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CONTROL OF HEPATIC AND INTESTINAL BLOOD FLOW: EFFECT OF ISOVOLAEMIC HAEMODILUTION ON BLOOD FLOW AND OXYGEN UPTAKE IN THE INTACT LIVER AND INTESTINES*

BY W. WAYNE LAUTT†

From the Department of Physiology, College of Medicine, University of Saskatchewan, Saskatoon, Saskatchewan, Canada S7N 0W0

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SUMMARY

1. Limited isovolaemic haemodilution was produced in cats by addition of dextran 75–Ringer solution to an extracorporeal blood reservoir connected in series with the cat. Total hepatic venous outflow was measured using a hepatic venous long-circuit and hepatic arterial flow was measured with an electromagnetic flow probe. Oxygen uptake was monitored in the guts and liver. Na-pentobarbitone anaesthesia was used.

2. Following reduction of the haematocrit (from 31 to 22) the oxygen uptake of the gut segment and liver were maintained. Gut conductance increased to 125% of control while the oxygen extraction ratio increased to only 109%. The hepatic arterial conductance did not change in spite of a greatly reduced (to 68%) oxygen delivery. Hepatic extraction increased to 140% of control.

3. The hepatic artery did not dilate to maintain constant oxygen supply to the liver thus confirming our previous observation that blood flow is not coupled to hepatic metabolism.

4. Oxygen extraction in the gut correlated well with changes in portal blood flow but not with changes in vascular conductance, arterial blood pressure or oxygen delivery.

5. The blood flow of the gut (vascular beds draining into the portal vein in the splenectomized preparation) was controlled in a manner that prevented changes in portal venous P_{O_2} in spite of a reduction in oxygen content. Local P_{O_2} and perhaps pH, are suggested as the factors controlling gut blood flow following haemodilution.

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6. Changes in portal blood flow correlated with changes in portal vascular (intrahepatic) conductance such that increased portal flow produced an increased portal conductance thereby maintaining portal venous pressure constant.

INTRODUCTION

Various aspects of clinical and experimental haemodilution have been reviewed recently by Moore (1974) and Messmer (1975). Although a great deal of work has been done concerning the effects of normovolaemic haemodilution, there remains a confusing array of responses and conflicting data. It is generally, though not universally accepted (Gump, Butler & Kinney, 1968), that over-all oxygen uptake is not impaired by moderate haemodilution. Messmer (1975) stated that increased tissue blood flow serves as the primary means of compensation for reduced oxygen content, while oxygen extraction remains unaltered. Von Restorff, Hofling, Holtz & Bassenge (1975), on the other hand, supported earlier work which demonstrated an increased oxygen extraction as well as an elevated cardiac output. The observation that venous oxygen tensions are different in blood draining different regions (Murray, 1964) suggests that not all organs respond to haemodilution in an identical manner.

If redistribution of blood flow occurs following haemodilution significant decreases in oxygen consumption of some vital organs could be concealed by increased uptake of less vital organs such as skeletal muscle (Chapler, 1976). Race, Dedichen & Schenk (1967) concluded that significant redistribution of blood flow occurred toward the coronary and vertebral artery systems and away from the renal, hepatic and carotid arteries. Chamorro, Rodriguiz, Dzindzio & Rapaport (1973) showed that total splanchnic oxygen uptake was not impaired. However with an increase in portal blood flow (Schwartz, Shay, Beebe & Robb, 1964) and a decrease in the hepatic arterial share of the cardiac output (Race *et al.* 1967), oxygen delivery to the liver is probably reduced by haemodilution. Brauer (1963) reported that oxygen uptake in the isolated rat liver was almost directly dependent upon the haematocrit of the perfusate. Others have shown a decreased oxygen uptake of isolated livers following very large reductions of the perfusate haematocrit (Mondon & Burton, 1971; Glinsman, Hern & Lynch, 1969). Bauereisen & Lutz (1975), on the other hand, report that the liver is capable of increasing its oxygen extraction ratio from control levels of 40–50 % to as high as 97 %.

In the present series of experiments we examine oxygen uptake and haemodynamics in the liver and in the organs draining into the portal vein. The response to isovolaemic haemodilution is examined to ascertain whether the liver shows metabolic impairment as a result of haemodilution

and secondly to compare the responses of the liver with those of the intestines in an attempt to underline some factors involved with local vascular control.

METHODS

Cats were anaesthetized with I.P. injections of pentobarbitone Na (30 mg/kg). The method used to simultaneously measure hepatic oxygen uptake as well as hepatic arterial and total hepatic blood flow has been described in detail (Lautt, 1976). Briefly the method involves recording the hepatic arterial flow with a non-cannulating electromagnetic flow probe and cannulation of the inferior vena cava in the thorax to measure total liver blood flow en route to an extracorporeal blood reservoir. The inferior vena cava is occluded below the liver and the caval blood flows in a retrograde manner to drain via femoral vein cannulae into the reservoir where the blood is warmed and pumped back to the animal via cannulae in the jugular veins. The spleen is removed and the liver is denervated. The animals respired unassisted. Hepatic oxygen uptake is calculated using the oxygen content in the hepatic artery, portal vein and hepatic vein in conjunction with hepatic arterial flow and portal venous flow. The vascular beds draining into the portal vein are considered together and referred to as the 'gut'; the spleen was removed and therefore did not contribute to flow or oxygen uptake of the gut. Full details on the method of calculation, sampling of blood and evaluation of the preparation are given elsewhere (Lautt, 1976).

Control determinations were made after at least 30 min were allowed for stabilization. Isovolaemic haemodilution was achieved by addition of 60 ml. of a warmed solution consisting of a 1:1 mixture of Ringer solution and dextran 75 (Abbott Laboratories) directly to the extracorporeal blood reservoir. Determinations were made 30 min following addition of the solution to the reservoir. During the period of haemodilution the rate of the pump which returned blood to the animal was not altered, thereby maintaining a constant cardiac output (see Results and Discussion).

The extracorporeal flowprobe (hepatic venous flow) calibration was done periodically throughout the experiment as outlined previously (Lautt, 1976). Following haemodilution the probe recalibration could be done quickly and without interference with the preparation since direct measurement of flow was possible. The hepatic arterial probe was less simply calibrated. An *in vitro* calibration of probe sensitivity versus haematocrit was obtained using warmed blood from cats. The haematocrit was determined for each blood sample taken during the experiment and the probe factor was altered according to the haematocrit (as per instructions by the manufacturer). At the termination of the experiment the probe was calibrated *in situ* in the manner previously described (Lautt, 1976).

RESULTS

Control parameters were in the same range as previously reported (Lautt, 1976) using an identical preparation. In eleven splenectomized cats the control arterial blood pressure was $130 \pm 7{\cdot}8$ mmHg (mean $\pm$ S.E.), hepatic blood flow was $27 \pm 1{\cdot}2$ ml./kg.min, portal venous pressure was $5{\cdot}3 \pm 0{\cdot}4$ mmHg. Arterial haematocrit ($31 \pm 1{\cdot}4\%$) was normal for cats (Lautt, 1976).

Following haemodilution the haematocrit fell to $22 \pm 1{\cdot}2\%$. Systemic

arterial pressure did not change significantly following haemodilution ($96 \pm 2{\cdot}0\,\%$ of control). Control values using this methodology have been published and discussed (Lautt, 1976) and the results in Tables 1–3 are expressed as the mean of the changes seen following haemodilution calculated as a percentage of the control values ($n = 11$). Standard errors are used throughout to indicate variability. All measurements shown were taken 30 min following haemodilution but the responses measured at 15 and 45 min were similar.

TABLE 1. Changes in hepatic metabolism and haemodynamics following moderate, normovolaemic haemodilution

	% of control
Hepatic blood flow	$102 \pm 1{\cdot}8$
Hepatic arterial flow	$94 \pm 4{\cdot}4$
Portal venous flow	$118 \pm 6{\cdot}5$**
Portal venous pressure	$103 \pm 4{\cdot}5$
Hepatic arterial conductance	$99 \pm 5{\cdot}0$
Portal conductance	$116 \pm 6{\cdot}4$
Oxygen uptake	$96 \pm 4{\cdot}8$
Proportion of splanchnic uptake	$101 \pm 3{\cdot}3$
Oxygen delivered	$68 \pm 2{\cdot}8$***
Oxygen extraction	$140 \pm 3{\cdot}6$***

Statistical significance calculated from paired t test. * $P < 0{\cdot}05$; ** $P < 0{\cdot}025$; *** $P < 0{\cdot}01$.

TABLE 2. Blood gas changes following haemodilution (% control)

	Oxygen content	P_{O_2}	P_{CO_2}	CO_2 content	pH (Δ units)
Arterial blood	$73 \pm 2{\cdot}4$***	$99 \pm 2{\cdot}3$	$92 \pm 1{\cdot}6$***	$90 \pm 4{\cdot}2$*	$-0{\cdot}005 \pm 0{\cdot}004$
Portal blood	$63 \pm 3{\cdot}2$***	$95 \pm 2{\cdot}6$	$92 \pm 2{\cdot}9$**	$90 \pm 3{\cdot}3$**	$-0{\cdot}008 \pm 0{\cdot}005$
Hepatic vein	$41 \pm 3{\cdot}8$***	$78 \pm 3{\cdot}6$***	$96 \pm 3{\cdot}4$	$96 \pm 5{\cdot}0$	$-0{\cdot}007 \pm 0{\cdot}005$

* $P < 0{\cdot}05$; ** $P < 0{\cdot}025$; *** $P < 0{\cdot}01$. pH changes are given as mean changes in pH units.

Table 1 shows the response of the liver to haemodilution. Mean hepatic arterial conductance did not change in response to haemodilution in spite of a greatly reduced delivery of oxygen to the liver. Hepatic oxygen uptake ($1{\cdot}15 \pm 0{\cdot}08$ ml./min.kg was maintained entirely by an increase in the oxygen extraction ratio (Table 1). Following haemodilution, 68 % ($\pm 3{\cdot}2\,\%$) of the oxygen delivered to the liver was taken up by the tissues. Hepatic venous oxygen content and P_{O_2} declined while P_{O_2}, CO_2 content and pH did not change (Table 2).

The gut, in contrast to the liver, showed vascular compensation for the reduced oxygen supply (Table 3). Gut vascular conductance increased thereby preventing a marked decrease in oxygen delivered. Oxygen extrac-

tion in the gut increased moderately and mean oxygen consumption was maintained at control levels.

Blood gases in the portal blood showed some unexpected changes. The P_{CO_2} and CO_2 content decreased slightly and the oxygen content decreased. The P_{O_2} remained normal following haemodilution. The portal venous blood thus contained a much lower content of oxygen than the control portal blood of the same animal, yet the P_{O_2} in the blood remained unchanged. Control portal venous P_{O_2} was $35 \pm 1{\cdot}5$ mmHg. Portal pH also was unchanged.

TABLE 3. Changes in gut metabolism and haemodynamics following moderate, normovolaemic haemodilution

	% control
Portal venous blood flow	$118 \pm 6{\cdot}5$**
Gut conductance	$125 \pm 8{\cdot}9$**
Oxygen uptake	$93 \pm 4{\cdot}0$
Oxygen delivered	$86 \pm 4{\cdot}3$**
Oxygen extraction	$109 \pm 2{\cdot}7$***

Statistical significance calculated from paired t test.
* $P < 0{\cdot}05$; ** $P < 0{\cdot}025$; *** $P < 0{\cdot}01$.

The sum of blood flowing from the thoracic cannula and the femoral venous cannulas accounts for the entire blood flow of the inferior vena cava and therefore a major proportion of the cardiac output. Total flow in the vena cava did not change ($103 \pm 1{\cdot}7$% of control, $P > 0{\cdot}1$) following haemodilution. If cardiac output is altered, the change should be reflected in the blood flow of the inferior vena cava.

Correlation plots

Correlation analysis was done to determine if the degree of change in one variable was related to the degree of change of a second variable. For example, although the mean hepatic arterial conductance showed no change from control, some animals showed vasodilation (as much as 137% in one cat) while others showed a decreased conductance (to as low as 78%) Correlation analysis was used to determine if those animals showing vasodilation also consistently showed changes in some other parameter. It must be emphasized that while no correlation could be discerned between many variables, the small range of changes of some of these variables would seem to preclude demonstration of such a correlation; however, if hepatic arterial conductance were under the control of one variable a correlation plot should reveal the relationship. Hepatic arterial conductance changes did not correlate with changes in portal or arterial blood gases or blood pressures, oxygen delivery, haematocrit or hepatic oxygen extraction ratios.

Correlation plots of changes in arterial conductance with control conductance indicated that those vessels that had a higher resting tonus in the control state did not necessarily dilate the most in response to haemodilution. Even though mean arterial conductance did not change significantly there was a relationship between portal flow and arterial flow over the ranges seen ($r = 0{\cdot}61$). As portal flow increased, the hepatic artery tended to vasoconstrict. This reciprocal relationship between portal flow and hepatic arterial flow has been examined by others (Hanson & Johnson, 1966; Ternberg & Butcher, 1965; Greenway, Lawson & Mellander, 1967).

Portal vascular flow changes were also correlated with portal conductance changes (intrahepatic). As flow in the portal vein increased so did portal conductance ($r = 0{\cdot}70$), the result being a constant portal venous pressure (103%). This relationship is discussed.

Similar correlation analyses were carried out for the gut conductance responses. Gut conductance changes were plotted against changes in arterial blood pressure and haematocrit, arterial P_{O_2}, P_{CO_2} and oxygen content, all portal blood gas parameters, gut oxygen extraction and control gut conductance. Similar to the liver, the gut conductance changes were not related to control conductance, that is, the vessels which were initially constricted to the greatest extent did not dilate the most following haemodilution. Gut conductance changes did not correlate with oxygen content changes or any other parameter analysed.

Changes in hepatic oxygen extraction ratio did not correlate with arterial or portal pressure changes, arterial conductance, arterial blood gas changes or blood flow changes (arterial, portal or total). The gut oxygen extraction changes showed a dramatic correlation with changes in portal blood flow (Fig. 1) but were not correlated with changes in arterial pressure or vascular conductance, arterial oxygen content, P_{O_2} changes or changes in oxygen delivery.

Uncontrolled cardiac output

In three cats the hepatic arterial and superior mesenteric blood flow was measured in the absence of the venous long circuit. The spleen was removed. Hepatic arterial denervation was done in one cat. Cardiac output was measured using the Fick principle. Haemodilution was achieved by removal of 20 ml. blood and replacement with 40 ml. of a 1 : 1 dextran 75 and Ringer solution. In these experiments the cardiac output was elevated and hepatic arterial blood flow increased both with and without nerves. The increase in hepatic arterial flow was similar to the increase in flow of the superior mesenteric artery but less than the cardiac output. The experiments demonstrate only that under appropriate conditions following haemodilution the hepatic artery does vasodilate. However, in these

experiments there were large reductions in haematocrit (53 %); arterial blood pressure and P_{O_2} declined and oxygen content in the portal blood decreased to 30 %. Oxygen delivered to the liver via the artery was reduced to 26 % and via the superior mesenteric arterial components of portal flow to 31 %. Thus in the situations with moderate to severe haemodilution and

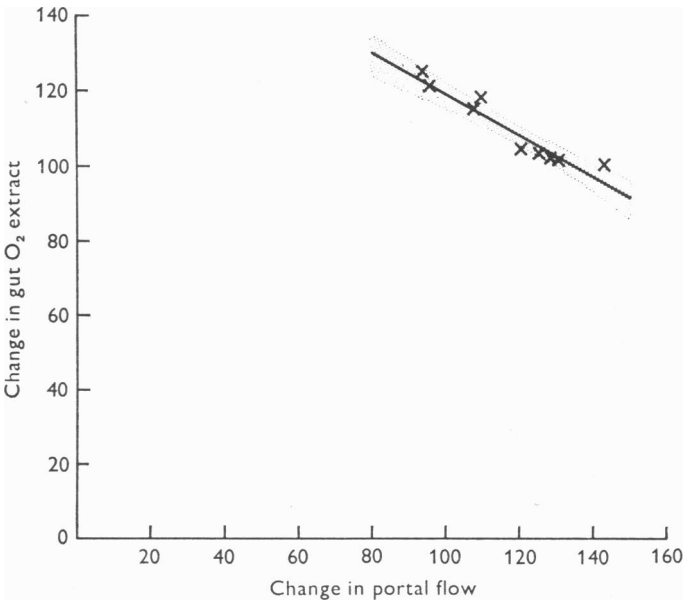

Fig. 1. Correlation of changes in gut oxygen extraction with changes in portal venous flow following haemodilution (r = 0·95). Gut oxygen extraction did not correlate with changes in oxygen delivered, arterial or portal blood pressure or gut vascular conductance. Shaded area represents 95 % confidence limits.

elevated cardiac output, the hepatic artery dilates while the preparation using the long-circuit (preventing the cardiac output from rising) and moderate levels of haemodilution, the artery did not dilate in spite of a marked reduction in oxygen delivery to the liver.

DISCUSSION

Normovolaemic haemodilution

Because of the tendency of plasma substitutes to escape the vascular compartment, haemodilution is generally accomplished by removal of a set volume of blood followed by fluid replacement with 2–3 times the volume of blood removed. Moore (1974) stated that to achieve normovolaemic

haemodilution, the replacement fluid must be larger in volume than the plasma and red cells lost, by a factor of about 2·75. Under these circumstances haemodilution will result in a normovolaemic situation after a period of time but initially the blood volume will be markedly elevated as will the cardiac output.

In the present set of experiments, haemodilution was achieved by addition of a 1:1 mixture of Ringer solution and dextran 75 into an extracorporeal reservoir. In the control situation, the reservoir level remains constant for long periods of time, declining by no more than 5–10 ml. in 1 hr. If the incisions ooze inordinately or if blood samples are taken, the reduction in circulating blood volume appears as a decrease in the reservoir level. The blood volume of the cat is thus maintained by the existence of the extracorporeal reservoir. If addition of the diluent to the reservoir had produced a decrease in blood volume in the present experiments the reservoir level would have declined following the haemodilution. This did not occur. Similarly hypotension was not induced by these procedures. Therefore haemodilution produced by addition of diluent to the extracorporeal reservoir produced a true normovolaemic haemodilution.

In order to assess the ability of an organ to withstand haemodilation it is preferable to select a time point or set of conditions where the cardiac output is not greatly elevated. The ability of an organ to maintain normal oxygen uptake following haemodilution in spite of an unaltered cardiac output is clearly more crucial than when cardiac output is greatly elevated. Cardiac ouput was not measured in these experiments, but since total venous flow in the inferior vena cava did not change it is clear that cardiac output was not greatly affected by haemodilution as a result of addition of fluids to the extracorporeal reservoir.

Vascular conductance

The gut and the liver showed quite different responses to isovolaemic haemodilution when cardiac output was held at control levels. Oxygen uptake was well maintained in both organs but the mechanism of compensation for the reduced oxygen content of the blood varied. The gut vascular conductance increased to 118% of control which was sufficient to maintain the oxygen delivery of the gut close to control levels (86%). The hepatic artery, on the other hand, did not show a dilation in spite of a greatly reduced oxygen supply to the liver (to 68% of control).

The lack of dilation of the hepatic artery cannot be attributed to an artifactual response of an already fully dilated artery since conductance was within normal control ranges (Lautt, 1976) and well below the range that is seen on maximium vasodilation of the hepatic artery (Lautt & Plaa, 1974). Race *et al.* (1967) also showed a redirection of cardiac output away

from the hepatic artery. The response of the hepatic artery is clearly different from the response of the arteries supplying blood to the gut.

Correlation studies were done in an attempt to determine whether any one factor appeared to control vascular conductance changes following haemodilution. Reduced haematocrit produces a reduction in blood viscosity (Whittaker & Winton, 1933). If altered viscosity is to be atrributed as the major factor causing increased conductance following haemodilution as argued by Messmer (1975) then the extent of change in conductance should correlate with the extent of change in haematocrit. Correlation analysis indicated that such a relationship did not exist in the gut ($r = 0{\cdot}136$). The hepatic artery appears in fact to have vasoconstricted since mean hepatic arterial conductance remained constant in the face of a reduced haematocrit.

The lack of correlation with viscosity seems reasonable since, if blood flow is normally controlled by local needs within the tissue, then any alteration in viscosity should be counteracted by the local control mechanisms. Von Restorff *et al.* (1975) came to a similar conclusion. The reduced haematocrit would however permit a greater degree of vasodilation than the maximum obtained at normal viscosity. With the reductions in haematocrit seen in these experiments it appears that viscosity changes were compensated for, the hepatic arterial conductance remaining constant in spite of a reduced viscosity and the changes in gut conductance showing no correlation with the changes in haematocrit.

Other factors that might be expected to control vascular tone are the local oxygen needs of the tissues or accumulation of metabolites within the organ. Although the mean hepatic arterial conductance did not change, the conductance increased to as high as 137 % and decreased to as low as 78 % of control values. In an attempt to ascertain whether the hepatic arterial conductance was altered by changes in the blood gases of the portal blood we compared the changes in portal blood gas measurements with the change in hepatic arterial conductance. There was no significant correlation between changes in portal venous oxygen content, P_{O_2}, carbon dioxide content, pH or P_{CO_2} with changes in hepatic arterial conductance. The arterial conductance was not consistently under the control of any of these measured parameters in the portal blood. It is clear that oxygen demand is not a major controlling factor in hepatic hemodynamic regulation. Hepatic venous oxygen content and P_{O_2} decreased markedly (to 41 and 78 % respectively) while hepatic arterial conductance did not change. The arterial conductance was not controlled by local oxygen levels or P_{O_2}, otherwise marked vasodilation should have occurred in each preparation. The role of the hepatic artery is thus not one of providing variable amounts of arterial blood to maintain the hepatic oxygen delivery constant.

If the gut conductance is controlled by local oxygen demand, flow should change to an appropriate extent to keep the local P_{O_2} nearly constant. Venous P_{O_2} is a fair index of tissue P_{O_2} (Tenney, 1974), therefore local vascular changes should occur such that venous P_{O_2} would remain constant or show only a slight decrease. Decreases in local oxygen delivery should produce a vasodilation sufficient to maintain P_{O_2} within normal ranges. Only after the vascular capacity for compensation is exceeded should the P_{O_2} decline more severely. Total portal venous oxygen content declined to 63% of control while P_{O_2} remained within normal limits (95% of control), suggesting that P_{O_2} was part of a feed-back control system. Carbon dioxide content was reduced to 90% and P_{CO_2} was reduced to 92%. If CO_2 were the controlling factor it should be at least as high as control levels or slightly higher. Portal pH also did not change. Portal pH and P_{O_2} seem the most likely contenders for local control of gut flow under these experimental conditions. Smith & Vane (1966) showed that the resting tension of vascular smooth muscle varied directly with the P_{O_2} of the perfusing medium. When the oxygen content perfusing the intestine was reduced, intestinal vascular resistance decreased (Fleisch, Sibul & Ponomarev (1932). Similarly pH changes induced by addition of CO_2 to the perfusate produced a vasodilation of the gut (Pals & Steggerda, 1966; Mohamed & Bean, 1951). Stowe, Owen, Anderson, Haddy & Scott (1975) showed that the vasodilation of skeketal muscle seen during prolonged exercise could be entirely accounted for by the changes in venous P_{O_2} and pH. Neither factor alone was sufficient to account for the dilation. This dual control system may apply to other vascular beds. The present data are compatible with such a role in the gut following haemodilution.

Hanson & Johnson (1966; Fig. 7) showed that portal and hepatic arterial flows were linearly related in a reciprocal manner until portal flow was reduced to levels less than 50% of normal. They did not examine the effect of increased portal flow; however, their data indicate that over the linear range a decrease in portal flow produced a much smaller increase in arterial flow. Our data confirm their observation both in the tendency for a reciprocal relationship as well as the fact that the change in hepatic arterial flow is of smaller magnitude than the change in portal flow. In the present study the mean portal flow increased to 118% while the hepatic arterial flow decreased only to 94% of control. The mechanism of the reciprocal control is unclear but various theories are discussed by Greenway *et al.* (1967) and Ternberg & Butcher (1965).

Portal blood flow is controlled by the vascular conductance of arteries supplying the organs draining into the portal vein. Changes in portal (intrahepatic) conductance, on the other hand, affect portal pressure and have a minor affect on portal flow except in situations of severe portal

hypertension. It is therefore interesting to note that changes in vascular conductance of the portal radicles within the liver also correlated well with changes in portal blood flow. As blood flow in the portal vein increased so did the portal vascular conductance (intrahepatic). Portal flow also correlated directly with portal conductance in the dog (Hanson & Johnson, 1966). Although the mechanism relating portal flow to portal vascular conductance in the liver is unknown the data support previous work suggesting that portal conductance is regulated in such a manner as to prevent or minimize changes in portal venous pressure since mean portal pressure in these experiments did not change ($103 \pm 4{\cdot}5\%$ of control) in spite of a mean increase in portal blood flow (to $118 \pm 6{\cdot}4\%$). Adjustment of the portal vascular resistance sites in the liver has previously been discussed from the point of view of maintenance of a constant capillary pressure within the intestine (Greenway *et al.* 1967).

Oxygen extraction ratio and oxygen uptake

Messmer (1975) concluded that 'in agreement with an unchanged oxygen extraction, central venous P_{O_2} remained unchanged during limited normovolaemic haemodilution'. Oxygen consumption and oxygen content cannot however be accurately determined using P_{O_2} measurements. In the present study oxygen content and P_{O_2} were determined independently. Portal venous oxygen content declined to 63% of control while the P_{O_2} showed no change. This may suggest a decrease in haemoglobin affinity for oxygen in the portal blood following haemodilution. Further investigation of this phenomenon is ongoing. Oxygen consumption calculations in the present experiments were done using direct measurements of arterial and venous oxygen contents.

The oxygen extraction changes following haemodilution were different in the gut and liver. The oxygen extraction ratio in the gut increased to only 109% of control. Most of the compensation was due to vascular conductance changes. Blood flow and oxygen extraction were however inversely related. The observation that extraction ratios were related to blood flow and not to oxygen delivery is compatible with the hypothesis that the rate of blood flow controls precapillary sphincter tone and therefore the capillary surface area available for diffusion (Mellander & Johansson, 1968). Flow is believed to control the spincter tone by virtue of washing away a continuously produced dilator (Schayer, 1974). Decreases in blood flow result in an accumulation of dilator substance and a dilation of the sphincters. This increases the surface area of the capillary bed and increases oxygen availability to the tissues.

This sort of relationship did not occur in the liver. The liver is able to extract oxygen more efficiently than the gut (Bauereisen & Lutz, 1975).

In the present experiments the liver was able to compensate for haemodilution solely through a more efficient extraction of the oxygen available to it. Mitochondrial metabolism is independent of cell P_{O_2} until oxygen tension falls below a critical level (Chance, Oshino, Sugano & Mayersky, 1973; Granger, Goodman & Cook, 1975). The liver is able to deliver oxygen to the parenchymal cells in a manner that permits the highest availability of oxygen to the cells with the minimum of non-nutritive shunting.

The anatomy of the hepatic vascular bed is ideally suited to the creation of high arterial-to-hepatic venous concentration gradients. Goresky (1975 and Goresky, Bach & Nadeau, 1973) has pointed out that the input and output points of the hepatic vasculature within each hepatic lobule are symmetrical; all of the sinusoid entrances are adjacent and all of the exit points are adjacent. Flow in adjacent sinusoids is concurrent and there is no opportunity within the lobular structure for diffusible materials to shortcircuit the vascular pathways. Oxygen cannot diffuse readily from the arterial or portal blood into the venous blood. Oxygen extraction in the liver is therefore potentially more efficient than in most other organs. The mean oxygen content of the hepatic venous blood was only 2·0 ml./100 ml. blood following haemodilution and under severe reduction of oxygen delivery we have seen oxygen levels in the venous blood as low as 0·2 ml./100 ml. (unpublished observations). Hepatic oxygen extraction ratios as high as 97% have been reported (Bauereisen & Lutz, 1975). In the present series, oxygen extraction increased to 140% of control levels with no reduction in the rate of oxygen uptake.

The oxygen uptake was not compromised under a situation that duplicates the most severe example of vascular responses to haemodilution. In these experiments, the cardiac output did not acutely rise, due, as discussed previously, to the existence of an extracorporeal blood reservoir and long-circuit in series with the animal. The cardiac output response was similar to that which occurs during chronic anaemia or which would occur acutely if the heart were not able to increase the cardiac output (Moore, 1974).

The degree of haemodilution produced in this series is similar to that recommended by Moore (1974) as the lowest level of haematocrit (20%) that should be obtained during clinical haemodilution. Under these conditions haemodilution appears to be a safe procedure, producing no compromise of tissue oxygenation in the liver or gut.

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