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PRESSURE-FLOW RELATIONSHIPS AND EFFECTS OF NORADRENALINE AND ISOPRENALINE ON THE HEPATIC ARTERIAL AND PORTAL VENOUS VASCULAR BEDS OF THE DOG

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SUMMARY

1. The innervated hepatic arterial and portal venous vascular beds of the dog were perfused simultaneously, *in situ*. Under control conditions, the pressures, blood flows and calculated vascular resistances in these beds were similar to those previously reported in preparations where one bed was perfused alone.

2. The pressure-flow curves in both the hepatic arterial and portal venous vascular beds were almost linear over the pressure ranges 30–200 and 2·5–12·0 mmHg respectively. There was no evidence of pressure-induced autoregulation of flow in either circuit.

3. Increases in hepatic arterial blood flow and perfusion pressure were associated with a linearly related increase in hepatic portal vascular resistance. Occlusion of the hepatic artery caused a mean fall of 21·3 % in portal vascular resistance.

4. Increases in hepatic portal blood flow and perfusion pressure were associated with a linearly related increase in hepatic arterial vascular resistance. Occlusion of the hepatic portal vein caused a mean fall of 16·0 % in hepatic arterial vascular resistance.

5. Intra-arterial injections of noradrenaline (0·1–50 μg) caused biphasic changes in hepatic arterial vascular resistance, and a rise in hepatic portal vascular resistance. Both hepatic vascular effects had a significantly shorter latency than any succeeding systemic cardiovascular effects.

6. Intraportal injections of noradrenaline (0·1–50 μg) caused hepatic portal vasoconstriction, and a biphasic change in the hepatic arterial resistance. Both of these effects had a significantly shorter latency than any succeeding systemic effects.

7. Intra-arterial injections of isoprenaline (0·1–10 μg) caused dose-dependent hepatic arterial vasodilatation but little change in portal vascular resistance. Intraportal isoprenaline caused little change in portal resistance but elicited dose-dependent hepatic arterial vasodilatation.

8. The time courses of the responses to intra-arterial and intraportal noradrenaline and isoprenaline indicate that the responses of the liver vascular bed which does not receive the direct injection were not due to recirculation of the vasoactive material.

9. It is postulated that vasoactive material injected into one inflow circuit of the liver elicits changes in the vascular resistance of the other inflow circuit by an intrahepatic effect.

INTRODUCTION

There is structural evidence that direct connexions exist between the hepatic arterial and portal venous vascular bed and, indeed, unidirectional arterio-portal blood flow has been observed (Wakim & Mann, 1942; Bloch, 1955; McCuskey, 1966; Cliff, 1976). It has been suggested, on the basis of studies in which the liver was perfused both normally and retrogradely through the hepatic vein, that there is a low impedance pathway between the hepatic artery and portal vein, which enables the hepatic arterial blood to reach the portal venous system directly (Field & Andrews, 1967; Field, 1970). Further functional evidence for arterio-portal inter-relationships lies in the observations that occlusion of the hepatic artery leads to a reduction in portal vascular resistance and that occlusion of the hepatic portal venous inflow occasions vasodilatation of the hepatic arterial vascular bed (Hanson & Johnson, 1966; Greenway & Stark, 1971). However, the extent of the mutual interactions between the two hepatic inflow circuits has not been quantitatively defined over the range of flows and pressures likely to be encountered under physiological conditions. One aim of the present series of experiments was to examine the physical inter-relationships of the hepatic arterial and portal inflow tracts under controlled conditions where they were separately perfused *in situ* by pumps with autologous blood. The relationship between the portal and arterial flows, pressures and calculated vascular resistances were analysed over a wide range of values.

In addition observations were made to assess the functional significance of these arterio-portal connexions by analysing the responses of the simultaneously perfused hepatic arterial and portal venous vascular beds to both intra-arterial (I.A.) and intraportal injections of graded doses of noradrenaline and isoprenaline.

METHODS

Anaesthesia was induced in eleven dogs (13·2–23·5 kg) which had not been fed for 24 hr, but which had been allowed access to water *ad libitum*, by an I.V. injection of methohexitone sodium (Brietal, Lilly 5–8 mg/kg). Anaesthesia was maintained by an I.V. injection of chloralose (Kuhlmann, 50 mg/kg) and urethane (BDH, 500 mg/kg) followed by supplements in the same proportion to maintain a constant level of anaesthesia.

The hepatic arterial and portal venous vascular beds were perfused simultaneously using a combination of techniques previously described for the separate perfusion of the two inflow circuits (arterial: Richardson & Withrington, 1976; portal: Richardson & Withrington, 1977*b*).

Perfusion of the hepatic artery and portal vein

The cannulated common hepatic artery was perfused from a cannulated femoral artery. Hepatic arterial blood flow was recorded using a cannulating flow probe and electromagnetic flowmeter (Cardiovascular Instruments 3765T) and hepatic arterial perfusion pressure was measured from a T-piece close to the point of cannulation of the hepatic artery using a Consolidated Electrodynamics L-0001 transducer. Other T-pieces were used for I.A. injections of drugs. For the construction of pressure-flow curves, a Watson–Marlow MHRE200 pump was incorporated into this circuit, but when the effects of noradrenaline and isoprenaline were examined, the hepatic arterial bed was perfused at essentially constant arterial pressure. In all experiments the hepatic periarterial sympathetic nerves were retained intact.

The portal vein was cannulated and perfused at constant flow using a Watson–Marlow MHRE200 pump, with blood derived from the superior mesenteric vein *via* the retrogradely cannulated splenic vein. The hepatic portal inflow was monitored with a cannulating flow probe

and electromagnetic flowmeter (Cardiovascular Instruments, CV500). The hepatic portal venous pressure was recorded from a T-piece close to the point of cannulation of the portal vein, using a Statham P23V transducer. To ensure that the portal inflow remained constant despite changes in the outflow from the superior mesenteric vein, the inflow to the pump was also connected *via* the cannulated right external jugular vein to the right atrium. The flow of blood in either direction in this cannula (jugular 'flux') was set to zero at the beginning of each perfusion, and monitored continuously with an electromagnetic flowmeter.

Other measurements

Systemic arterial pressure (B.P.) was measured from a cannulated femoral artery using a Statham P23Gb transducer. Pulsatile pressure was recorded and mean pressure derived as diastolic + $\frac{1}{3}$ pulse-pressure, a derivation in agreement with that obtained by passing the pulsatile signal through an averaging circuit. Heart rate was derived from the B.P. record with a Devices 4520 rate-meter. Inferior vena cava (i.v.c) pressure was recorded from a cannula advanced through a femoral vein so that the catheter tip lay at the level of the hepatic veins, using a Statham P23Bb transducer. The catheter tip position was confirmed post mortem. The superior mesenteric venous flow was recorded using a cannulating flow probe in the cannula leading from the splenic vein to the reservoir from which the portal vein was perfused. This measurement reflects flow changes in an extrahepatic vascular bed resulting from the recirculation of vasoactive material injected into the hepatic artery or the portal vein.

Pressure and flow calibrations were carried out as described previously (Richardson & Withrington, 1976, 1977*b*).

Haematocrit. When both liver perfusions were established, the systemic arterial haematocrit was determined.

Arterial blood pH. Samples of arterial blood were taken within 20 min of induction of anaesthesia for measurement of arterial blood pH at 38 °C using a Radiometer pH meter. In three experiments, arterial blood P_{CO_2} was measured in addition.

Calculations

Hepatic arterial vascular resistance (*h.a.v.r.*) was calculated as (hepatic arterial mean perfusion pressure in mmHg)/(hepatic arterial mean blood flow as ml./min, or ml. min^{-1} 100 g^{-1}) and expressed in mmHg $ml.^{-1}$ min, or mmHg $ml.^{-1}$ min 100 g. The i.v.c pressure, being negligible compared with the arterial pressure was ignored in this calculation.

Hepatic portal vascular resistance (*h.p.v.r.*) was calculated as (hepatic portal venous pressure − i.v.c. pressure in mmHg)/(hepatic portal mean blood flow as ml./min, or ml. min^{-1} 100 g^{-1}) and expressed in the same units as the h.a.v.r. The pressure drop across the portal vascular bed (i.e. hepatic portal venous − i.v.c. pressure) is referred to as the hepatic portal perfusion pressure (h.p.p.p.).

Pressure-flow curves

Pressure-flow curves were constructed by altering the speeds of the hepatic arterial and portal perfusion pumps. When the speed of the portal pump was altered, the hepatic arterial bed was perfused at constant pressure and when the speed of the arterial pump was altered, the portal bed was perfused at constant flow (the same as the mesenteric outflow).

Noradrenaline and isoprenaline

Noradrenaline acid tartrate (Levophed, Winthrop: doses expressed in terms of the base) and isoprenaline sulphate (Macarthays: doses in terms of the salt) were injected intra-arterially (I.A.) and intraportally in graded increasing doses (total injectate volume = 1·5 ml.) for construction of $\log_{10}$ dose–response curves. For control purposes, 1·5 ml. injections of NaCl, 154 m-mole/l. were made. All injections produced small injection artifacts (Fig. 5) and the saline injections were without any further measurable effect.

Time courses. Times to onset and peak responses of the systemic arterial pressure, heart rate, hepatic arterial blood flow, hepatic portal perfusion pressure and the outflow from the superior mesenteric vein were measured for selected doses of the two drugs.

'Transhepatic' effects. Drugs injected I.A. and intraportally produced changes not only in the circuit receiving the direct injection, but also in the other inflow circuit to the liver. For

comparison, the percentage change in vascular resistance (e.g. hepatic arterial) produced by injection into the other inflow circuit (the portal) was divided by the change in vascular resistance produced by direct injection (i.e. in hepatic arterial resistance on I.A. injection).

Statistics

Initial control data are expressed as means ± 1 S.D. and all other values as means ± S.E. means. Unless stated to the contrary, n refers to the number of experiments in which observations were made. The significance of differences between paired data samples was assessed using Student's t test.

RESULTS

Initial control values

Under control conditions in eleven dogs, weighing 17·2 ± 3·2 kg, the systemic arterial mean pressure (B.P.) was 127·0 ± 18·7 mmHg, the heart rate 181·2 ± 9·7 beats/min. and the inferior vena cava pressure (i.v.c.p.) 1·8 ± 1·2 mmHg. The haematocrit was 48 ± 2 % and the arterial blood pH 7·28 ± 0·03, from which value there was no significant change during the course of the experiments ($P > 0·30$). In three experiments in which the arterial blood pH was 7·28 ± 0·04, the arterial blood P_{CO_2} was 37·5 ± 3·27 mmHg. The livers weighed 323·8 ± 62·1 g post mortem, representing 1·89 ± 0·25 % of the body weight of the dogs.

The hepatic arterial mean perfusion pressure (h.a.p.p.) was 115·4 ± 15·8 mmHg and the hepatic arterial blood flow (h.a.b.f.) 136·5 ± 43·6 ml./min or 42·7 ± 14·1 ml.min^{-1} 100 g^{-1}, giving a calculated h.a.v.r. of 0·93 ± 0·35 mmHg ml.$^{-1}$ min or 2·91 ± 0·82 mmHg ml.$^{-1}$ min 100 g. The hepatic portal venous inflow, when set to equal the outflow from the superior mesenteric vein, was 211·0 ± 40·6 ml./min, or expressed in terms of the liver weight, 66·1 ± 9·4 ml. min^{-1} 100 g^{-1}: the jugular 'flux' under these conditions was zero. The hepatic portal venous pressure (h.p.v.p.) was 7·2 ± 0·9 mmHg, the h.p.p.p. (h.p.v.p.–i.v.c.p.) 5·3 ± 1·6 mmHg and the calculated h.p.v.r. 0·026 ± 0·010 mmHg ml.$^{-1}$ min, or 0·085 ± 0·011 mmHg ml.$^{-1}$ min 100 g.

These initial control values are similar to those previously reported from this laboratory for preparations in which the hepatic artery and portal vein were perfused separately in different experiments (arterial: Richardson & Withrington, 1976, 1977*c*, *d*; portal: 1977*b*, *c*).

Pressure-flow and pressure-resistance relationships of the hepatic arterial and hepatic portal vascular beds

1. *Effect of separate occlusion of either the hepatic artery or portal vein*

Occlusion of the hepatic portal inflow resulted in an immediate and sustained increase in the h.a.b.f. which at constant pressure perfusion indicated a fall in h.a.v.r. In ten experiments, occlusion of the hepatic portal venous inflow caused a fall in h.a.v.r. of 21·3 ± 1·4 % from 2·76 ± 0·31 to 2·41 ± 0·28 mmHg ml.$^{-1}$ min 100 g ($P < 0·001$).

In nine experiments, occlusion of the hepatic arterial inflow caused an immediate and sustained fall in hepatic portal venous pressure which at constant inflow and i.v.c.p. reflected a reduction in hepatic portal vascular resistance of 16·0 ± 3·4 % from 0·085 ± 0·018 to 0·075 ± 0·018 mmHg ml.$^{-1}$ min 100 g ($P < 0·001$).

2. *Effects of graded alterations in hepatic portal perfusion pressure and flow*

(*a*) *Hepatic portal pressure, flow and vascular resistance.* Pressure-flow curves of the hepatic portal bed were constructed in each of eleven experiments and the imposed increases in inflow resulted in immediate and sustained increases in portal pressure (Fig. 1). There was an approximately linear relationship between the two variables over the range of portal pressures and flows investigated. The data were averaged for the series by constructing the pressure–flow curves in the individual preparations and then reading the values for h.p.v.f. at points corresponding to 0·5 mmHg steps of the h.p.p.p. from 2·5 to 12 mmHg. Since many settings of the perfusion pumps were used, such a procedure did not involve interpolation of more than one value between each pair of data points. The averaged pressure–flow curve for all experiments is shown in Fig. 2*B*.

The relationship between the h.p.p.p. and the calculated h.p.v.r., was assessed in a similar manner (Fig. 2*C*). In none of these experiments was any sign of autoregulation of hepatic portal blood flow apparent since no tendency for the h.p.v.r. to increase at high portal pressures or decrease at low portal pressures was observed. The portal perfusion pressure scale was divided arbitrarily into three sections and the significance of the changes in h.p.v.r. evaluated. Increasing the h.p.p.p. from 2·5 to 5·0 mmHg led to a significant reduction in h.p.v.r. ($P < 0{\cdot}005$). In contrast, increases in h.p.p.p. from 5·0 to 7·5 and from 7·5 to 10 mmHg were not associated with significant changes in h.p.v.r. ($P > 0{\cdot}50$ and $P > 0{\cdot}10$ respectively).

(*b*) *Hepatic arterial flow and vascular resistance.* Concomitant with the construction of the portal pressure–flow curves the hepatic artery was perfused at constant pressure. Although the alterations in portal flow and inflow pressure did not elicit any changes in hepatic or systemic arterial blood pressure there were immediate and sustained decreases in h.a.b.f. with increasing portal perfusion (Fig. 1).

The h.a.v.r. was calculated at each setting of the portal perfusion pump, and in each experiment there was an approximately linear relationship between the increases in portal perfusion pressure and increasing h.a.v.r. In individual experiments, linear regression line analysis of the relationship between portal perfusion pressure and h.a.v.r. revealed the two variables to be significantly and positively correlated (r values between 0·879 and 0·994; P values less than 0·005). A similar procedure to that described above was adopted to present the averaged results from this series (Fig. 2*A*), and statistical analyses indicate that the changes in h.a.v.r. accompanying elevation of the h.p.p.p. from 2·5 to 5·0, 5·0 to 7·5 and 7·5 to 10·0 mmHg were all significant ($P < 0{\cdot}001$, 0·01 and 0·05 respectively). The mean slope of the line relating h.p.p.p. and h.a.v.r. reveals that for each 1 mmHg rise in h.p.p.p., there is an increase in h.a.v.r. of $0{\cdot}212 \pm 0{\cdot}031$ mmHg ml.$^{-1}$ min 100 g, which is significantly different from zero ($P < 0{\cdot}001$).

3. *Effects of graded alterations in hepatic arterial perfusion pressure and flow*

(*a*) *Hepatic arterial pressure, flow and vascular resistance.* In each of nine experiments, increases in the hepatic arterial blood flow were associated with sustained and immediate increases in hepatic arterial perfusion pressure (Fig. 3), the relationship between the two variables being approximately linear over the range of

pressures investigated (up to 200 mmHg). To present the averaged data, the h.a.b.f. changes corresponding to 10 mmHg step increases in h.a.p.p. were read from the curves of individual experiments (Fig. 4*B*).

In each experiment, the h.a.v.r. decreased with increasing h.a.p.p. at all pressures up to 200 mmHg, such that the pressure–resistance curve was concave to the two axes. There was no sign of autoregulation in the hepatic arterial vascular bed in any of these experiments, the calculated resistance declining at all points up to and including 200 mmHg. An averaged curve was obtained as described before and is shown in Fig. 4*C*.

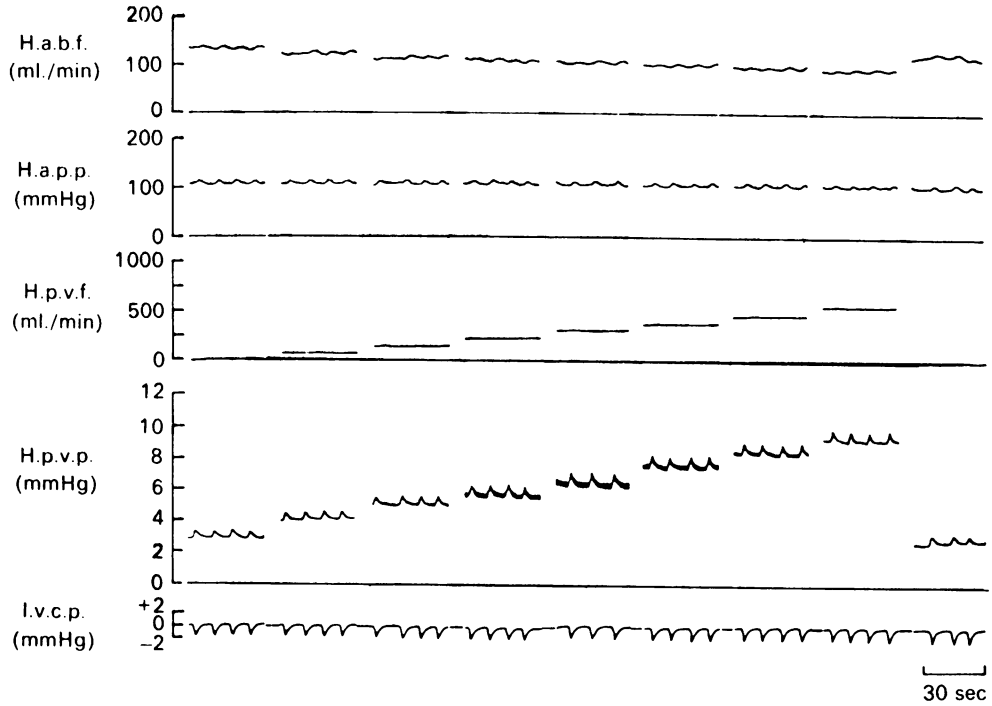

Fig. 1. Effects of variations in hepatic portal venous perfusion on the simultaneously perfused hepatic arterial and portal venous vascular beds of the anaesthetized dog. The variables shown are, from above downwards, hepatic arterial blood flow (h.a.b.f.: ml./min), hepatic arterial perfusion pressure (h.a.p.p.: mmHg), hepatic portal venous inflow (h.p.v.f.: ml./min), hepatic portal venous pressure (h.p.v.p.: mmHg) and the inferior vena cava pressure (i.v.c.p.: mmHg). The time scale is shown by the horizontal bar which respresents 30 sec; the intervals between sections of the experimental records shown were between 20 and 30 sec. Weight of dog = 21·8 kg; liver weight = 401 g.

(*b*) *Portal venous perfusion pressure and resistance.* Whilst the pressure–flow curves were constructed on the hepatic arterial bed, the portal venous vascular bed was perfused at a constant flow equal to the mesenteric outflow. Increases in hepatic arterial perfusion pressure and flow were, in each experiment, associated with immediate and sustained increases in hepatic portal venous pressure (Fig. 3). There was an approximately linear relationship between the increases in h.a.p.p. and in h.p.v.r. (Fig. 4*A*) which linear regression line analysis revealed to be significantly correlated

(r values between 0·939 and 0·990 and P values all < 0·001). The hepatic arterial perfusion pressure scale was divided arbitrarily into three sections, and statistical analysis revealed that increasing h.a.p.p. from 50 to 100, from 100 to 150 and from 150 to 200 mmHg was in each case associated with significant increases in h.p.v.r.

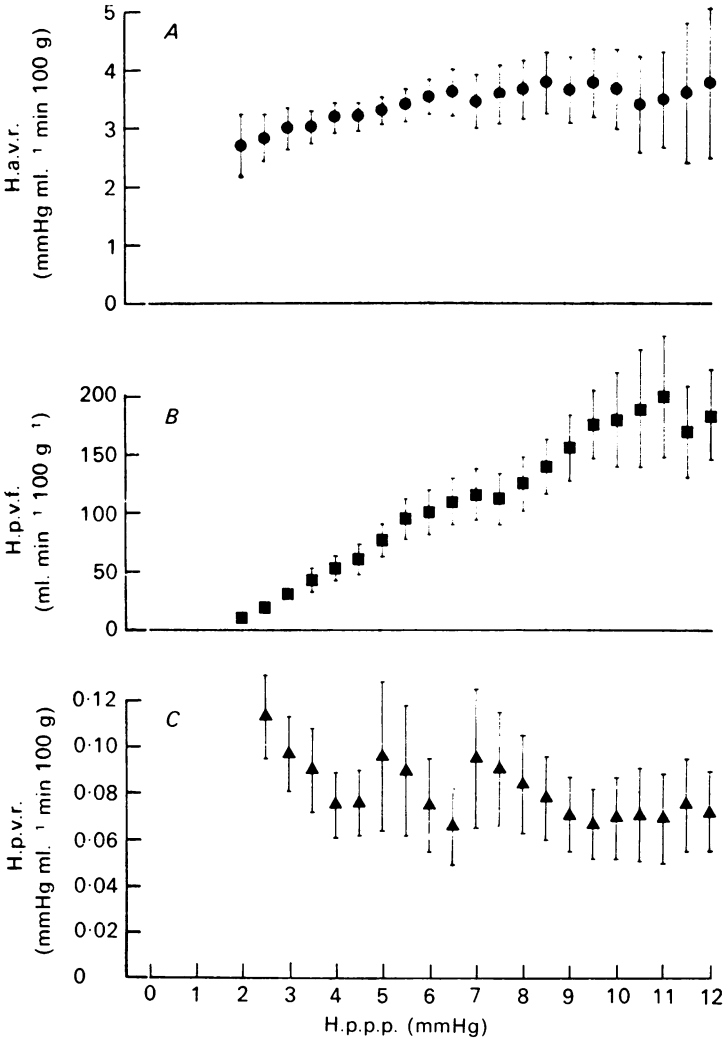

Fig. 2. The effects of increasing the hepatic portal venous inflow on the hepatic portal venous and hepatic arterial vascular bed of the dog. Averaged data from eleven experiments; points shown the means and vertical bars the S.E. means. H.p.p.p. (abscissa) = hepatic portal perfusion pressure gradient (hepatic portal venous pressure − i.v.c.p.). Ordinate scales: *A*, calculated hepatic arterial vascular resistance (h.a.v.r.), *B*, hepatic portal venous flow (h.p.v.f.), *C*, calculated hepatic portal venous resistance (h.p.v.r.).

P < 0·001, 0·005 and 0·01 respectively). The mean slope of the line relating h.a.p.p. and h.p.v.r. in each experiment showed that an increase of 1 mmHg in h.a.p.p. resulted in an increase in h.p.v.r. of 1·18 ($\pm$ 0·19) $\times 10^{-4}$ mmHg ml.$^{-1}$ min 100 g.

Responses of the hepatic arterial and portal venous vascular beds to noradrenaline

1. *Effects of intra-arterial noradrenaline*

(*a*) *Hepatic arterial bed.* Doses of 0·1, 0·5, 1, 5, 10, 20 and 50 μg noradrenaline were injected into the hepatic artery in seven experiments, and in a further two, the five highest doses of this range. Dose-dependent hepatic arterial vasoconstriction was observed to follow the injection of all doses, 100 ng I.A. being above the threshold

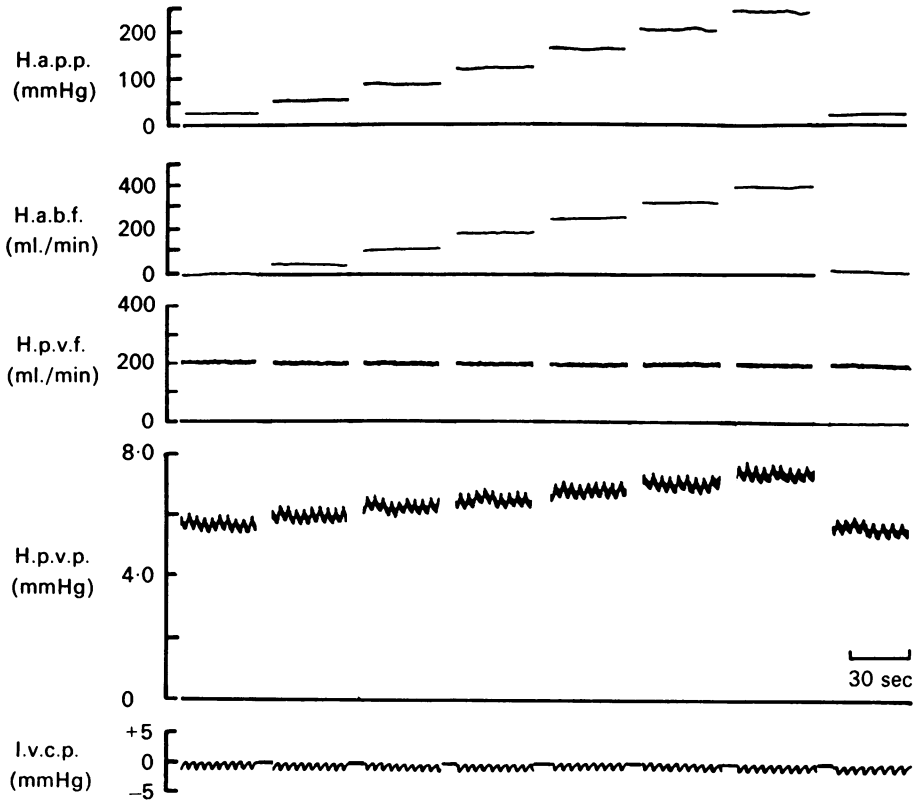

Fig. 3. Effects of variations in hepatic arterial perfusion on the simultaneously perfused hepatic arterial and portal venous vascular beds of the anaesthetized dog. The variables shown are, from above downwards: hepatic arterial perfusion pressure (h.a.p.p.: mmHg), hepatic arterial blood flow (h.a.b.f.: ml./min), hepatic portal venous flow (h.p.v.f.: ml./min), hepatic portal venous pressure (h.p.v.p.: mmHg) and the inferior vena cava pressure (i.v.c.p.: mmHg). The time scale is shown by the horizontal bar which represents 30 sec; the interval between sections of the experimental record were between 20 and 30 sec. Weight of dog = 21·8 kg, liver weight 401 g.

previously reported for this effect. A secondary vasodilatation was observed to follow most injections (Richardson & Withrington, 1977*d*). A response to 10 μg noradrenaline is shown in Fig. 5 and the dose–response curve in Fig. 6.

(*b*) *Hepatic portal venous vascular bed.* In each experiment, I.A. injections of noradrenaline caused dose-dependent and monophasic increases in h.p.v.r. (Fig. 5)

with a threshold of 0·5–5·0 μg I.A. Injection of 50 μg I.A. caused an increase in h.p.v.r. of 68·4 ± 7·9 %; this was not maximal but higher doses were not injected because of the marked systemic effects.

(*c*) *Time courses of the arterial, portal and systemic vascular responses to* I.A. *noradrenaline.* The lower doses (0·1–5 μg I.A.) of noradrenaline caused increases in h.a.v.r. and in most experiments increases in h.p.v.r. (Table 1); there were usually no measurable systemic effects indicative of passage of the catecholamine into the systemic

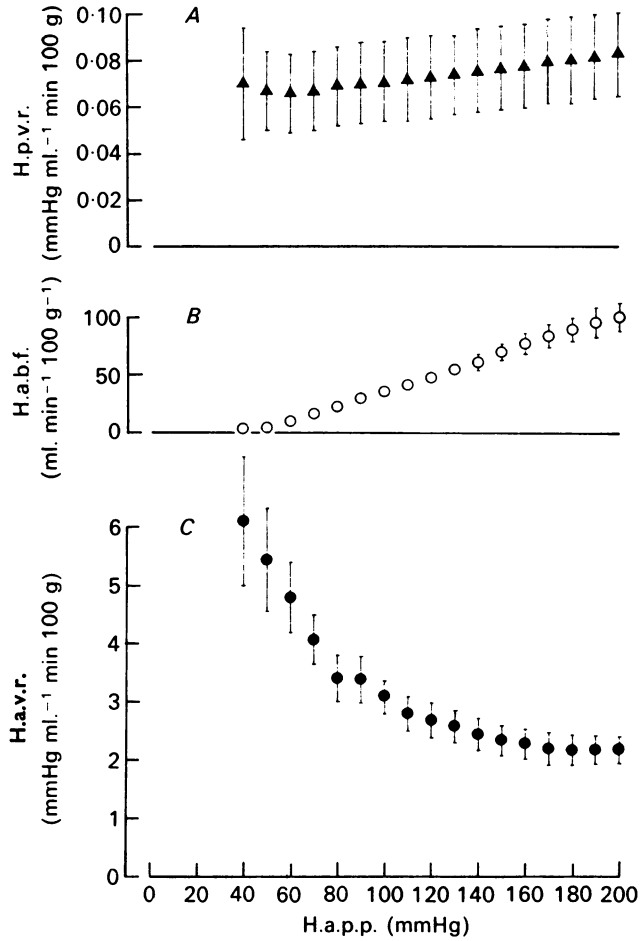

Fig. 4. The effects of increasing the hepatic arterial inflow on the hepatic arterial and portal venous vascular beds of the dog. Averaged data from nine experiments; points show the means and verticals bars the S.E. means. H.a.p.p. (abscissa) = hepatic arterial perfusion pressure. Ordinate scales: *A*, hepatic portal vascular resistance (h.p.v.r.), *B*, hepatic arterial blood flow (h.a.b.f.), *C*, hepatic arterial vascular resistance (h.a.v.r.).

circulation. In contrast, doses of 10 μg I.A. and above elicited changes in B.P., heart rate and mesenteric outflow in addition to the effects on h.a.v.r. and h.p.v.r. The temporal relationships for these responses to 10 μg noradrenaline I.A. were analysed in detail.

The first response seen following I.A. injection of 10 μg noradrenaline was the fall

in h.a.b.f. with an onset of $3{\cdot}1 \pm 0{\cdot}4$ sec (peak at $6{\cdot}7 \pm 0{\cdot}8$ sec) which was quickly followed by the onset of the increase in h.p.v.p. at $5{\cdot}1 \pm 0{\cdot}8$ sec (peak at $17{\cdot}8 \pm 0{\cdot}8$ sec). Both hepatic vascular effects had onsets ($P < 0{\cdot}02$) and peaks ($P < 0{\cdot}01$) occurring significantly before the changes in B.P. at $16{\cdot}3 \pm 3{\cdot}2$ sec (peak = $26{\cdot}0 \pm$

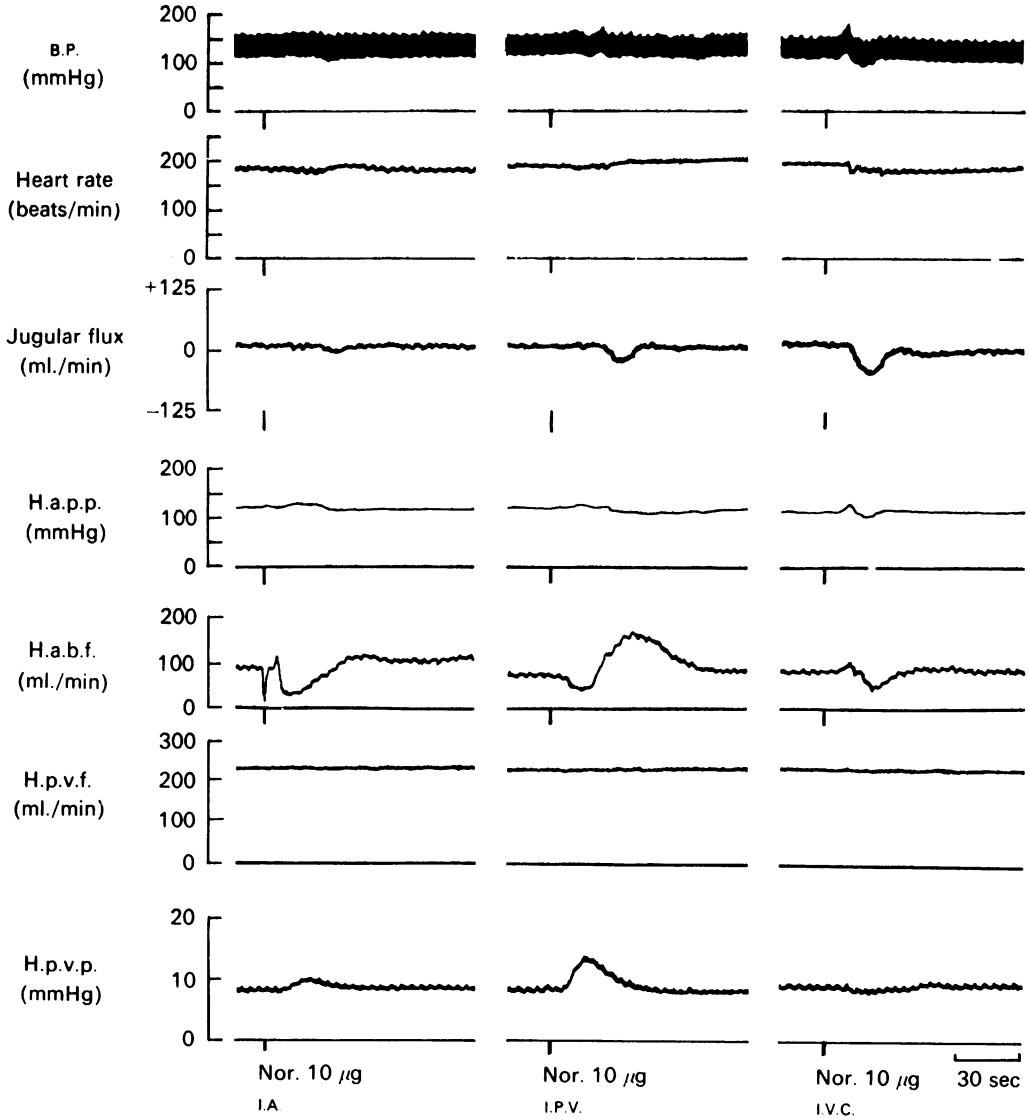

Fig. 5. The effects of noradrenaline (10 μg) administered into the hepatic artery (I.A.), the hepatic portal vein (I.P.V.) and the inferior vena cava at the level of the hepatic veins (I.V.C.) on: the systemic arterial blood pressure (B.P.: mmHg), the heart rate (beats/min), the jugular venous 'flux' (see Methods: ml./min), the hepatic arterial perfusion pressure (h.a.p.p.: mmHg), the hepatic arterial blood flow (h.a.b.f.: ml./min), the hepatic portal venous flow (h.p.v.f.: ml./min) and the hepatic portal venous pressure (h.p.v.p.: mmHg). The inferior vena cava pressure (i.v.c.p.) remained constant throughout. The time scale is shown by the horizontal bar which represents 30 sec, and the points of injection are shown by the small vertical bars.

2·5 sec), heart rate at 25·8 ± 1·6 sec (peak = 37·8 ± 3·1 sec) and superior mesenteric venous flow (s.m.v.f.) at 20·8 ± 1·4 sec (peak = 30·6 ± 1·6 sec). The time course of the mesenteric change is particularly important since, following I.A. injection, any surviving noradrenaline would have to pass through the mesenteric vascular bed to enter the hepatic portal vein.

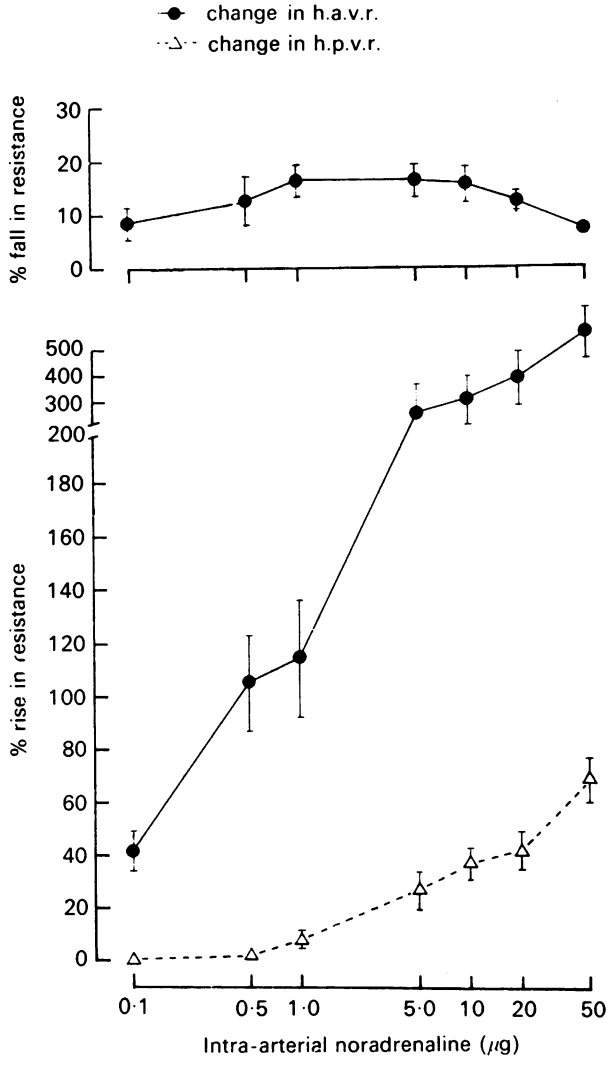

Fig. 6. Effects of I.A. injections of noradrenaline on the calculated hepatic arterial (●) and portal venous (△) vascular resistances. Abscissa scale: dose of noradrenaline injected I.A., in μg. Upper ordinate scale: per cent fall in vascular resistance. Lower ordinate scale: per cent rise in vascular resistance. Points show the means of between seven and nine observations and the vertical bars shown the S.E. means.

2. *Effects of intra-portal noradrenaline*

(*a*) *Hepatic portal venous vascular bed.* The present experiments confirm previous observations that intraportal injections of noradrenaline evoke monophasic and dose-dependent increases in calculated h.p.v.r. (Richardson & Withrington, 1977*b*).

In the present experiments intraportal doses of 0·1 or 0·5 μg and above of noradrenaline caused increases in h.p.v.r. which reached a maximum of 125·2 ± 13·0% at 50 μg. The dose–response curve is shown in Fig. 7. The hepatic portal vasoconstrictor response was always greater for a particular dose of noradrenaline injected intraportally than for the same dose injected I.A. (Figs 5, 6 and 7). In no case did the

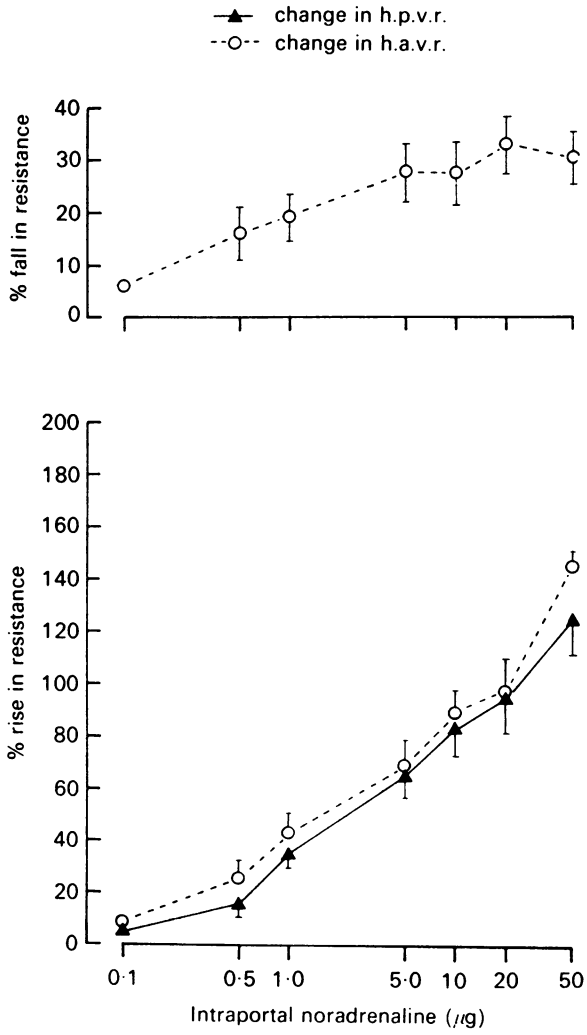

Fig. 7. Effects of intraportal injections of noradrenaline on the calculated hepatic arterial (○) and portal venous (▲) vascular resistances. Abscissa scale: dose of noradrenaline injected intraportally (in μg). Ordinate scales and points as in Fig. 6.

'transhepatic effect' i.e. the portal response to arterial administration exceed 80% of the portal response to direct portal administration of noradrenaline over the dose range 0·1–50 μg in ten experiments (Table 1).

(*b*) *Hepatic arterial vascular bed.* In addition to the changes in h.p.v.r., intraportal injections of noradrenaline provoked biphasic changes in h.a.b.f. and calculated h.a.v.r., which as with the responses to I.A. injection, represented an initial

vasoconstriction succeeded by a vasodilatation; both hepatic arterial responses were dose-dependent (Fig. 7). The threshold for the intra-portal injection of noradrenaline to elicit hepatic arterial vasoconstriction was 0·1 to 0·5 μg whilst the 0·1 μg injection in all experiments evoked hepatic arterial vasodilatation.

TABLE 1. Relative effects of I.A. and intraportal injections of noradrenaline and isoprenaline on hepatic portal venous and hepatic arterial vascular resistance in the anaesthetized dog

Dose of drug (μg)	0·1	0·5	1·0	5·0	10	20	50
A. Noradrenaline							
Increase in h.a.v.r.	24 ± 9 (7)	32 ± 3 (7)	49 ± 9 (9)	49 ± 10 (9)	53 ± 15 (10)	37 ± 9 (9)	33 ± 8 (9)
Decrease in h.a.v.r.	66 ± 21 (5)	162 ± 56 (6)	123 ± 26 (9)	201 ± 48 (9)	206 ± 43 (10)	289 ± 29 (7)	531 ± 194 (7)
Increase in h.p.v.r.	0 ± 0 (4)	12 ± 8 (6)	22 ± 4 (8)	39 ± 6 (8)	45 ± 3 (9)	45 ± 2 (8)	56 ± 3 (8)
B. Isoprenaline							
Decrease in h.a.v.r.	55 ± 20 (4)	99 ± 19 (4)	91 ± 9 (9)	87 ± 4 (8)	92 ± 9 (9)	—	—

All values are expressed as means ± S.E. means; the number of observations from which the data were derived in each case is shown by the numbers in parentheses below the data points. The values are the 'transhepatic' effects for the responses shown, calculated (see Methods) as (in the case of an arterial response) per cent change in h.a.v.r. due to intraportal injection/per cent change in h.a.v.r. due to I.A. injection of the same dose. H.a.v.r. = hepatic arterial vascular resistance; h.p.v.r. = hepatic portal vascular resistance.

Hepatic arterial vasoconstrictor responses were greater when noradrenaline was injected I.A. than when the same dose was injected intraportally (Figs. 5, 6 and 7, Table 1). The vasodilator effects of noradrenaline were often greater if the noradrenaline was injected intraportally than if it was injected I.A.: forty-three out of fifty-one injections, the 'transhepatic' effect of noradrenaline evoking hepatic arterial vasodilatation exceeded 100% (Table 1).

(*c*) *Time courses of the portal, arterial and systemic vascular responses to intraportal noradrenaline.* The lower dose-range of noradrenaline injected intraportally evoked changes in both h.p.v.p. and h.a.b.f. but no measurable systemic effects indicative of passage of noradrenaline through the liver to enter the systemic circulation. However intraportal doses of 10 μg noradrenaline and above evoked systemic cardiovascular responses in addition to the effects on the liver vascular beds, and the time courses of these responses to 10 μg injections were analysed in detail.

On intraportal injection of 10 μg noradrenaline, the onset of the increase in h.p.v.p. occurred after 6·4 ± 0·5 sec (peak after 16·8 ± 0·4 sec) and the latency to the onset of the hepatic arterial vasoconstrictor response at 5·8 ± 0·6 sec (peak at 17·3 ± 1·0 sec) was not significantly different ($P > 0·02$). However, both liver vascular effects significantly preceeded the times to onset ($P < 0·005$) and peak ($P < 0·01$) of the changes in B.P. at 16·8 ± 2·2 sec (peak = 25·6 ± 2·3 sec), heart rate at 23·0 ± 1·9 (peak = 39·8 ± 6·7 sec) and s.m.v.f. at 23·9 ± 0·8 sec (peak = 34·2 ± 1·3 sec). The absence of a significant delay in the arterial response to intraportal noradrenaline (indeed, the arterial response preceded the portal response in six

out of eleven experiments) demonstrates that the hepatic arterial response to intraportal noradrenaline cannot be attributed to recirculation.

3. *Effects of noradrenaline injected into the inferior vena cava*

Noradrenaline was injected (10 μg) into the inferior vena cava (i.v.c.) at the level of the hepatic veins: the temporal relationship of the responses was different from that seen on I.A. or intraportal injection. The first response on the i.v.c. injection of noradrenaline was the increase in B.P. with a latency of $8{\cdot}5 \pm 0{\cdot}8$ sec (peak at $15{\cdot}2 \pm 2{\cdot}2$ sec), and the fall in heart rate at $8{\cdot}2 \pm 1{\cdot}1$ sec (peak = $18{\cdot}6 \pm 3{\cdot}7$ sec). These effects significantly precedeed ($P < 0{\cdot}01$) the changes in hepatic arterial blood flow at $13{\cdot}2 \pm 1{\cdot}3$ sec (peak = $26{\cdot}5 \pm 2{\cdot}8$ sec) and hepatic portal venous pressure at $19{\cdot}6 \pm 7{\cdot}2$ sec (peak = $33{\cdot}2 \pm 11{\cdot}1$ sec). When noradrenaline was injected into the i.v.c., the response of h.p.v.p. was a fall, in contrast to that seen on I.A. or intraportal injection (Fig. 5) and was probably the result of physical interaction between the two liver vascular circuits as described in the first part of the results.

Responses of the hepatic arterial and portal venous vascular beds to isoprenaline

1. *Effects of intra-arterial isoprenaline*

(*a*) *Hepatic arterial vascular bed.* Isoprenaline was injected intra-arterially in doses from 0·1 to 10 μg in four experiments and from 1 to 10 μg in a further five experiments; these injections caused dose-dependent reductions in hepatic arterial vascular resistance as described previously (Richardson & Withrington, 1976, 1977*d*). The dose-response curve for the present experiments is shown in Fig. 8. The fall in the calculated h.a.v.r. at 10 μg I.A. was $49{\cdot}1 \pm 5{\cdot}0$ %.

(*b*) *Hepatic portal venous vascular bed.* The responses of the portal vascular bed to I.A. injections of isoprenaline were weak and very variable: in no instance was an unequivocal reduction in the calculated portal vascular resistance observed. In some experiments, small but not dose-dependent rises in the calculatated h.p.v.r. were obtained, whilst in other experiments no change in h.p.v.r. was elicited on injection of any dose of isoprenaline over the range 0·1–10 μg I.A.; in a total of eighteen out of thirty-four injections there was no change in the h.p.v.r.

2. *Effects of intraportal isoprenaline*

(*a*) *Hepatic portal venous vascular bed.* The portal responses to intraportal injections of isoprenaline were in all experiments small and not dose-dependent; a total of thirty-four injections were made in nine experiments over the dose range 0·1–10 μg, and of these only fifteen elicited any measurable effect. The responses that were elicited represented reductions in h.p.v.r. of between 2 and 11 %.

(*b*) *Hepatic arterial vascular bed.* All injections of isoprenaline (n = 34) over the dose range 0·1–10 μg (four experiments) or 1–10 μg (five experiments) elicited dose-dependent hepatic arterial vasodilatation (Fig. 8). The responses were similar in character to those elicited by I.A. injections of isoprenaline. The reduction in the calculated h.a.v.r. elicited by these injections of 10 μg isoprenaline intraportally was $43{\cdot}5 \pm 3{\cdot}8$ %, though since higher doses were not injected intraportally, it is not established that this is the maximum possible reduction in h.a.v.r. attainable on intraportal injection of isoprenaline.

Although the hepatic arterial vasodilator responses were in all but eight out of thirty-four injections greater when isoprenaline was injected I.A. than when the same doses were injected intraportally (Fig. 8), with the higher doses this difference between the effects of the injections by the two different routes was small. The mean 'transhepatic' effect (effect produced by one dose intraportally/effect produced by the same dose I.A.) for the 0·1 μg dose of isoprenaline was 55 %, but this value rose to almost 100 % for the higher doses (Table 1).

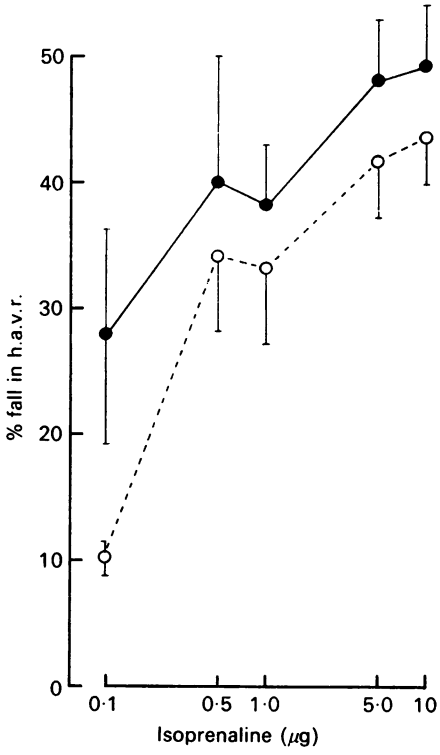

Fig. 8. Effects of isoprenaline injected I.A. (●) and intraportally (○) on the calculated hepatic arterial vascular resistance (h.a.v.r.). Abscissa scale: dose of isoprenaline injected I.A. or intraportally (μg). Ordinate scale: percentage reduction in the calculated hepatic arterial vascular resistance. Points show the means of 4 (0·1, 0·5 μg) or 9 (1, 5, 10 μg) observations, and the vertical bars show the S.E. means.

3. *The effects of isoprenaline injected into the inferior vena cava*

Isoprenaline was injected into the i.v.c. in doses of 1·0 μg (n = 3) and 10 μg (n = 5) producing reductions in the calculated hepatic arterial vascular resistance of 21·8 ± 1·7 % and 34·3 ± 5·5 % respectively, values which were not significantly different (P > 0·05) from the effects produced in the same experiments by the same injections either I.A. or intraportally. However, i.v.c. injections were associated with marked falls in B.P. (131·2 ± 8·3 to 80·4 ± 5·6 mmHg) on injection of 10 μg isoprenaline, in contrast to the same dose injected I.A. (119·4 ± 7·6 to 110·3 ± 7·2 mmHg) or intraportally (112·6 ± 8·2 to 104·8 ± 8·9 mmHg).

4. *Time courses of the hepatic arterial and systemic responses to isoprenaline*

(*a*) *Intra-arterial isoprenaline.* The systemic responses to small doses (1·0 μg I.A.) of isoprenaline were very small: in nine experiments, such injections were without measurable effect on s.m.v.f. or B.P., and in only one experiment was there a small rise in heart rate. In contrast, 10 μg isoprenaline I.A. evoked systemic responses as well as liver vascular effects. The first response was the increase in h.a.b.f. with a latency of 2·9 $\pm$ 0·2 sec (peak at 25·7 $\pm$ 2·4 sec) followed significantly later ($P < 0{\cdot}01$) by any small changes in h.p.v.p. at 7·7 $\pm$ 1·3 sec (peak = 2·4 $\pm$ 2·9 sec); the peaks of these two responses were not significantly different ($P > 0{\cdot}05$). In contrast, the onset and peak of the extrahepatic vascular responses were significantly delayed beyond the responses of the liver vascular beds (all $P < 0{\cdot}005$). The onset of the fall in B.P. was at 25·9 $\pm$ 2·4 sec (peak at 52·3 $\pm$ 5·3 sec), that of the rise in heart rate at 39·2 $\pm$ 2·6 sec (peak at 52·0 $\pm$ 6·6 sec) and that of the rise in s.m.v.f. at 20·4 $\pm$ 2·8 sec (peak = 35·0 $\pm$ 1·7 sec).

(*b*) *Intraportal isoprenaline.* In nine experiments, intraportal injections of 1·0 μg isoprenaline were without measurable systemic effects. Injections of 10 μg caused changes in h.a.b.f. and h.p.v.p. which significantly preceeded any systemic cardiovascular effects ($P < 0{\cdot}005$). The onset of the h.a.b.f. change at 7·4 $\pm$ 0·5 sec (peak = 29·0 $\pm$ 1·9 sec) was not significantly different from that of the change in h.p.v.p. at 7·8 $\pm$ 2·0 sec (peak = 28·2 $\pm$ 5·9 sec). The systemic responses followed with the B.P. changes at 31·4 $\pm$ 5·0 sec (peak at 57·6 $\pm$ 6·2 sec), the heart rate changes at 26·9 $\pm$ 1·9 sec (53·9 $\pm$ 6·0 sec peak) and the s.m.v.f. changes at 28·6 $\pm$ 3·2 sec (peak at 41·8 $\pm$ 2·5 sec).

(*c*) I.V.C. *isoprenaline.* As with noradrenaline, the temporal relationships of the isoprenaline (10 μg) responses after i.v.c. injection were different from those after I.A. or intraportal injection. The first responses to be seen were the falls in B.P. at 9·6 $\pm$ 1·1 sec (peak = 28·8 $\pm$ 1·6 sec) and the rises in heart rate at 7·2 $\pm$ 3·6 sec (peak = 28·8 $\pm$ 4·8 sec), followed by the changes in mesenteric flow at 14·2 $\pm$ 7·3 sec (peak = 34·3 $\pm$ 4·1 sec), and later than all of the systemic effects, by the hepatic arterial response at 16·3 $\pm$ 5·0 sec (peak = 35·8 $\pm$ 5·1 sec) and the portal responses at 18·4 $\pm$ 3·2 sec (peak = 46·8 $\pm$ 7·3 sec).

DISCUSSION

The pressure–flow curves constructed in the hepatic arterial and portal venous vascular beds of the dog revealed no evidence of autoregulation in either inflow circuit to the liver. Previous reports in which autoregulation in the hepatic arterial bed has been examined have produced conflicting evidence, reflecting the different species and types of preparation used; evidence for the existence of hepatic arterial autoregulation has come mainly from sympathetically denervated preparations (Torrance, 1961, Hanson & Johnson, 1966), though even in these preparations, the extent of the autoregulation was small. Previous experiments on the sympathetically-innervated hepatic arterial circuit perfused *in situ* (Shoemaker, 1964) have, as in the present experiments, not revealed hepatic arterial autoregulation. Pressure–flow curves constructed in the portal venous vascular beds have all been approxi-

mately linear, revealing no clear evidence of autoregulation (Condon, Chapman, Nyhus & Harkins, 1962; Hanson & Johnson, 1962; Greenway & Stark, 1971).

Hydrodynamic interactions between the hepatic artery and the portal vein have been established previously (Burton-Opitz, 1911; Greenway & Stark, 1971; Rappaport & Schneiderman, 1976); in general, a fall in inflow volume and inflow pressure in one circuit leads to a reduction in the inflow resistance of the other circuit (Hanson & Johnson, 1966; Price, McFate & Shaw, 1964), though it is apparent from these and other investigations that such falls in the vascular resistance would not result in an increase in inflow in that circuit adequate to compensate for the compromised circuit (Green, Hall, Sexton & Deal, 1959; Brauer, 1964). These observations have been confirmed, and extended to a quantitative examination of the relationships between inflow pressures and volumes in one circuit and the calculated vascular resistance of the other circuit; it is apparent that although such interactions occur and are clearly graded they are quantitatively small, and it is improbable that these small changes in inflow vascular resistance would bring about physiologically significant alterations in total liver blood flow.

The physiological significance of these hydrodynamic interactions is further limited since changes in portal vascular resistance consequent upon alterations in hepatic arterial perfusion would not necessarily bring about changes in portal inflow, as the blood flow in the portal vein is primarily determined by the resistance in the intestinal and splenic circulations. Indeed, in generalized sympathetic activation, the reduction in portal venous flow resulting from mesenteric and splenic vasoconstriction may induce reductions in hepatic arterial vascular resistance which would functionally antagonize the fall in hepatic arterial blood flow expected to result from increased sympathetic discharge (Carneiro & Donald, 1977; Richardson & Withrington, 1977*e*). Further, in digestion, the large increases in portal venous blood flow (Fronek & Stahlgren, 1968) would be predicted by the hydrodynamic interaction to result in hepatic arterial vasoconstriction; this would however be overwhelmed by the effects of the gastrointestinal hormones released during digestion (Fara, Rubenstein & Sonnenschein, 1972) which generally cause hepatic arterial vasodilatation (Richardson & Withrington, 1977*a*).

The mechanism of the hydrodynamic interactions between the two circuits is as yet not fully explained. Since it occurs in both innervated (this paper) and denervated (Hanson & Johnson, 1966; P. D. I. Richardson & P. G. Withrington, unpublished observations) preparations, it is not dependent on extrinsic innervation, though the involvement of a local reflex remains a possibility. Arterioportal vascular connexions exist (Cliff, 1971; Rappaport & Schneiderman, 1976) and unidirectional arterioportal flow has been observed (Field & Andrews, 1967; Field, 1970; Rappaport & Schneiderman, 1976): this may offer an explanation for the change in portal vascular resistance occasioned by altering the hepatic arterial inflow pressure and volume which would alter the transmission of arterial pressure and flow to the portal bed. An alternative explanation involves the common outlet channel from the two inflow circuits; alterations in the pressure-flow gradients between the hepatic sinusoids and the hepatic veins might cause changes in the calculated vascular resistance of the other circuit.

A further possible explanation of the hydrodynamic interactions lies in the

observation of Rappaport (1972) that the inlet sphincters to the hepatic sinusoids exhibit cyclic intermittent opening and closing patterns. It is possible that alterations in the inflow volume or inflow pressure in one circuit may affect these cyclic movements which govern the inlet sphincter resistance in the other circuit so that they remain longer in either the open or closed phase. Since the measurements in the present experiments represent an integrated assessment of the state of the microvascular units in the liver, such changes would be expected to be reflected in alterations in the calculated vascular resistances of the respective inflow circuits.

The extent of the hydrodynamic interactions between the hepatic arterial and portal venous vascular beds was small, confirming the view that such hydrodynamic interactions are inadequate to compensate for compromised blood flow in one inflow circuit to the liver. In these experiments, although the systemic arterial pressure and the control vascular resistances of both the hepatic arterial and portal venous circuits fell within normal limits, there was a high heart rate perhaps suggesting a high degree of ongoing sympathetic nerve activity; the animals were also slightly acidotic. However, previous experiments have shown that the hepatic arterial vascular bed is relatively insensitive to sympathetic nerve stimulation (Richardson & Withrington, 1977*e*) and to alterations in arterial pH and P_{CO_2} (Scholtholt & Shiraishi, 1970). These effects may, nevertheless, have influenced the degree of the hydrodynamic interactions observed.

In contrast to the extent of the hydrodynamic interaction between the hepatic arterial and portal venous vascular beds, the effects of injections of noradrenaline and isoprenaline on the resistance of the vascular bed not receiving the direct injection were large, and qualitatively different from that predicted on hydrodynamic grounds.

That the 'transhepatic' effects of the drugs was not a consequence of the hydrodynamic relationship between the two circuits is apparent from the fact that I.A. noradrenaline caused an increase in portal vascular resistance but a reduction in hepatic arterial blood flow; further, intraportal injections of isoprenaline caused virtually no change in inflow pressure (and no change in inflow volume) of the portal bed, but elicited pronounced and dose-dependent hepatic arterial vasodilatation. It is also apparent that the 'transhepatic' effects of the drugs cannot be ascribed to recirculation of the vasoactive material since the time courses of the responses of the hepatic arterial and portal venous beds on both I.A. and intraportal injections significantly preceeded any systemic cardiovascular effects; furthermore, the pattern of responses elicited on injecting test doses of noradrenaline and isoprenaline into the i.v.c. at the level of the hepatic veins was different from that obtained on I.A. or intraportal injection.

The 'transhepatic' effect of alterations in portal vascular resistance following I.A. injection could be explained by the arterioportal pressure gradient conducting vasoactive material from the hepatic artery to the portal venous resistance sites via arterioportal vascular connexions. However, a converse explanation cannot be offered for conduction of material from the low-pressure portal system to the hepatic arterial resistance sites. One possible explanation for the 'transhepatic' effects is a common action on the outlet sphincter resistance sites which exist in the dog (Greenway & Stark, 1971): although outlet sphincter constriction is established to

contribute to the effects of histamine (Greenway & Oshiro, 1973), the primary resistance to blood flow through the hepatic arterial and portal venous systems is generally accepted as residing in the sphincter sections at the inlets to the hepatic sinusoids. Even though histamine constricts the sphincters at the outlet from the hepatic sinusoids (Greenway & Oshiro, 1973), I.A. and intraportal injections of histamine in the dog elicit dose-dependent hepatic arterial vasodilatation (Richardson & Withrington, 1976*b* and unpublished observations).

One explanation for the 'transhepatic' effects of drugs is that introduction into either inflow circuit affects the cyclic opening–closing sequences of the sphincteric sections guarding the entrances to the hepatic sinusoids (Rappaport & Schneiderman, 1976). Drug-induced changes in the time course of such a cycle would affect the calculated hepatic arterial and portal venous vascular resistances, either by a direct effect on pharmacological receptors, or by an intermediate metabolic effect.

Functionally, the implications of these results are important in that substances such as the established hormones released from the gastrointestinal tract, pancreas and spleen into the portal vein may influence hepatic arterial vascular resistance even though they do not attain vasoactive systemic levels. Furthermore, a wide range of substances present in portal venous blood under a variety of physiological and pathological circumstances but which are destroyed in passage either through the liver or in the cardiopulmonary circuit may also affect hepatic arterial blood flow without attaining vasoactive systemic concentrations. These possibilities have been discussed previously with respect to histamine and bradykinin (Richardson & Withrington, 1976, 1977*c*). Similar considerations apply to orally-administered drugs absorbed from the gastrointestinal tract which may affect hepatic arterial perfusion without reaching systemic blood concentrations considered adequate for cardiovascular effects.

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