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## BLOOD MOBILIZATION FROM THE LIVER OF THE ANAESTHETIZED DOG

B. J. NOBLE, M. J. DRINKHILL, D. S. MYERS AND R. HAINSWORTH\*

*Institute for Cardiovascular Research, University of Leeds, Leeds LS2 9JT, UK*

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### SUMMARY

The abdominal circulation contains a high proportion of the total blood volume and this can change either passively in response to changes in vascular distending pressure or actively (termed a capacitance response) to changes in sympathetic nervous activity. The liver is the largest abdominal organ and this study was designed to evaluate its potential contribution to overall vascular capacitance and compliance. In chloralose anaesthetized dogs, the liver was vascularly isolated, perfused through the portal vein and hepatic artery at either constant pressures or constant flows and drained from the hepatic veins at constant pressure. Changes in vascular resistance were assessed from changes in inflow pressures or flows and hepatic blood volume was determined by differences between net inflow and outflow. During constant flow perfusion the change in hepatic volume (capacitance change) in response to supramaximal stimulation of sympathetic nerves at 16 Hz was (mean  $\pm$  S.E.M.)  $-2.40 \pm 0.61$  ml (kg body weight)<sup>-1</sup>. This response was not significantly different during constant pressure perfusion. The changes in portal venous and hepatic arterial pressures during stimulation at constant flow perfusion were  $+0.67 \pm 0.13$  and  $+4.92 \pm 0.67$  kPa, respectively. The compliance of the liver, assessed as the change in volume to a change in hepatic venous pressure, was  $+5.44 \pm 0.18$  ml kg<sup>-1</sup> kPa<sup>-1</sup>. These results indicate that the liver has a major capacitance role, comparable to that of the canine spleen and, in addition, is highly compliant. No evidence was found to suggest that a sphincter on the hepatic outflow exists. Assuming similar responses occur in humans, who do not possess a large contractile spleen, the liver would be the most important controllable blood reservoir in the body.

### INTRODUCTION

Changes in the volume of blood in a region of the body may be effected in two main ways. One is by constriction of capacitance blood vessels which is referred to as active or a capacitance response. The other is a passive effect due to changes in vascular transmural pressures. Transmural pressures may change when blood flow changes, due for example to changes in constriction of resistance vessels, and the magnitude of the volume change is dependent on the compliance of the blood vessels, mainly veins. Experiments using dogs have indicated that the abdominal circulation makes the largest contribution to the overall capacitance and compliance function (Hainsworth, 1986). However, results obtained cannot be extrapolated quantitatively to humans because in the dog a major contribution to capacitance is from the spleen which, in that species and unlike humans, is very large and contractile. Indeed, in the dog, changes in splenic blood volume can account for up to half the total volume response to sympathetic stimulation (Karim & Hainsworth, 1976; Carneiro & Donald, 1977; Noble, Drinkhill, Myers & Hainsworth, 1997). The liver is the other large organ in the abdomen and previous work has indicated that its vascular volume can change in response to various interventions, including efferent sympathetic nerve stimulation and haemorrhage (Greenway, Stark & Lauth, 1969; Carneiro & Donald, 1977; Greenway, Innes & Scott, 1994). These earlier

\* Corresponding author

studies have indicated that the liver is likely to have a role in the control of the distribution of blood volume. However, they do not adequately distinguish the extent to which changes in hepatic volume are the result of active changes in capacitance as compared with passive effects resulting from changes in portal venous or hepatic arterial blood flow.

It has been speculated that an additional mechanism for regulation of the volume of blood in the liver could be a change in hepatic vein resistance to the outflow of blood. It has been suggested that there may be a sphincter mechanism regulating hepatic venous outflow (Knisely, Harding & Debacker, 1957; Greenway & Oshiro, 1973). However, the only physiological evidence in support of this has been indirect and has shown hepatic outflow to be influenced by various humoral stimuli (Imai, Satoh & Taira, 1978; Rutlen, Supple & Powell, 1981; Rothe, Flanagan & Maass-Moreno, 1990). No information was provided on where any potential site of obstruction to flow may have been.

The present study was undertaken to determine quantitatively the role of the liver in terms both of its capacitance and of its contribution to vascular compliance. We also wished to determine whether there was any evidence of a physiological sphincter mechanism on the hepatic veins controlled by sympathetic nerves, which could regulate the rate of outflow of blood from the liver.

#### METHODS

Beagle dogs weighing 14–20 kg were anaesthetized with  $\alpha$ -chloralose (100 mg kg<sup>-1</sup>; Vickers Laboratories, Leeds, UK), dissolved in normal saline (0.9% NaCl) and infused through a catheter inserted under local anaesthesia through a saphenous vein into the inferior vena cava. A stable level of surgical anaesthesia was subsequently maintained by a continuous infusion of chloralose (0.5–1.0 mg kg<sup>-1</sup> min<sup>-1</sup>). The neck was opened in the mid-line, the trachea cannulated, and the animal ventilated with oxygen enriched air (inspired O<sub>2</sub> fraction ( $F_{I,O_2}$ ), 0.4) using a Starling 'Ideal' pump. The chest was opened in the left side and the aorta was mobilized by tying and dividing the lowest four pairs of intercostal arteries. The inferior vena cava was also dissected free. The splanchnic nerves immediately above the diaphragm were identified and loose threads placed around them. The abdomen was opened through an upper mid-line incision to allow access to the liver. The hepatic artery and the portal vein were identified and mobilized close to their points of entry to the liver. A loose thread was placed round the inferior vena cava immediately below the liver. The animal was then given heparin (500 i.u. kg<sup>-1</sup> i.v.) and the perfusion circuit (see Fig. 1) was connected to the animal.

The circuit was primed with a mixture of dextran (MW, 90000) in 5% dextrose solution and mammalian Ringer solution with washed blood cells obtained from a dog from a previous experiment. The arrangement of the circuit is illustrated in Fig. 1. A cannula inserted centrally in the aorta conveyed blood to the arterial reservoir from which some was pumped (model 604U, Watson-Marlow Ltd, Falmouth, UK) at constant flow into the abdominal aorta. Another pump (505U, Watson-Marlow) perfused the hepatic artery. Constant pressure perfusion was achieved by pumping blood into a pressurized reservoir leading to the hepatic artery. Bypassing the reservoir allowed constant flow perfusion. The splanchnic circulation drained from a cannula inserted into the peripheral end of the portal vein into the venous reservoir. Blood from the venous reservoir was used to perfuse the hepatic end of the portal vein at either constant pressure or constant flow in a manner similar to that used for the hepatic artery. The hepatic venous blood drained into the venous reservoir from a cannula inserted into the inferior vena cava immediately above the diaphragm with the non-splanchnic blood excluded by tying the ligature on the inferior vena cava below the liver. The non-splanchnic blood drained through cannulae in the central ends of the femoral veins into the venous reservoir. The level of blood in the venous reservoir was controlled by a float switch which regulated a pump (604U) returning blood to the external jugular veins. Blood pressures were recorded using P231d transducers (Gould-Statham Medical Instruments, OH, USA) connected to catheters in the central end of the descending aorta, the hepatic artery, the abdominal aorta (via a femoral artery), the hepatic end of the portal vein, and the inferior vena cava at the point of entry of the hepatic veins. In some animals a catheter was passed in a retrograde manner into a small tributary of the hepatic

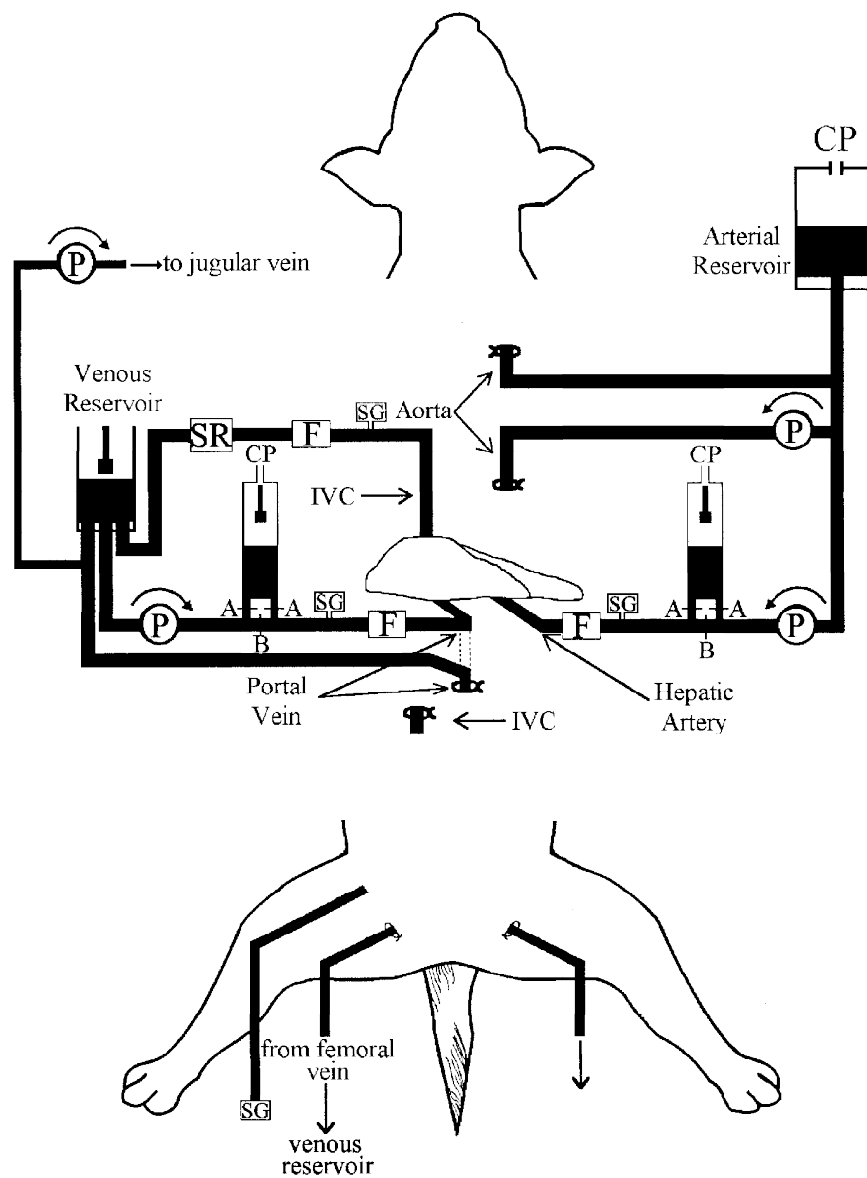


Fig. 1. Diagram of experimental preparation. Blood from the thoracic aorta passes to a pressurized arterial reservoir from which it is pumped at constant flow into the descending aorta immediately above the diaphragm, and either at constant flow or constant pressure into the hepatic artery. For constant pressure perfusion, blood is pumped into a small pressurized reservoir at a rate automatically controlled to maintain a constant level of blood (clips at A removed). For constant flow perfusion the reservoir is bypassed (clip at B removed). Cannulae in the splanchnic end of the portal vein, the inferior vena cava above the diaphragm and the central ends of the femoral veins drain blood by gravity to a dependent venous reservoir from which some is pumped into the hepatic end of the portal vein at either constant pressure or constant flow (system as for hepatic artery). The remainder of the venous blood is returned to the external jugular veins at a rate automatically controlled to keep the blood level in the reservoir constant. Abbreviations: CP, constant pressure; F, flow transducer; IVC, inferior vena cava; P, pump; SG, blood pressure strain gauge; SR, Starling resistor.

vein. Blood flows were recorded using electromagnetic flowmeters (Narco Bio-systems, Houston, TX, USA) on the portal inflow and the inferior vena caval outflow. Hepatic arterial flow was assessed using a tachometer on the perfusion pump. All flow recorders were calibrated using blood at the ends of the experiments. Zero readings were taken at intervals during the experiments. Arterial blood gases and pH were measured frequently throughout the experiment using a blood gas analyser (model 1610, Instrumentation Laboratory, Lexington, MA, USA). Arterial O<sub>2</sub> pressure ( $P_{a,O_2}$ ) was maintained above 15 kPa, arterial CO<sub>2</sub> pressure ( $P_{a,CO_2}$ ) between 5–6 kPa, and pH between 7.35–7.45, by adjustments of  $F_{I,O_2}$ , respiratory pump stroke, and infusion of molar bicarbonate as required. The temperature of the animal was recorded by a thermistor probe (Yellow Springs Instruments) in the oesophagus. This was maintained at 37–39 °C by heat exchangers in the circuit and by heaters under the table. Pressures and flows were recorded on a direct-writing electrostatic recorder (model ES 1000, Gould Electronics, Ballainvilliers, France) and also on magnetic tape (Racal V-Store, Racal Recorders, Southampton, UK). Data were analysed using a real-time data acquisition unit (Fastdaq, Lectromed, Letchworth, UK).

#### *Experimental procedure*

After connection of the perfusion circuit, blood pressures and flows were allowed to stabilize and blood gases and pH were corrected where necessary. The sympathetic nerves were crushed above the level of the diaphragm and a pair of silver bipolar stimulating electrodes placed just distal to the crushed area to allow supramaximal stimulation (12 V, 2 ms) at frequencies of 4 and 16 Hz. These frequencies were chosen to give near-maximal responses of vascular capacitance and resistance, respectively (Karim & Hainsworth, 1976). The pumps perfusing the descending aorta and the hepatic artery were set to bring arterial perfusion pressures near to arterial pressure before cannulation. Portal venous perfusion pressure was set to about 2 kPa. Responses were first determined to sympathetic stimulation during constant flow perfusion of the liver. Then the hepatic artery and portal vein were perfused at constant pressures and the splanchnic nerves were again stimulated. Finally the test at constant flow perfusion was repeated.

In some dogs, the effects were studied of increasing hepatic venous pressure by applying a pressure to a Starling resistance on the hepatic outflow (Fig. 1). This was carried out during constant flow perfusion. In these experiments we also determined the difference in pressure between a hepatic venous tributary and the inferior vena cava to assess whether sympathetic stimulation influenced hepatic venous constriction.

#### *Calculation of volume changes*

During constant flow perfusion volume changes were calculated by integration of the change in outflow from the start of stimulation to the point at which flow, having transiently changed, had returned to baseline. During constant pressure perfusion, volume changes were calculated from the differences between both inflows and hepatic venous outflow. Initially, a control period was taken before stimulation and any small difference between the net inflow and outflow was assumed to represent an unchanged volume. The change in this subtracted signal was then integrated from the start of stimulation until a new steady level had been achieved. Volume changes occurring in response to changes in pressure in the inferior vena cava were assessed after release of the pressure from the Starling resistor by integration of the area beneath the resulting outflow curve. All values are reported as means  $\pm$  S.E.M., using the means of all tests in each dog. Significance levels were assessed using Student's *t* test for paired data.

## RESULTS

#### *Constant flow perfusion*

Experiments were carried out in eleven dogs. In the absence of sympathetic stimulation, hepatic artery and portal inflows were  $73 \pm 2.9$  and  $241 \pm 16.4$  ml min<sup>-1</sup>, respectively, and hepatic venous outflow was  $325 \pm 8.5$  ml min<sup>-1</sup>. Baseline pressures were: hepatic arterial,  $17.8 \pm 0.76$  kPa; portal venous,  $0.87 \pm 0.11$  kPa; and inferior vena caval pressure at the base of the liver,  $0.22 \pm 0.13$  kPa. Stimulation of both splanchnic sympathetic nerves resulted in increases in portal venous and hepatic arterial perfusion pressures with minimal changes in inferior vena caval pressure. Following the onset of stimulation hepatic venous outflow immediately increased, then gradually decreased close to its original level in about 1 min. After stopping the stimulus, the perfusion pressures returned to baseline and the hepatic

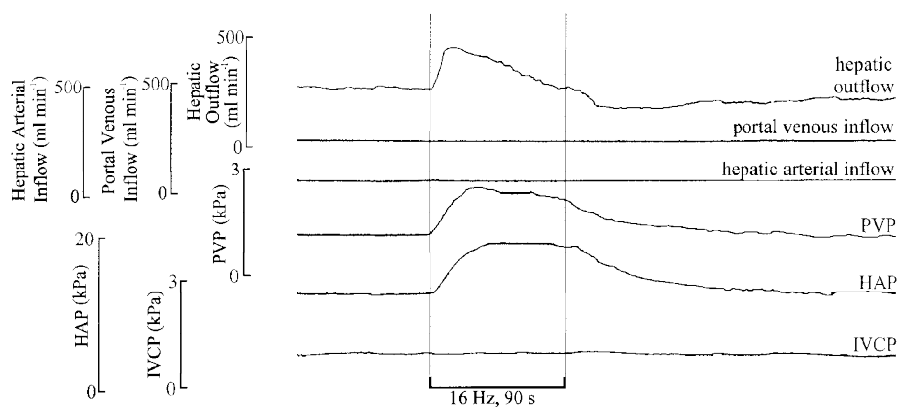


Fig. 2. Responses in one dog to supramaximal stimulation of both splanchnic nerves at a frequency of 16 Hz for 90 s during constant flow perfusion to hepatic artery and portal vein. Abbreviations: PVP, portal venous pressure; HAP, hepatic arterial perfusion pressure; IVCP, inferior vena caval pressure. Traces show increases in hepatic venous outflow and in both perfusion pressures during stimulation. The change in volume was calculated from the change in venous outflow and in this test amounted to 73.5 ml.

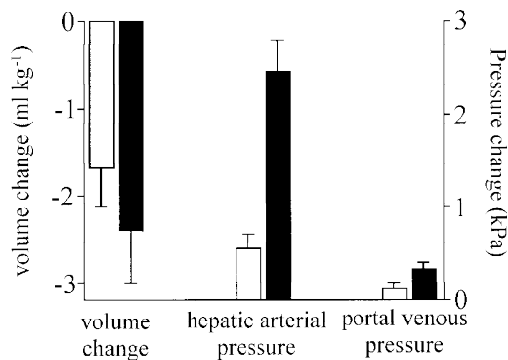


Fig. 3. Results (means and S.E.M.) from eleven dogs of responses of hepatic volume and perfusion pressure to splanchnic stimulation at 4 Hz (open columns) and 16 Hz during constant flow perfusion. Note relatively small additional volume changes at the higher frequency compared to the large further changes in perfusion pressures.

outflow decreased below the baseline and then gradually increased again to baseline. Figure 2 shows original traces from one animal of the responses to stimulation at 16 Hz. Overall in the eleven dogs, stimulation at 4 and 16 Hz resulted in decreases in hepatic volume of  $1.68 \pm 0.45$  and  $2.40 \pm 0.61$  ml (kg body weight)<sup>-1</sup>, respectively. The responses of hepatic volume and of the two perfusion pressures are compared in Fig. 3 and this shows that stimulation at 16 Hz compared with 4 Hz results in a relatively small further change in hepatic volume but much larger responses of both perfusion pressures.

#### *Constant pressure perfusion*

Studies of responses at constant pressure perfusion were carried out in the same dogs as those studied at constant flow. In the absence of stimulation, hepatic and portal inflows were  $51 \pm 2.6$  and  $290 \pm 14.4$  ml min<sup>-1</sup>, respectively, and hepatic arterial, portal venous and inferior

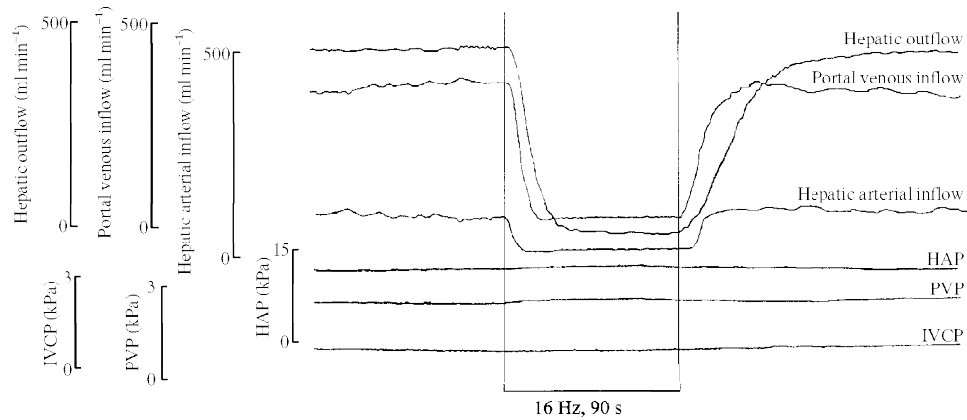


Fig. 4. Responses from same dog as in Fig. 2 to sympathetic stimulation at 16 Hz during constant pressure perfusion of hepatic artery and portal vein. Stimulation decreased both inflows and the outflow. The outflow change occurred more slowly and integration of the difference in flow changes indicates a reduction in liver volume of 81 ml.

vena caval pressures were  $18 \pm 0.94$ ,  $2.3 \pm 0.12$  and  $1.2 \pm 0.79$  kPa, respectively. Sympathetic stimulation caused decreases in both inflows and hepatic venous outflow. The outflow changes lagged behind those of inflows, denoting a reduction in liver volume. These changes reversed on stopping stimulation. An example showing the responses to stimulation at 16 Hz is shown in Fig. 4. The responses to stimulation at 4 and 16 Hz during constant pressure perfusion are shown in Fig. 5. The changes in volume to stimulation at these frequencies,  $1.81 \pm 0.40$  and  $2.13 \pm 0.89$  ml kg<sup>-1</sup>, respectively, were not significantly different from the corresponding responses during constant flow perfusions.

#### *Responses to changes in hepatic venous pressure*

In four dogs, in which a catheter had been passed into a small hepatic venous tributary and the portal vein and hepatic artery were perfused at constant flows, hepatic venous pressure was increased in steps by applying various pressures to the Starling resistance on the venous outflow cannula. Each step increase in venous pressure resulted in similar increases in both perfusion pressures and a transient reduction in outflow. All changes promptly reversed on release of the obstruction. An example showing the response to a step increase and decrease in inferior vena caval pressure is shown Fig. 6.

The results from the four dogs show an approximately linear increase in hepatic volume with changes in venous pressure up to about 2.5 kPa (Fig. 7). The average compliance of the liver was unaffected by sympathetic stimulation. Over a range of hepatic venous pressures between 0.5 and 2.5 kPa, compliance was  $5.44 \pm 0.18$  ml kg<sup>-1</sup> kPa<sup>-1</sup>.

#### *Hepatic outflow resistance?*

In six dogs during constant flow perfusions we determined the pressure difference between the pressure recorded from a catheter with its tip in a lobar tributary of the hepatic vein and one at the same hydrostatic level in the inferior vena cava. This pressure difference was very small and unaffected by sympathetic stimulation. Values without and during stimulation at 16 Hz were  $0.02 \pm 0.04$  and  $-0.03 \pm 0.14$  kPa, respectively. Stimulation, however, increased the gradient between the portal vein and hepatic vein from  $0.17 \pm 0.04$  to  $1.23 \pm 0.35$  kPa ( $P < 0.005$ ).

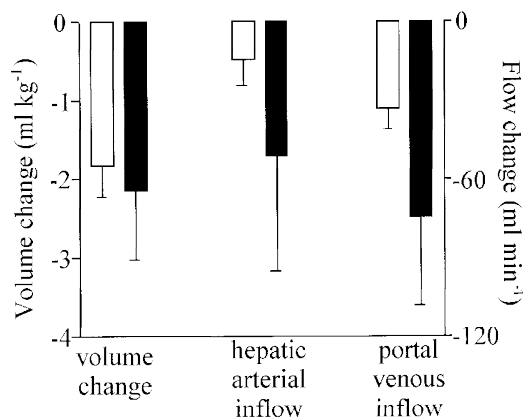


Fig. 5. Results (means and S.E.M.) from eleven dogs of responses to stimulation at 4 Hz (open columns) and 16 Hz during constant pressure perfusion. The higher stimulus frequency caused a relatively smaller change in volume but a larger response of vascular resistance (flow change).

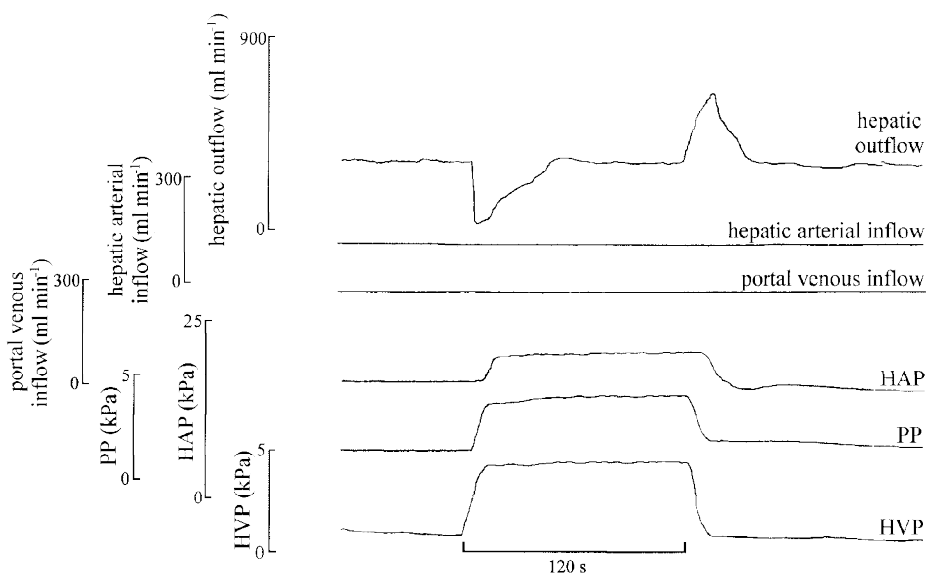


Fig. 6. Effects of change in hepatic venous pressure from 0.5 to 3.5 kPa by application of pressure to a Starling resistor on the venous outflow. This resulted in similar changes in both perfusion pressures and cessation of venous outflow until venous pressure had increased to be equal to that of the Starling resistance. Release of pressure on Starling resistor caused a rapid increase in outflow.

DISCUSSION

There is now abundant evidence that the majority, if not the whole, of the active capacitance response of the body is from vessels within the abdominal circulation (Hainsworth, 1986). Vessels in musculocutaneous regions do not appear to make any significant contribution (Lesh & Rothe, 1969; Hainsworth, Karim, McGregor & Wood, 1983). Furthermore, not only does



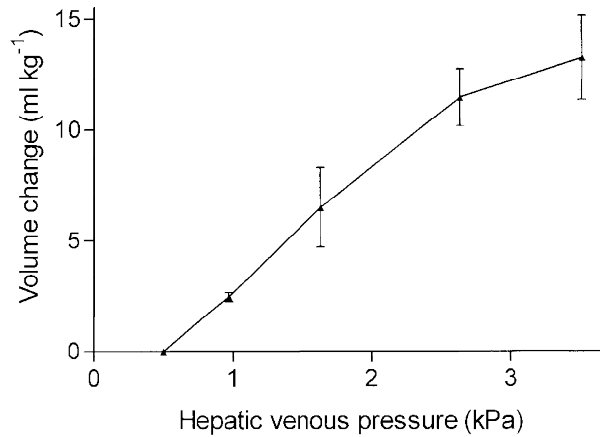


Fig. 7. Changes in volume of liver to changes in hepatic venous pressure in steps from 0.5 to 3.5 kPa. This shows a linear compliance ( $5.44 \pm 0.18 \text{ ml kg}^{-1} \text{ kPa}^{-1}$ ) up to about 2.5 kPa.

the abdominal circulation make the major contribution to capacitance control (Karim & Hainsworth, 1976; Noble *et al.* 1997) but its high compliance, at about  $9.25 \text{ ml kg}^{-1} \text{ kPa}^{-1}$ , accounts for about half the entire vascular compliance of the whole body (Echt, Lange & Gauer, 1974; Drees & Rothe, 1974; Larochelle & Ogilvie, 1976). In the dog, a large contribution to the active response is from the spleen (Greenway, Lawson & Stark, 1968; Donald & Aarhus, 1974; Noble *et al.* 1997). Since humans do not possess a large contractile spleen, any extrapolation of results from dogs to humans should take account of the fact that the canine spleen contributes 40% or more of the active volume change.

The other large abdominal organ is the liver and there is evidence that hepatic blood volume can change in response to sympathetic stimulation, either direct or reflex (Greenway *et al.* 1968; Carneiro & Donald, 1977; Bennett, MacAnespie & Rothe, 1982; Cousineau, Goresby, Rose & Lee, 1985). However, with the exception of the study by Bennett *et al.* (1982), the investigations of changes in liver blood volume did not carefully control the hepatic inflows and hepatic venous pressure making the interpretation of volume changes difficult. Ours is the first study to have made comparisons of changes in hepatic blood volume during constant portal venous and hepatic arterial inflows with the changes occurring when both pressures were controlled and flows allowed to change. These results have shown that, during constant flow perfusion of both hepatic artery and portal vein, stimulation of the sympathetic nerves resulted in decreases in hepatic blood volume of a magnitude similar to those we had previously calculated to have come from the canine spleen. A further interesting finding was that the volume changes from the liver were not significantly different during constant pressure and constant flow perfusion. This is in contrast to what we recently reported for the abdominal circulation as a whole where, following splenectomy, the volume changes during constant pressure perfusion were nearly three times as great as those during constant flow (Noble *et al.* 1997). This implies that passive changes in volume in the liver, due to changes in blood flow, are relatively unimportant and that the large difference in volume changes during constant flow and constant pressure perfusions of the entire abdominal circulation are likely to have been due to changes in intestinal blood flow and the compliance of the intestinal vessels.

Even though its volume is little affected by flow changes, the hepatic vascular bed was seen to be highly compliant and large changes in volume occurred when hepatic venous pressure was changed. We observed a relatively linear relationship between the hepatic vascular pressures and volume, and obtained values of hepatic compliance similar to those reported by Sato, Shirataka, Ikeda & Grodins (1977) and Bennett & Rothe (1981). It seems at first surprising that, for such a compliant circulation as the liver, the volume expelled in response to sympathetic stimulation is no greater during constant pressure perfusion when flow decreases, than during constant flow perfusion. This finding may, however, be explained by the unique features of the hepatic circulation. The splanchnic and hepatic circulations are in series and the hepatic inflow (portal vein) provides a much greater resistance to flow than the venous outflow (hepatic vein). This implies that a change in splanchnic flow would have a large effect on splanchnic venous pressure but much less effect on hepatic vascular pressures downstream to the portal vein. Changes in inferior vena caval pressure, on the other hand, are completely transmitted to the liver and, due to the high compliance of the liver, result in large changes in hepatic volume.

Another way in which it has been suggested that the liver might regulate blood volume distribution is through sphincter-like mechanisms somewhere on the hepatic venous outflow (Knisely *et al.* 1957; Greenway & Oshiro, 1973). Such a mechanism, if it existed, could not only regulate the volume of blood within the liver itself, but also that within the splanchnic vessels (Greenway, 1987). There is, however, no direct evidence for the existence of such a mechanism and even less that it is under sympathetic nervous control. In the present experiments, to determine whether there was any evidence of constriction in the hepatic veins, we passed a fine catheter in a retrograde fashion into a small hepatic venous tributary to measure the gradient between it and the inferior vena cava. There was no appreciable pressure drop either during or without sympathetic stimulation. This implies that there is a minimal outflow resistance, at least in the larger hepatic veins. The absence of a marked flow dependent change in hepatic volume and the complete transmission of hepatic venous pressure changes to the hepatic artery and portal vein also provide evidence against the existence of hepatic sphincters.

Although we did not see any evidence for the existence of hepatic outflow sphincters, there was evidence of changes in inflow resistance. Portal venous perfusion pressure increased during sympathetic stimulation at constant flow perfusion. The magnitude of this increase (0.25 and 0.67 kPa at 4 and 16 Hz stimulation, respectively), if transmitted back to the splanchnic circulation, would result in large changes in volume in the splanchnic vasculature. These changes would only be apparent during constant flow perfusion because the reduction in splanchnic, and therefore portal, flow during stimulation at constant pressure perfusion would be likely to maintain low portal venous pressures. However, it is possible that in some of the situations where there appeared to have been an effect of a change in hepatic resistance, at least part of the effect may have been due to the changes in portal venous resistance.

To conclude, this study has increased our understanding of how blood is mobilized from the liver during increases in the level of activity in the sympathetic nervous system. The liver has been shown to be a most important organ for mobilizing blood, releasing volumes of a magnitude similar to those previously seen only from the canine spleen. In humans, with the small size of the spleen, these results would suggest that the major part of the active capacitance response in the abdominal circulation and, therefore, in the whole body, occurs from the liver. Since the function of vascular capacitance is the control of venous return and, therefore, of cardiac output, control of hepatic capacitance could well have a pivotal role in cardiovascular homeostasis, particularly during exercise and orthostatic stress.

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