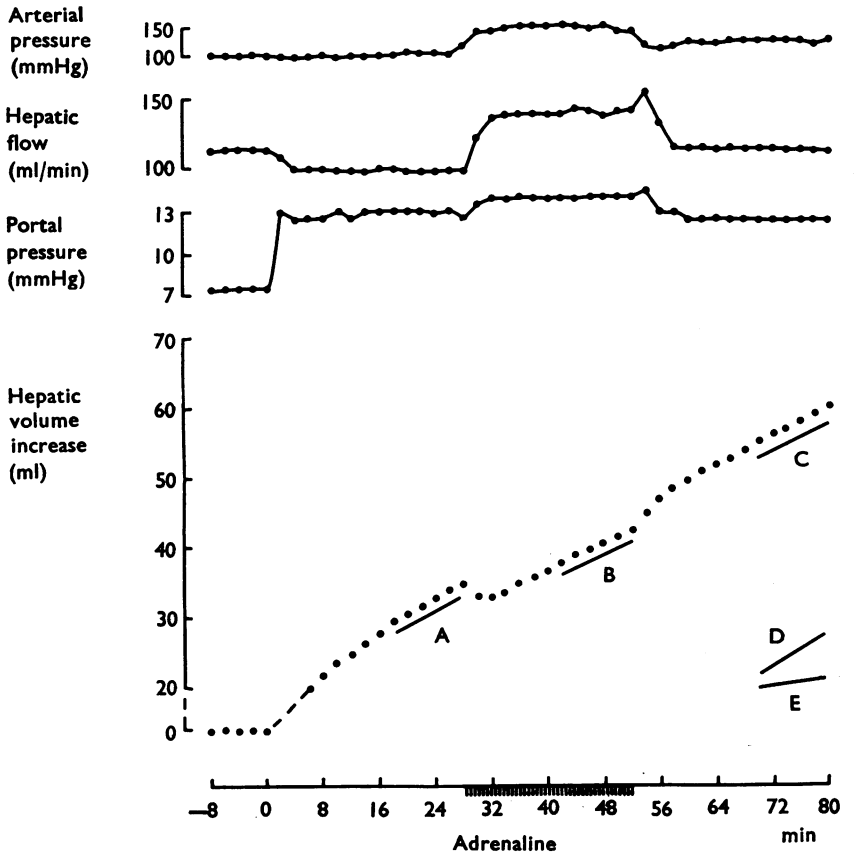

FIG. 1. Data for an experiment in one cat (2·2 kg body weight, 83 g liver) replotted on scales suitable for publication. At zero time, hepatic venous pressure was increased to 7 mmHg. The steady state volume increase (slope A) was 0·52 ml/min. Adrenaline ((2 μg/min)/kg) was infused intravenously and the steady state volume increase (slope B) was 0·48 ml/minute. After cessation of the adrenaline, the steady state volume increase (slope C) was 0·48 ml/minute. When hepatic venous pressure was subsequently increased to 8·5 mmHg and reduced to 5·5 mmHg, the steady state volume increases were 0·60 (slope D) and 0·15 (slope E) ml/min respectively.

of the venous bed in the liver while the steady increase is due to transsinusoidal fluid filtration (Greenway & Lautt, 1970). Adrenaline was then infused intravenously for 24 minutes. Arterial and portal pressures increased and hepatic blood flow increased due to intestinal vasodilatation (Greenway & Lawson, 1966, 1968). The steady increase in hepatic volume was interrupted at the onset of the adrenaline infusion due to the effects of adrenaline on the hepatic blood content, but these were complete in less than 15 minutes. (Blood volume changes did not occur with isoprenaline and histamine—see Greenway & Lautt, 1972.) Thereafter, hepatic volume increased at a steady rate (slope B). On cessation of the adrenaline infusion,

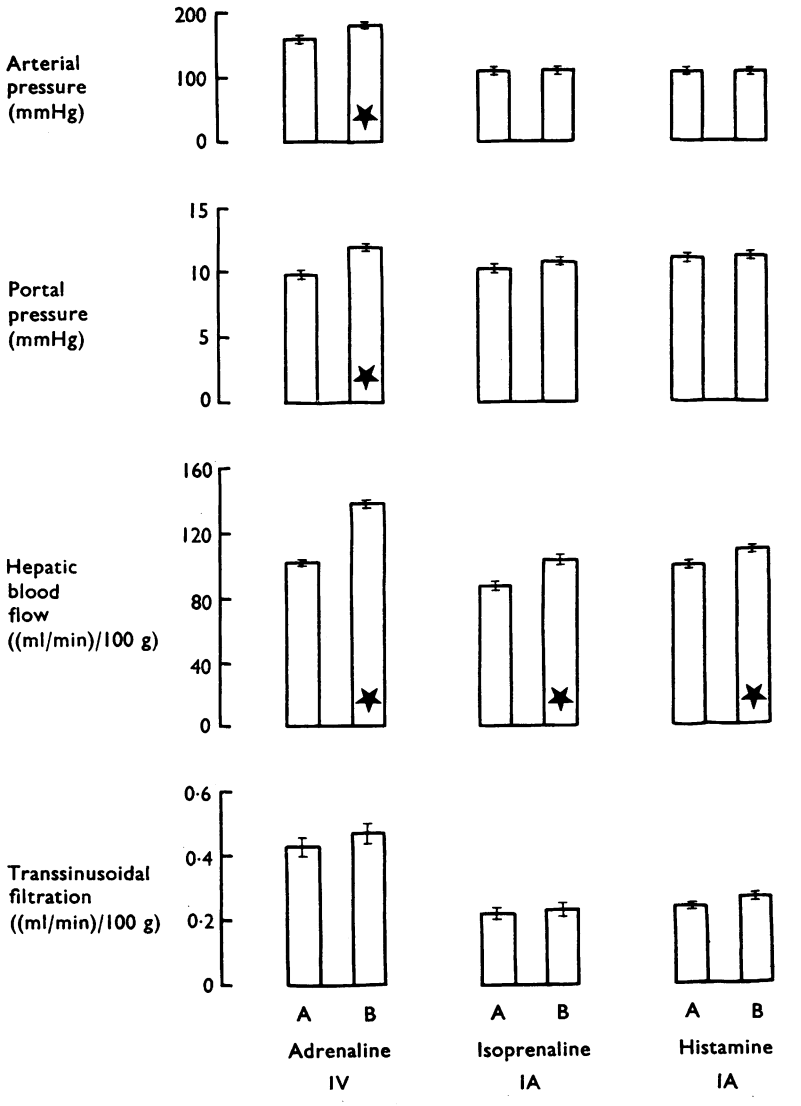

FIG. 2. The mean results before (A) and during (B) the infusions of adrenaline ((2 μg/min)/kg) intravenously, isoprenaline ((0·2 μg/min)/kg) into the hepatic artery and histamine ((5 μg/min)/kg) into the hepatic artery in cats with a hepatic venous pressure of 7 mmHg. Each bar represents the mean ± S.E. of at least seven infusions into four cats. * Indicates significance in the t test for paired data ($P<0·01$).

initial changes in blood content occurred and then the steady volume increase was resumed (slope C). The filtration rates before and after the drug (slopes A and C) were very similar and not significantly different. These slopes were compared with slope B during the drug infusion by Student's *t* test for paired data (Steel & Torrie, 1960). After the period shown in Fig. 1, hepatic venous pressure was raised to 8·5 mmHg and then lowered to 5·5 mmHg. The steady state slopes (D and E respectively) are shown in Fig. 1. In the original record, these slopes were markedly different from the slope at 7 mmHg (slopes A and C) and analysis of the paired data from several experiments shows that the slopes are significantly different ($P<0·001$). Thus the method would readily detect a change in filtration due to a change in sinusoidal hydrostatic pressure of 1·5 mmHg (see **Discussion**).

Adrenaline infusions

Adrenaline ((2 μg/min)/kg) was infused on seven occasions in four cats. It was given intravenously in order that its vasodilator action on the intestinal vascular bed would occur, thereby increasing portal flow. The results are shown in Fig. 2. Arterial and portal pressures and hepatic blood flow increased ($P<0·001$) but the steady filtration during the infusion (slope B, Fig. 1) was not significantly different ($P>0·3$) from those before (slope A) and after (slope C) the infusion. It is concluded that adrenaline does not alter the rate of transsinusoidal fluid filtration induced by an elevated hepatic venous pressure.

Isoprenaline infusions

Isoprenaline ((0·2 μg/min)/kg) was infused into the hepatic artery on nine occasions in five cats. This dose caused maximal vasodilatation of the hepatic arterial bed (Greenway & Lawson, 1969). The results are shown in Fig. 2. The increase in total hepatic flow was significant ($P<0·001$) but the steady filtration during the infusion was not significantly different ($P>0·8$) from those before and after the infusion. It is concluded that isoprenaline does not alter the rate of transsinusoidal fluid filtration induced by an elevated hepatic venous pressure.

Histamine infusions

Histamine ((5 μg/min)/kg) was infused into the hepatic artery on eleven occasions in four cats. This dose would produce an increase in capillary filtration coefficient in skeletal muscle (Kjellmer & Odelram, 1965). Total hepatic flow showed a small but significant ($P<0·01$) increase due to hepatic arterial vasodilatation (Greenway & Stark, 1971). The steady filtration during the infusion was not significantly different ($P>0·05$) from those before and after the infusion. It is concluded that histamine does not alter the rate of transsinusoidal fluid filtration induced by an elevated hepatic venous pressure.

Discussion

An increase in hepatic venous pressure causes an increase in hepatic volume which is due partly to an increased hepatic blood volume and partly to transsinusoidal fluid filtration. The latter continues for at least 5 h and the rate is linearly related to the increase in hepatic venous pressure. In these experiments, the increase in

hepatic venous pressure caused a mean filtration rate of (0·047 ml/min)/(mmHg/100 g). This constant incorporates several factors. The critical pressure governing filtration is the mean sinusoidal hydrostatic pressure but it is probable that changes in hepatic venous pressure are transmitted almost quantitatively to the sinusoids (Greenway & Lautt, 1970). However, if only 80% of the rise in venous pressure was transmitted to the sinusoids, this transmission factor would be incorporated in the constant. The constant also incorporates the capillary filtration coefficient—the product of surface area and sinusoidal permeability. A change in any of these factors would change the filtration rate. For example, an increase in sinusoidal pressure from 7 mmHg to 8·5 mmHg would increase the mean filtration from (0·33 to 0·40 ml/min)/100 g (this is the mean increase for all the animals; the animal shown in Fig. 1 showed a greater increase). Such a change would be readily detectable by our plethysmographic technique. An increase in surface area of 20% would also be expected to produce a change in filtration rate from (0·33 to 0·40 ml/min)/100 g. This discussion suggests that our method would readily detect a change in sinusoidal pressure of 1·5 mmHg or a change in sinusoidal surface area of 20%. Even smaller changes than this might be statistically significant. The effects of a permeability change are more difficult to quantitate but in skeletal muscle, permeability changes produce large changes in filtration (Kjellmer & Odelram, 1965).

Thus the data suggest that adrenaline, isoprenaline and histamine do not change sinusoidal pressure by more than 1·5 mmHg, do not change sinusoidal surface area by more than 20% and do not alter sinusoidal permeability. These data support and extend our previous conclusions (Greenway & Stark, 1971):

1. Since an increase in portal flow (adrenaline) and maximal vasodilatation of the hepatic arterial bed (isoprenaline) do not alter sinusoidal hydrostatic pressure, post-sinusoidal resistance must be very low and sinusoidal pressure is probably close to hepatic venous pressure. Contraction of the capacitance vessels (adrenaline) can also occur without a change in sinusoidal pressure.

2. In resting skeletal muscle, about two-thirds of the precapillary sphincters are closed at any one time and exchange ceases in the capillaries controlled by these sphincters. The resting capillary surface area is only about one-third of the maximum possible surface area and it can be increased by isoprenaline and by exercise in the cat (Mellander & Johansson, 1968). In the liver, isoprenaline and histamine do not increase sinusoidal surface area. The sinusoids appear to be open all the time, although the velocity of flow and the proportions of arterial and portal blood flowing in any one sinusoid can vary from moment to moment (Greenway & Stark, 1971). It is possible that presinusoidal sphincters are present but do not respond to isoprenaline or histamine even though arteriolar smooth muscle is relaxed. However, it seems more likely that these sphincters are absent in the liver. No anatomical sphincters have been detected (Elias & Sherrick, 1969), myogenic changes in sinusoidal surface area do not occur (Greenway & Lautt, 1970), and sinusoidal surface area does not change during sympathetic nerve stimulation (Greenway, Stark & Lautt, 1969).

3. The sinusoids are lined by discontinuous endothelium and are permeable to protein (Mayerson *et al.*, 1960). It is perhaps not surprising that histamine does not increase permeability and fluid filtration as it does in skeletal muscle capillaries which are lined by continuous endothelium.

4. The data therefore support the hypothesis that the major factor determining transsinusoidal fluid filtration is hepatic venous pressure. Changes in sinusoidal hydrostatic pressure secondary to alterations in hepatic arterial or portal flow and changes in sinusoidal surface area and permeability do not occur at least under conditions which have been tested to date.

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