EFFECTS OF CHANGES IN ARTERIAL BLOOD GAS TENSIONS, ACID-BASE BALANCE AND ANAESTHETIC AGENTS UPON LIVER BLOOD FLOW AND OXYGEN CONSUMPTION IN THE GREYHOUND

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ACKNOWLEDGEMENTS AND STATEMENT OF COLLABORATION

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SUMMARY

There have been major technical advances in the surgery of hepatobiliary disease during the past few years. However, the knowledge of the effects upon the liver of changes in blood gases and acid base balance or of the effects of anaesthetic agents, remains limited. The investigations detailed in this thesis were designed to utilise recent advances in construction of electromagnetic flowmeters which allow the simultaneous continuous measurement of blood flow in the hepatic artery and portal vein.

This thesis describes studies upon liver blood flow and oxygen consumption in the greyhound. Greyhounds between 25 and 35 kg body weight were anaesthetised with thiopentone and paralysed with pancuronium. Anaesthesia was maintained with pentobarbitone. The dogs were ventilated artificially with a mixture of 75% nitrogen and 25% oxygen. Laparotomy was performed and electromagnetic flow-probes were placed upon the hepatic artery, portal vein and splenic vein, allowing continuous measurement of these blood flows with Statham SP 2202 flowmeters. A cannula was placed in the stump of the gastroduodenal vein to record portal venous pressure and allow portal venous blood sampling and another was placed in a hepatic vein via the external jugular vein. Systemic arterial blood pressure was recorded via a cannula placed in a femoral artery and cardiac output was measured using the thermodilution technique via a triple lumen thermistor tipped catheter placed in the pulmonary artery. Systemic arterial, hepatic venous and portal venous oxygen contents were measured using a Lex-O_2-Con oxygen content analyser and using the hepatic arterial and portal

venous blood flow measurements obtained, hepatic oxygen consumption was calculated.

The following groups of experiments were carried out:-

1. Control.

A control group was studied to assess the stability of the preparation over a three hour period. This series of experiments demonstrated that the preparation was stable and all the subsequent groups of experiments were designed to be completed in this three hour period.

2. Hypercarbia.

A group of animals were studied at four $PaCO_2$ tensions from 55 mm Hg to 100 mm Hg. Portal venous blood flow increased with a simultaneous decrease in hepatic arterial blood flow. Hepatic oxygen consumption was unchanged.

3. Hypocarbia and Positive Pressure Ventilation.

A group of animals were passively hyperventilated and the effects of the raised intrathoracic pressure accompanied by hypocarbia and then normocarbia were studied. Hypocarbic hyperventilation produced a decrease in portal venous and hepatic arterial blood flow. Normocarbic hyperventilation resulted in a restoration of portal venous blood flow but with a further decrease in hepatic arterial blood flow. A decrease in hepatic oxygen consumption with hypocarbia returning to control with normocarbia was seen.

4. Hyperoxia.

A group of animals were studied at three raised PaO_2 tensions from 200 to 400 mm Hg. The only significant change seen was a small increase in hepatic oxygen consumption.

5. Hypoxia.

This was studied at PaO_2 tensions of 70, 55, 40 and 25 mm Hg. Mean arterial pressure was found to increase significantly at each PaO_2 tension immediately the hypoxic gas mixture was introduced but returned to control by the time 20 min had passed. At the same time a significant decrease in hepatic arterial blood flow was seen, returning to control by 20 min. No changes in portal venous blood flow were seen. Hepatic oxygen consumption decreased significantly at 25 mm Hg PaO_2.

6. Metabolic Acidosis.

The effects of an infusion of lactic acid were studied at progressively increasing base deficits. Portal venous blood flow increased while hepatic arterial blood flow decreased. Total liver blood flow remained unchanged. There were no significant changes in hepatic oxygen consumption.

7. Metabolic Alkalosis.

The effects of an infusion of sodium bicarbonate were studied at a progressively increasing base excess. Portal venous blood flow increased significantly while hepatic arterial blood flow did not increase significantly. There were no significant changes in hepatic oxygen consumption.

8. Halothane Anaesthesia.

Increasing concentrations of halothane, from 0.5% to 2% were administered for thirty minute periods to a group of greyhounds. Portal venous blood flow decreased to 45% of control with 2% halothane. Hepatic arterial blood flow decreased to 35% of control at the same concentration. There were no

significant changes in peripheral resistance or hepatic arterial resistance. There was a small decrease in hepatic oxygen consumption which did not reach significance.

9. Enflurane Anaesthesia.

Increasing concentrations of enflurane from 1% to 3% were administered for thirty minute periods to a further group of greyhounds. Enflurane has half the anaesthetic potency of halothane, but it could not be given at the 4% concentration in order to compare it with 2% halothane due to the greater cardiovascular depression produced by the drug. Portal venous blood flow decreased in a similar manner to that seen with halothane. Hepatic arterial blood flow decreased significantly only at the 3% enflurane concentration. Peripheral resistance and hepatic arterial resistance decreased significantly. There were no changes seen in hepatic oxygen consumption.

10. Calibration Experiments.

In the appendix to this thesis a series of in vivo experiments are described in which the electromagnetic flow-probes used were calibrated over a wide range of flows.

Current published work suggests that a mechanism exists in the liver by which any increase or decrease in portal venous blood flow results in a compensatory change in hepatic arterial blood flow. This phenomenon has been termed the "reciprocity response" and is believed to be due to a myogenic mechanism in the hepatic arterioles. The results of these experiments lend support to this hypothesis with the exception of the results from the halothane experiments. It is suggested that halothane may produce a generalised increase in sympathetic nervous

activity thus overriding the local mechanism in the liver.

The study of hepatic oxygen consumption during these experiments showed that it remained constant despite widely varying blood flows due to the various experimental situations. Only marked hypocarbic hyperventilation and severe hypoxia producing significant decreases.

CHAPTER 1.

INTRODUCTION

Despite its homogenous macroscopic and microscopic appearance, the liver has a remarkedly wide range of functions. It has many endocrine functions such as the production of various plasma proteins and has the important exocrine function of the secretion of bile. The central role it plays in the breakdown and biotransformation of drugs makes a knowledge of its physiology important to all clinicians.

The peculiar blood supply of the liver with the portal vein supplying some 75-80% of liver blood flow but only 50% of the oxygen requirements while the hepatic artery supplies only 20% of liver blood flow but 50% of oxygen requirements (Witte, C.L. and Witte, M.H., 1974) renders the liver particularly sensitive to injury due to changes in blood flow.

Despite the many advances in the surgery of hepato-biliary disease and in anaesthesia for this, knowledge of the effects of the changes in arterial blood gas tensions and in acid base balance, which may occur during and after this surgery, upon liver blood flow is limited and contradictory (Greenway and Stark, 1971). Similarly detailed information upon the effects of anaesthetic drugs on portal venous blood flow and hepatic arterial blood flow is not available (Batchelder and Cooperman, 1975; Cooperman, 1972; Cooperman, Wallman and March, 1977; Goldberg, 1970 and Savolainen, 1969). In the light of the increasing suspicion that halothane produces liver damage (Inman and Mushin, 1978) more detailed knowledge of the effects of halothane and the proposed alternative

drug enflurane upon liver blood flow and the oxygen consumption of the liver would be valuable.

The electromagnetic flowmeter was first described nearly half a century ago (Kolin, 1936) and its use in the measurement of portal venous and hepatic arterial blood flow in the dog twenty years ago (Drapanas, Kluge and Schenk, 1960). However, these early flowmeters did not allow continuous recording of flows in two vessels so closely together, due to electrical interference between the two probes. In addition, the frequent occlusive zeroing necessary because of baseline drift presented particular problems in the dog as clamping of the portal vein leads to cardiovascular collapse (Green, Hall, Sexton, et al, 1959; Shafey and Hassab, 1968) possibly due to hyperkalaemia (Bengmark and Hafstrom, 1974). The more recently introduced electromagnetic flowmeters, such as the Statham SP2202 flowmeters used in this study allow the continuous recording of flows in two adjacent blood vessels and the electronic zeroing facility obviates the need for frequent occlusive zeroing.

The measurement of the separate portal venous and hepatic arterial components of liver blood flow allows, if the oxygen content of the hepatic vein, hepatic artery and portal vein are measured simultaneously, the oxygen consumption of the liver to be calculated. This provides an estimate of the aerobic metabolic activity of the liver. Direct measurement of blood oxygen content required until recently use of the difficult and time consuming method of Van Slyke (Van Slyke and Neill, 1924). The introduction of the Lex-O_2-Con oxygen analyser, which has been shown to compare well with the Van Slyke technique (Kusumi, Butts and Ruff, 1973;

Selman, White and Tait, 1975) has made the measurement of frequent samples a simpler proposition.

In the light of these recent advances in measurement techniques, a model therefore was designed in which the alterations in blood gas tensions and acid base balance which may be seen during or after major surgery and their effect upon the liver could be studied. It was thought that this model could also be used to study two of the most commonly used anaesthetic agents.

The studies detailed below were not possible in man as the dissection necessary to obtain good contact between vessel and flowprobe is dangerous and there are no sufficiently accurate alternative methods available (Ohnhaus, 1979). The isolated perfused liver, while theoretically allowing very stable conditions for measurement has proved difficult to use in practice because a venous outflow block normally occurs after a short period (Dionigi and Alexander, 1970; Abbott and Weinerth, 1971). Therefore, the intact greyhound was chosen for study, as this animal is readily available, usually in good condition and the use of the one breed of dog avoids the variability in cardio-vascular responses seen between different breeds of dog. This use of the intact animal, was decided upon as it is hoped the results of the experiments can be applied to clinical practice. It, of course, means that the detailed analyses of the physiological mechanisms involved must be conjectural.

Hepatic blood flow and oxygen consumption were studied in the following conditions.

(1) A Control Series.

(2) Hypercarbia.

(3) Hypocarbia and Positive Pressure Ventilation.

(4) Hyperoxia.

(5) Hypoxia.

(6) Metabolic Acidosis.

(7) Metabolic Alkalosis.

(8) Halothane Anaesthesia.

(9) Enflurane Anaesthesia.

CHAPTER 2.

A REVIEW OF DEVELOPMENTS IN THE MEASUREMENT OF LIVER BLOOD FLOW

The circulation to the liver has been a matter of debate since Harvey refuted Galen's concept of ebb and flow in the portal system (Whitteridge, 1971).

However, it is only in this century that measurement techniques have allowed detailed quantitative study of the flow in the hepatic artery and portal vein. Burton Opitz (1910, 1911 a & b) in his classic series of experiments, obtained measurements of flow in the hepatic artery and portal vein which were remarkably accurate despite the fact the measurements were made with an intra-arterial Stromuhr. This consists of a U-shaped tube inserted into the blood vessel. The upstream limb is filled with oil and the downstream limb with blood. The tube can be turned 180° by hand to connect the two limbs alternately to the proximal and distal ends of the vessel. The blood displaces the oil from the proximal limb and when the oil reaches the outlet the device is turned 180°. Each turn is marked on a kymograph and as the volume of the limb is known, flow per unit time can be calculated.

The methods used in studying liver blood flow have been (1) Indirect and (2) Direct. The indirect methods used have included:-

(a) The use of the Fick principle in the extraction of certain dyes.

(b) Single injection techniques of substances completely cleared from the blood by the liver.

(c) Indicator-dilution techniques.

(d) Gas clearance techniques.

1 (a). The two dyes most commonly used have been bromsulphthalein and indocyanine green. The use of bromsulphthalein was first described in 1945 (Bradley, Ingelfinger, Bradley, et al) and the technique involves the infusion of the dye, which it is assumed, is taken up only by the hepatocytes, with simultaneous blood sampling from a hepatic vein. However, it was shown in 1956 (Sapirstein and Reininger) that uniform mixing of the dye did not occur and varying the position of the hepatic venous cannula altered the result obtained. The use of indocyanine green was proposed as an alternative but in comparison with bromsulphthalein it has been shown to give the same wide variability of results (Winkler and Tygstrup, 1960) and more recently has been shown to produce a significant underestimate of liver blood flow in shock (Teranaka and Schenk, 1977). Another disadvantage of dye clearance techniques is that the assumption is made that the treatment being studied does not alter the extrahepatic removal of the dye or the intrahepatic regional clearance of it; this assumption probably cannot be made if anaesthetic agents are being studied (Abdel Salam, Drummond, Bauld, et al, 1976).

1 (b). The single injection technique involves the assumption that a substance is completely cleared by the liver in one circulation and that the hepatic venous content of the substance is zero (Dobson and Jones, 1952). To avoid repeated blood sampling radio isotope techniques, allowing changes in plasma concentrations of the tracer substance to be assessed by external gamma ray counting

over the liver, have been used most frequently (Gelman, 1976). Liver blood flow is estimated by:-

$$\text{ELBF} = K \times \text{Blood Volume, where } K = \frac{0.693}{T\frac{1}{2}}$$

(assuming a monoexponential decay curve). The drawback to this technique is that, as well as accepting the assumption that the substance is completely cleared by the liver, blood volume must be calculated, adding another potential source of error to the calculation.

1 (c). An indicator dilution technique for measuring liver blood flow has been described (Shoemaker, Steenburg, Smith, et al, 1961). However, this method again involves calculation of blood volume and the occurence of recirculation and nonuniform mixing in the liver makes it of doubtful value.

1 (d). In recent years techniques involving the use of inert, lipid soluble and highly diffusable radiotactive isotopes have been described in the measurement of liver blood flow (Darle, 1970). These gases are taken up by the liver almost instantaneously, following injection into the splanchnic circulation and the rate of elimination of the gas is directly proportional to liver blood flow. The two most commonly used gases are Krypton, a β emitter, requiring counting over an exposed liver and Xenon a γ emitter, which allows external counting over the liver, with a closed abdomen. Both these techniques have been shown to correlate well with measurements made with the electromagnetic flowmeter over a wide range of flow values (Leiberman, Mathie, Harper, et al, 1978; Mathie, Hughes, Harper, et al, 1978).

However, all these indirect measurements of liver blood flow allow only total liver blood flow to be measured. In order to measure the separate contributions of the portal vein and hepatic artery, direct measurements of flow must be made.

A large variety of methods of direct measurement of liver blood flow have been used since Burton-Opitz's experiments with the mechanical stromuhr. These have included the Bristle flowmeter (Selkurt and Brecher, 1956); a combination of dye and electromagnetic flowmeter (Katz and Bergman, 1969) and a method with possibly large future potential - the ultrasonic flowmeter (Loisance, Peronneau, Pellet, et al, 1973).

However, the device most frequently used at the present time for the measurement of portal venous and hepatic arterial blood flow is the electromagnetic flowmeter. This was first described in principle by Kolin in 1936. Nevertheless, it was not until 1960 that Drapanas, Kluge and Schenk described its use in the study of liver blood flow. The favourable impressions of these workers have since been confirmed by other groups (Muller and Smith, 1963; Price, Britton, Peterson, et al, 1965).

At present, problems with zero drift have precluded the successful use of these instruments in a chronic preparation (Sellers and Dobson, 1968). Routine use in man has also been prevented by the potentially hazardous disection of the adventitiae around the portal vein and hepatic artery necessary for accurate measurements (Ohnhaus, 1979). In acute animal studies the development recently of flowmeters with electronic zeroing facilities and synchronisation of excitation currents in multi flowmeter use now allows continuous accurate recording

of blood flow in the hepatic artery and portal vein. These devices are more fully discussed in the appendix to this thesis.

CHAPTER 3.

MATERIALS AND METHODS

This chapter describes the basic methodology used in all the groups of experiments subsequently described. The experiments were all carried out in the operating theatres of the Wellcome Surgical Research Institute, Garscube Estate, Glasgow.

Greyhounds of either sex of weight 25 to 35 Kg were used in these experiments. They were unpremedicated and starved overnight (Folkow and Neil, 1971). Anaesthesia was induced by intravenous injection of thiopentone (Intraval, May and Baker) 20 mg/Kg body wt and maintained by intravenous injection of pentobarbitone (Sagatal, May and Baker) 30 mg/Kg initially and supplements of 2 mg/Kg i.v. if required later in the investigations.

The trachea was intubated and the lungs were ventilated artificially with a Barnet Mark II Ventilator at a rate of 14 per minute and an inspiratory:expiratory time ratio of 1:2 with a mixture of 75% nitrogen and 25% oxygen. The minute volume and the inspired oxygen concentration were adjusted to maintain normal $PaCO_2$ and PaO_2 tensions of 40 mm Hg (5.3 kPa) and 100 mm Hg (13.3 kPa). Pancuronium bromide (Pavulon, Organon) 0.15 mg/Kg was administered at this time to allow sufficient relaxation of the abdominal musculature for easy dissection.

Laparotomy was performed via a midline abdominal incision using diathermy and haemostasis secured. The hepatic artery (HA) was then dissected free of adventitia, for a distance of 1 centimetre at a site 1-2 cm from the coeliac axis. Great care

was taken to leave the peri-arterial nerve plexus intact. A one centimetre length of the portal vein (PV) was dissected free of adventitia between the junctions with the splenic vein and gastroduodenal vein. A portion of the splenic vein was exposed distal to its junction with the left gastric vein.

Statham, cuffed, gated, electromagnetic flowprobes were placed around these three vessels (Fig. 1) and flow was measured with Statham SP 2202 flowmeters. A detailed account of the theoretical basis of this measurement technique and of the in vitro calibration experiments carried out is included in an appendix to this thesis. A 6mm flowprobe was normally applied to the portal vein and 3mm probes to the hepatic artery and splenic vein.

In order to ensure that the probe placed around the hepatic artery was only measuring blood flow to the liver, the right gastric and gastroduodenal branches of this artery were tied off with ligatures. Similarly, in order to ensure that the probe placed around the portal vein was measuring total portal blood flow, the gastroduodenal vein was tied.

A cannula was placed in the stump of this vein so that the tip lay at the junction of the gastroduodenal vein and portal vein. This cannula was used to allow samples of portal venous blood to be taken and to record portal venous pressure.

An "E-Z" catheter (Deseret) was inserted over an introducer percutaneously, into an external jugular vein. It was then passed through the right atrium and inferior vena cava into a hepatic vein until a wedged position was reached. The position

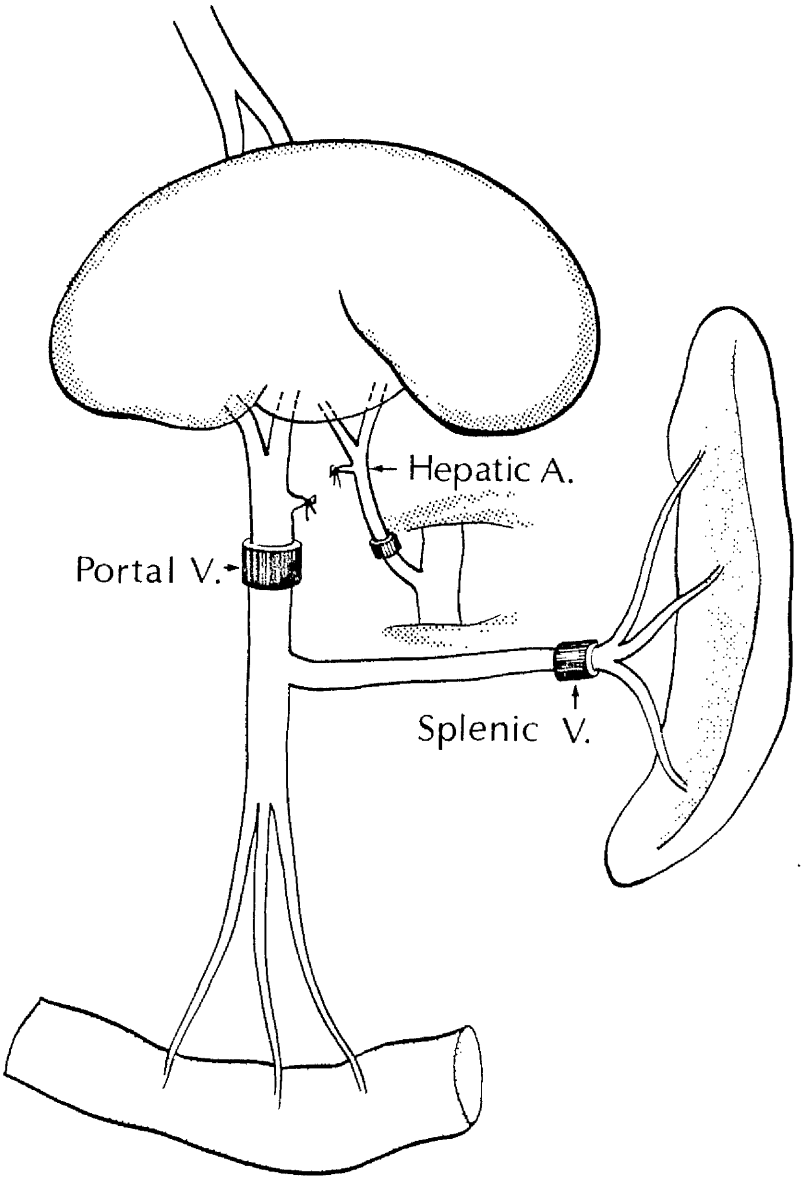

FIGURE 1. Diagrammatic illustration of the sites of application of the portal venous, hepatic arterial and splenic venous electromagnetic flowprobes. Ligatures are applied to the cut ends of the gastroduodenal artery and vein.

of the catheter was checked by direct manual palpation through the abdominal incision. The catheter was withdrawn until blood could be drawn back into a syringe and was used to allow hepatic venous blood sampling and the recording of hepatic venous pressure. The edges of the abdominal incision were opposed with clamps and the wound covered with towels to minimise heat and fluid loss.

An incision was made in the right groin and approximately 3 cms of the femoral artery and femoral vein were dissected free A cannula was passed into the abdominal aorta via the femoral artery to allow measurement of systemic arterial pressure. A thermistor tipped, triple lumen catheter (Cardio-Vascular Instruments) was passed via the right femoral vein through the right side of the heart into a main pulmonary artery. The distal lumen of this catheter was connected to a manometer and the signal displayed upon a multi channel heated stylus recorder (Devices). The position of the tip of the catheter was confirmed to be in a main pulmonary artery when the typical pressure waveform was seen. The catheter was used to measure cardiac output (Forrester, Ganz, Diamond, et al, 1972) when connected to a Cardiac Output Computer (Cardio-Vascular Instruments). Ten millilitres of cold saline were injected at each measurement and these measurements were made in triplicate. In addition, this catheter was used to monitor core body temperature and this was maintained at $38 \pm 0.5^{\circ}C$ by means of heat lamps and manipulation of the room temperature.

The portal venous, hepatic venous and arterial oxygen contents were measured using the Lex-O_2-Con electrolytic cell (Lexington Instruments).

The portal venous, hepatic venous and systemic arterial pressures were measured by strain gauge manometers, calibrated daily, and the signals obtained displayed upon a multi channel, heated stylus recorder (Devices).

The signals obtained from the Statham SP2202 electromagnetic flowmeters were also continuously recorded on a multi channel heated stylus recorder.

Using the values obtained from the blood samples measured by the Lex-O_2-Con electrolytic cell and the blood flow recordings measured by the Statham SP2202 electromagnetic flowmeters, hepatic oxygen consumption was calculated using the following equation.

Hepatic Oxygen consumption (mls/min) =

$$\frac{\text{Portal venous blood flow}}{100} \times (\text{Portal venous oxygen content} - \text{hepatic venous oxygen content})$$

$$+$$

$$\frac{\text{Hepatic arterial blood flow}}{100} \times (\text{Hepatic arterial oxygen content} - \text{hepatic venous oxygen content})$$

where portal venous and hepatic arterial blood flow is in mls/min.

Using the portal venous and hepatic arterial blood flow values, the pressure values obtained and the cardiac output measurements made, the following vascular resistance measurements were calculated:-

$$\text{Peripheral (PR) resistance} = \frac{\text{Mean arterial pressure (mm Hg)}}{\text{Cardiac output (litres/min)}}$$

$$\text{Hepatic arterial resistance (HAR)} = \frac{\text{Hepatic arterial pressure - Hepatic venous pressure (mm Hg)}}{\text{Hepatic arterial flow (mls/min)}}$$

$$\text{Portal venous Resistance (PVR)} = \frac{\text{Portal venous pressure - hepatic venous pressure (mm Hg)}}{\text{Portal venous flow (mls/min)}}$$

$$\text{Mesenteric Vascular Resistance (MVR)} = \frac{\text{Systemic arterial pressure - portal venous pressure (mm Hg)}}{\text{Portal venous flow (mls/min)}}$$

Arterial PO_2, PCO_2 and pH measurements were made using appropriate electrodes (Corning). The pH electrode was calibrated using buffers of known pH and the oxygen and carbon dioxide electrodes were calibrated with gas mixtures of accurately known oxygen and carbon dioxide concentrations. As these electrodes were maintained at a constant temperature of 37°C, all measurements of blood pH, PCO_2, and PO_2 were corrected for any difference between the animal's core temperature and the electrodes using the blood gas calculator designed by Severinghaus (1966).

Since it appears that dogs maintain normally a compensated metabolic acidosis (Zweens, Frankena, Van Kampen, et al, 1977) the base deficit was maintained at 4 m mol/litre by the administration of molar sodium bicarbonate when required.

The haematocrit was measured at hourly intervals to ensure that it remained above 40 in all the dogs studied.

Throughout each investigation the fluid balance of the animal was maintained by the intravenous infusion of 0.9% sodium chloride at a rate of 15 mls/Kg body weight/hour.

Treatment of Results

In the presentation of results values are expressed as mean ± standard error of the mean (SEM). Mean pressures have been determined as the diastolic pressure plus one third pulse pressure. In all the experiments, Student's t test for paired data was used to analyse the difference between the control values and the later values. A probability of $P < 0.05$ was taken as significant in all cases.

As it has been shown that there is a good correlation between liver blood flow and liver weight (Torrance, 1961), hepatic arterial and portal venous blood flow are expressed as mls/100g liver weight/min (the liver was dissected out and weighed at the end of each experiment). Similarly, hepatic oxygen consumption is expressed as mls per 100g liver weight/min.

Cardiac output is expressed as litres per Kg body weight and splenic blood flow as mls per Kg body weight.

CHAPTER 4.

CONTROL EXPERIMENTS

In order to assess the stability of the preparation, six greyhounds were prepared surgically as described above. Approximately three hours elapsed between the induction of anaesthesia and the termination of surgery. The preparation was allowed to stabilise and control measurements were made. Control conditions were maintained and measurements were repeated at hourly intervals for three hours.

The following measurements were made:-

1. Mean arterial pressure.
2. Portal venous pressure.
3. Hepatic venous pressure.
4. Portal venous blood flow (PVBF).
5. Hepatic arterial blood flow (HABF).
6. Total liver blood flow (PVBF + HABF).
7. Splenic venous blood flow.
8. Cardiac output.
9. Hepatic oxygen consumption.

These results are detailed in Table I.

Venous blood samples were taken at the beginning and end of each experiment and analysed for serum electrolyte concentrations and liver function tests. The results of these are detailed in Table II.

With the exception of splenic blood flow at 2 hours, all the measurements obtained in the six dogs in this group remained stable throughout the period of study. The 20% decrease in splenic blood flow may have been associated with handling of this large viscus. Serum electrolyte values remained unchanged, however, there were rises in transaminase levels. The interpretation of these rises is difficult as they may well be simply due to the tissue damage associated with the initial surgery (Strunin, 1977).

There was a decrease in plasma protein values. This is probably because protein is lost through abdominal lymphatics which are inevitably transected during the preparatory surgery and fluid replacement could not be with protein containing fluids. However, this loss did not appear to affect cardiovascular function or liver blood flow over the experimental period.

It was therefore concluded that the greyhound preparation, as described, is stable over a period of at least three hours. All the experiments detailed hereafter were designed to be completed within this period of time.

TABLE I.

	Control	1 Hour	2 Hours	3 Hours
MAP (mm Hg)	125.8 ± 10.0	132.7 ± 9.3	134.3 ± 10.1	135.0 ± 10.3
Cardiac Output (litre/min / kg)	0.193 ± 0.012	0.191 ± 0.009	0.188 ± 0.009	0.203 ± 0.019
PVBF (ml/100g / min)	116.8 ± 10.9	115.4 ± 10.4	113.1 ± 8.3	121.2 ± 11.9
HABF (ml/100g / min)	33.5 ± 7.3	32.3 ± 7.7	29.1 ± 4.9	28.6 ± 6.4
TLBF (HABF + PVBF) (ml/100g / min)	150.3 ± 11.0	147.7 ± 9.9	142.2 ± 8.2	149.8 ± 12.2
Splenic Venous Blood Flow (ml/min / kg)	4.04 ± 0.78	3.60 ± 0.57	3.20 ± 0.59*	3.24 ± 0.6
Hepatic Oxygen Consumption (ml O_2/100g / min)	3.32 ± 0.70	3.70 ± 0.60	3.63 ± 0.33	3.52 ± 0.56
Portal Venous Pressure (mm Hg)	7.30 ± 0.93	7.35 ± 0.84	7.60 ± 1.14	8.30 ± 1.1
Hepatic Venous Pressure (mm Hg)	3.96 ± 1.41	3.46 ± 1.38	3.08 ± 1.12	2.66 ± 1.14

Results (Mean ± SEM) obtained in 6 control animals over a 3 hour period. Significant difference from the initial control value
*$P < 0.05$.

TABLE II.

	Control	3 Hours	
Urea	4.46 ± 0.13	4.64 ± 0.38	m mols/litre
Na	144.6 ± 3.1	147.4 ± 2.5	m mols/litre
K	3.76 ± 0.04	3.62 ± 0.18	m mols/litre
Cl	114.2 ± 1.96	121.4 ± 3.2	m mols/litre
Ca	1.88 ± 0.08	1.87 ± 0.07	m mols/litre
Mg	0.64 ± 0.04	0.59 ± 0.03	m mols/litre
PO_4	1.4 ± 0.09	1.7 ± 0.09	m mols/litre
Glucose	4.3 ± 0.6	3.9 ± 0.3	m mols/litre
Bilirubin	2.2 ± 0.9	3.2 ± 0.9	u mols/litre
Alk. Phos.	38 ± 3.2	47 ± 7.1	l units/litre
AS Transaminase	106 ± 24	251 ± 99*	l units/litre
Al Transaminase	121 ± 31	191 ± 59**	l units/litre
Total Protein	43.4 ± 3.5	34.6 ± 3.8*	g/litre
Albumin	21 ± 2	16.8 ± 2.0**	g/litre
Globulin	22.4 ± 2.4	17.8 ± 1.8	g/litre

Results (mean ± SEM) obtained in six control animals over a 3 hour period.
Significant differences from the initial value $P < 0.05$, $P < 0.01$.

CHAPTER 5.

THE EFFECT OF HYPERCARBIA UPON LIVER BLOOD FLOW AND OXYGEN CONSUMPTION

Experimental Protocol

Seven greyhounds were prepared surgically as previously described. The end tidal carbon dioxide concentration was monitored continuously by means of an infra red analyser (Goddart). The infra red carbon dioxide analyser cannot be used to provide an accurate estimate of $PaCO_2$ but does allow changes in $PaCO_2$ to be monitored (Nunn, 1977). Therefore this was used to allow a stable $PaCO_2$ to be maintained once the required tension had been achieved as shown by arterial blood gas analysis.

Following surgery the preparation was allowed to stabilise and baseline values were determined. Carbon dioxide was then added to the inspired gas mixture to achieve a $PaCO_2$ of 55 mm Hg (7.3 kPa). Mean arterial pressure, hepatic arterial blood flow, portal venous blood flow and splenic venous blood flow were all measured continuously. All the baseline measurements were repeated after twenty minutes of the raised $PaCO_2$ tension. The carbon dioxide was then withdrawn from the inspired gas mixture, and the preparation allowed to stabilise. Measurements of all the experimental values being studied were then repeated. Carbon dioxide was added and the same protocol repeated to achieve $PaCO_2$ tensions of 70 mm Hg (9.3 kPa), 85 mm Hg (11.3 kPa) and 100 mm Hg (13.3 kPa), returning to control $PaCO_2$ (40 mm Hg) between each step change.

Results

The mean arterial blood pressure decreased significantly at $PaCO_2$ values of 70, 85 and 100 mm Hg and there was no difference in the values obtained immediately (1-3 mins) or 20 min after administration of carbon dioxide. Cardiac output (measured only at 20 min) increased with each raised $PaCO_2$, the change being significant with a $PaCO_2$ of 100 mm Hg (Table III).

Hepatic arterial blood flow decreased significantly at all raised $PaCO_2$ tensions immediately on administration of the carbon dioxide, but by 20 min the decreases were significant only at a $PaCO_2$ of 85 mm Hg (Figs. 2, 3) (Table III). Likewise, the portal venous blood flow increased significantly with increased $PaCO_2$ in the initial measurements but by 20 min the increases were significant only at $PaCO_2$ tensions of 85 and 100 mm Hg (Figs. 2, 3) (Table III). The changes in portal venous blood flow were greater than those in hepatic arterial blood flow and as a result, total liver blood flow (the sum of the two) increased significantly at 85 and 100 mm Hg immediately after introduction of the CO_2 (Fig. 2) (Table III).

Portal venous pressure rose at all $PaCO_2$ tensions studied, significantly at a $PaCO_2$ of 55 and 100 mm Hg (Table III).

There was a significant decrease both in peripheral resistance with $PaCO_2$ tensions of 70, 85 and 100 mm Hg and in mesenteric vascular resistance (Table IV). It was only possible to measure the steady state changes in portal vascular resistance due to technical problems and this rose at each $PaCO_2$ studied, significantly only at 55 mm Hg. Hepatic arterial resistance increased significantly immediately after CO_2 was introduced, returning towards control by the

TABLE III.

	55 mm Hg			70 mm Hg		
	a	b	c	a	b	c
MAP (mm Hg)	109 ±8.9	111 ±9.8	111 ±10.2	118 ±10.6	107* ±10.6	106* ±10.2
Cardiac Output (litre/min / kg)	0.148 ±0.008		0.147 ±0.011	0.140 ±0.007		0.156 ±0.012
PVBF (ml/100g / min)	115.3 ±11.0	126.0 ±16.7	115.0 ±14.0	99.5 ±10.6	116.0* ±13.5	113.0 ±14.3
HABF (ml/100g/ min)	22.3 ±4.1	16.1* ±3.3	17.1 ±3.1	20.2 ±4.2	12.1** ±2.8	15.7 ±3.7
TLBF (HABF + PVBF) (ml/100g / min)	137.6 ±15.9	142.1 ±17.6	132.1 ±17.8	119.7 ±11.8	128.1 ±14.7	128.7 ±16.3
Splenic Venous Blood Flow (ml/min / kg)	5.89 ±2.22		5.56 ±3.39	4.83 ±1.86		4.92 ±3.58
Hepatic Oxygen Consumption (ml O_2/100g / min)	5.74 ±0.65		6.33 ±0.78	5.60 ±1.70		4.93 ±0.42
Hepatic Venous Oxygen Content (ml O_2/100 mls)	15.6 ±1.9		17.1 ±1.6	15.9 ±1.9		17.1 ±1.5
Portal Venous Pressure (mm Hg)	8.7 ±1.8		10.7* ±1.7	10.0 ±2.2		12.0 ±2.8
Haematocrit	0.50 ±0.03		0.54 ±0.04	0.53 ±0.03		0.55 ±0.03

Results (mean ± SEM) obtained in six animals subjected to increases in $PaCO_2$ (55, 70, 85 and 100 mm Hg). Results obtained immediately before each administration of carbon dioxide (a) and 1-3 min (b) and 20 min (c) after commencement of the administration are presented. Significant differences from values obtained at a * $P < 0.05$ ** $P < 0.01$

TABLE III.

(cont.)

	85 mm Hg			100 mm Hg		
	a	b	c	a	b	c
MAP (mm Hg)	117 ±11.8	102* ±11.8	102* ±10.6	118 ±11.4	102** ±11.0	97** ±11.0
Cardiac Output (litre/min / kg)	0.140 ±0.013		0.160 ±0.018	0.164 ±0.014		0.182* ±0.017
PVBF (ml/100g / min)	84.2 ±11.9	124.0** ±19.6	107.0* ±18.8	91.2 ±15.9	139.0* ±22.9	113.1* ±27.3
HABF (ml/100g / min)	21.5 ±3.6	11.2** ±2.2	15.9* ±3.3	23.7 ±3.9	10.5* ±1.9	16.9 ±3.1
TLBF (HABF + PVBF) (ml/100g / min)	105.7 ±12.7	135.2** ±18.8	123.9 ±18.8	114.9 ±15.9	149.5* ±22.0	130.0* ±24.6
Splenic Venous Blood Flow (ml/min / kg)	4.41 ±2.10		4.70 ±2.36	4.80 ±2.23		4.34 ±2.37
Hepatic Oxygen Consumption ($ml/O_2/100g$ / min)	4.86 ±2.13		5.62 ±1.22	5.85 ±3.41		6.0 ±2.81
Hepatic Venous Oxygen Content (ml O_2/100 mls)	17.1 ±1.8		17.3 ±1.3	15.9 ±1.4		18.1* ±1.5
Portal Venous Pressure (mm Hg)	9.8 ±2.6		12.4 ±1.8	11.6 ±2.8		14.3* ±2.9
Haematocrit	0.52 ±0.02		0.56* ±0.03	0.53 ±0.03		0.57* ±0.03

Results (mean ± SEM) obtained in six animals subjected to increases in $PaCO_2$ (55, 70, 85 and 100 mm Hg). Results obtained immediately before each administration of carbon dioxide (a) and 1-3 min (b) and 20 min (c) after commencement of the administration are presented. Significant differences from values obtained at a * $P < 0.05$

** $P < 0.01$

TABLE IV

	55 mm Hg			70 mm Hg		
	a	b	c	a	b	c
Peripheral Resistance mm Hg/l/min	24 ±3.24		26.3 ±4.01	28.1 ±2.9		22.6 ±2.7
Hepatic Arterial Resistance mm Hg/ml/min	1.12 ±0.26	1.53 ±0.38*	1.58 ±0.46	1.32 ±0.32	2.22 ±0.56*	1.74 ±0.51
Portal Venous Resistance mm Hg/ml/min $\times 10^5$	702 ±109		922 ±139	1106 ±217		1405 ±268
Mesenteric Vascular Resistance mm Hg/ml/min	0.17 ±0.02	0.16 ±0.02	0.17 ±0.02	0.21 ±0.02	0.17 ±0.02**	0.17 ±0.02*

Results (mean ± SEM) obtained in six animals subjected to increases in $PaCO_2$ (55, 70, 85 and 100 mm Hg). Results obtained immediately before each administration of carbon dioxide (a) and 1-3 min (b) and 20 min (c) after commencement of the administration are presented.
Significant differences from values obtained at a * $P < 0.05$
** $P < 0.01$

TABLE IV (cont.)

	85 mm Hg			100 mm Hg		
	a	b	c	a	b	c
Peripheral Resistance mm Hg/l/min	28.6 ±3.9		22.2 ±2.98*	23.8 ±2.9		18 ±2.68***
Hepatic Arterial Resistance mm Hg/ml/min	1.21 ±0.34	2.08 ±0.53*	2.06 ±0.7	1.2 ±0.35	3.17 ±0.9*	2.06 ±1.14
Portal Venous Resistance mm Hg/ml/min $x10^5$	1389 ±226		1426 ±234	1191 ±309		1786 ±425
Mesenteric Vascular Resistance mm Hg/ml/min	0.25 ±0.03	0.15 ±0.02**	0.18 ±0.02*	0.25 ±0.04	0.16 ±0.03*	0.21 ±0.05

Results (mean ± SEM) obtained in six animals subjected to increases in $PaCO_2$ (55, 70, 85 and 100 mm Hg). Results obtained immediately before each administration of carbon dioxide (a) and 1-3 min (b) and 20 min (c) after commencement of the administration are presented.
Significant differences from values obtained at a * $P < 0.05$
** $P < 0.01$

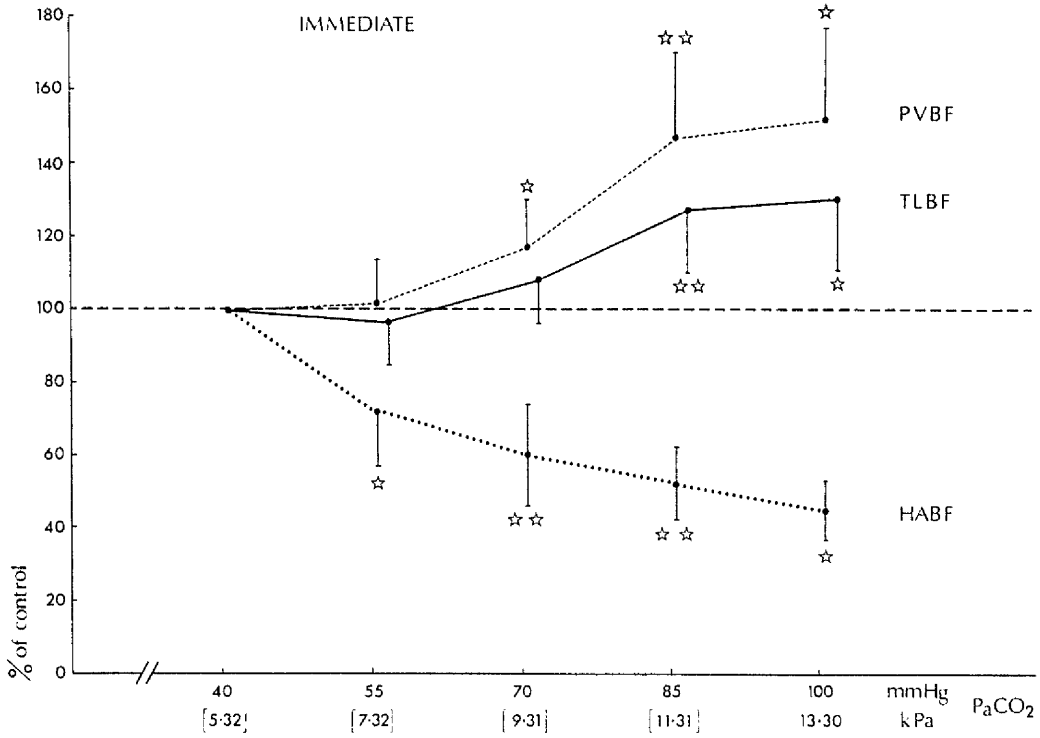

FIGURE 2. The effects of four tensions of carbon dioxide upon total liver blood flow (TLBF), portal venous blood flow (PVBF) and hepatic arterial blood flow (HABF) immediately after the administration of carbon dioxide. The values are shown as percentages of each preceding control value expressed as 100%; bars indicate ± SEM; *$P < 0.05$, ** $P < 0.01$. (The analysis was performed upon absolute values in Table III).

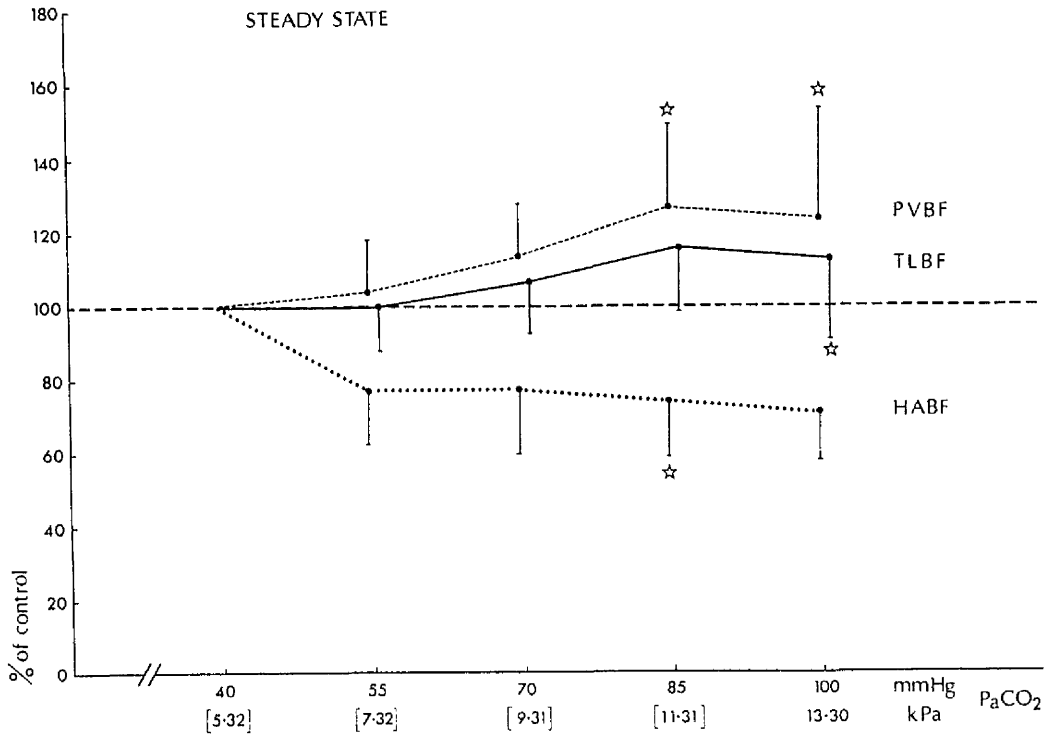

FIGURE 3. The effects of four tensions of carbon dioxide upon total liver blood flow (TLBF), portal venous blood flow (PVBF) and hepatic arterial blood flow (HABF) after a 20 min administration of carbon dioxide. The values are shown as percentages of each preceding control value expressed as 100%; bars indicate ± SEM; * $P < 0.05$. (The analysis was performed upon absolute values in Table III).

time twenty minutes had elapsed (Table IV) at all $PaCO_2$ tensions.

Hepatic oxygen consumption, twenty minutes after the addition of carbon dioxide did not change significantly from control (Table III). However, hepatic venous oxygen content increased significantly at a $PaCO_2$ of 100 mm Hg (Table III). Splenic blood flow did not change significantly at any $PaCO_2$ studied (Table III). The haematocrit increased significantly at $PaCO_2$ tensions of 85 and 100 mm Hg (Table III).

Discussion

Hypercarbia was seen in these experiments to result in a decrease in mesenteric vascular resistance and an increase in portal venous blood flow, that is splanchnic vasodilation.

This increase in portal venous blood flow confirms previous results (Tashkin, Goldstein and Simmons, 1969; Scholtholt and Shiraishi, 1970; Dutton, Levitsky and Berkman, 1976) obtained in the dog with electromagnetic flow meters. However, Epstein, Wheeler, Frumin, et al (1961) showed a decrease in estimated liver blood flow in man with hypercarbia using the bromsulphthalein clearance technique. Apart from possible inaccuracies due to the measurement technique (vide supra), anaesthesia was maintained with only nitrous oxide which may have resulted in stress due to too light anaesthesia and therefore splanchnic vasoconstriction. A more recent report by Juhl and Einer-Jensen (1977) in dogs showed a decrease in liver blood flow and increase in splanchnic resistance in the presence of decreased peripheral resistance. These somewhat confusing results could be due to the use of the anaesthetic agent fluroxene, which stimulates the sympathetic nervous system, (Cullen

Eger, Smith, et al, 1971).

The observation that the major change in resistance across the splanchnic and liver vascular beds is to be seen in the splanchnic bed, confirms the findings of Tashkin, Goldstein and Simmons, 1969.

However, none of these other studies measured portal venous blood flow continuously but only took measurements some considerable time after the introduction of carbon dioxide. Continuous recording of portal venous blood flow demonstrates that there is a biphasic response to hypercarbia in the splanchnic bed. This biphasic response to carbon dioxide has been previously described in the coronary vessels (Kittle, Aoki and Brown, 1965). It has been suggested that the direct depressant effect of carbon dioxide produces an initial vasodilatation followed by a sympathetically mediated vasoconstriction (Manley, Nash and Woodbury, 1964). Alternatively, this biphasic change may be due to the presence of autoregulation in the splanchnic vessels (Johnson, 1967) of the greyhound.

The observed decrease in hepatic arterial blood flow was accompanied by an increase in hepatic arterial resistance, again in a biphasic manner but in the opposite direction to the changes in portal flow. The decrease in total peripheral vascular resistance and mesenteric vascular resistance produced by hypercarbia in these experiments taken with the increase in cerebral blood flow (Harper, Glass and Glover, 1961) and myocardial blood flow (Ledingham, McBride, Parratt, et al, 1970) previously described suggests that this initial decrease in hepatic arterial blood flow is a local phenomenon. It seems possible that this decrease in

hepatic arterial blood flow is due to the observed increase in portal venous pressure and by inference hepatic sinusoidal pressure producing a mechanical impedance to hepatic arterial blood flow. This hypothesis is supported by the demonstration that small increases in portal venous pressure similar to those seen in this investigation result in a marked decrease in hepatic arterial blood flow (Ternberg and Butcher, 1965; Hanson and Johnson, 1966; Lutz, Peiper and Bauereisen, 1968). This is thought to be due to a myogenic mechanism being primarily responsible for the control of hepatic arterial blood flow (Hanson and Johnson, 1966). The biphasic nature of this change in hepatic arterial blood flow may be simply due to a myogenic response to the changes in portal venous blood flow. However, in addition, it may be that the hepatic artery rapidly escapes any neurogenic stimuli produced by the increase in CO_2 (Mundschau, Zimmerman, Gildersleeve, et al, 1966; Lautt, 1977) leaving only the response due to the myogenic mechanism.

In this study there was a progressive decrease in the base-line values for portal venous blood flow after each administration of carbon dioxide. The control series demonstrated that portal venous blood flow remains stable in this preparation if it is not exposed to carbon dioxide. This would suggest that the secondary increase in portal venous tone seen with carbon dioxide administration persists after withdrawal of the gas, resulting in the decreased baseline values.

Although there were no significant changes in hepatic oxygen consumption at any $PaCO_2$ studied, hepatic venous oxygen content increased significantly suggesting that, in the steady state, carbon dioxide does not affect oxygen consumption by the liver

and, in view of the increased liver blood flow and therefore oxygen supply, may be beneficial.

As some 15-20% of portal venous blood flow in the greyhound was seen to be supplied by the splenic vein it was considered of value to see if hypercarbia affected splenic venous blood flow. It has been previously shown that severe hypercarbia (30% carbon dioxide) produced splenic contraction (Ramlo and Brown, 1959); however, at the tensions of carbon dioxide studied in these investigations no significant change in splenic blood flow were seen. However, small, but significant increases in haematocrit were seen at $PaCO_2$ tensions of 85 and 100 mm Hg. It has been shown that the spleen is the most important vascular reservoir in the dog (Guntheroth and Mullins, 1963) and it would seem likely that a degree of splenic contraction, too small to affect flow may be occurring with hypercarbia.

Cardiac output was seen to increase with the higher tensions of carbon dioxide studied. This appears to be a universal finding in studies in dogs and man, the only exception being studies on conscious dogs (Horvitz, Bishop and Stone, 1968) it being suggested that general anaesthesia blocks a vagal mediated depressant effect of carbon dioxide.

Mean arterial pressure decreased in these experiments at $PaCO_2$ tensions of 70 mm Hg and above. In man, moderate hypercarbia appears to result in an increase in blood pressure (Sechzer, Egbert, Linde, et al, 1960; Richardson, Wasserman and Patterson, 1961) accompanied by a decrease in peripheral resistance while in dogs this decrease in peripheral resistance usually is accompanied by an unchanged or decreased mean arterial pressure (Kittle, Aoki

and Brown, 1965; Horwitz, Bishop and Stone, 1968; Tashkin, Goldstein and Simmons, 1969; Dutton, Levitzky and Berkman, 1976). It can therefore be inferred that the smooth muscle relaxant effect of carbon dioxide on peripheral blood vessels predominates in the greyhound, over the central sympathetic stimulation (Price, 1960).

In conclusion, this data demonstrates that hypercarbia in the greyhound produces an increase in liver blood flow without affecting oxygen consumption. This effect could prove valuable in a liver with a compromised blood supply.

CHAPTER 6.

THE EFFECT OF HYPOCARBIA AND INTERMITTENT POSITIVE PRESSURE VENTILATION UPON LIVER BLOOD FLOW AND OXYGEN CONSUMPTION

Experimental Protocol

Eleven greyhounds were prepared surgically as previously described. The end tidal carbon dioxide concentration was monitored continuously by means of an infra red analyser. As in the hypercarbia experiments, this was used to allow a stable $PaCO_2$ to be maintained; once the required tension had been achieved as shown by arterial blood gas analysis. Approximately three hours after the induction of anaesthesia baseline values were determined.

In eight of the dogs the following protocol was observed. The peak inspiratory airway pressure, measured on an aneroid manometer by means of a cannula passed through the endotracheal tube to the carina, was raised by 5 cms H_2O by increasing the tidal volume delivered by the ventilator and after twenty minutes the alterations in the various indices being measured were noted. This rise in tidal volume, as well as increasing airway pressure, produced hypocarbia. Carbon dioxide was then added to the inspired gas mixture, to return the $PaCO_2$ to 40 ± 2 mm Hg while maintaining the raised airway pressure and increased tidal volume. Measurements of the experimental values under study were then repeated. The carbon dioxide was then withdrawn and the tidal volume reduced to restore the airway pressure to control. The animal was allowed to stabilise and control measurements were

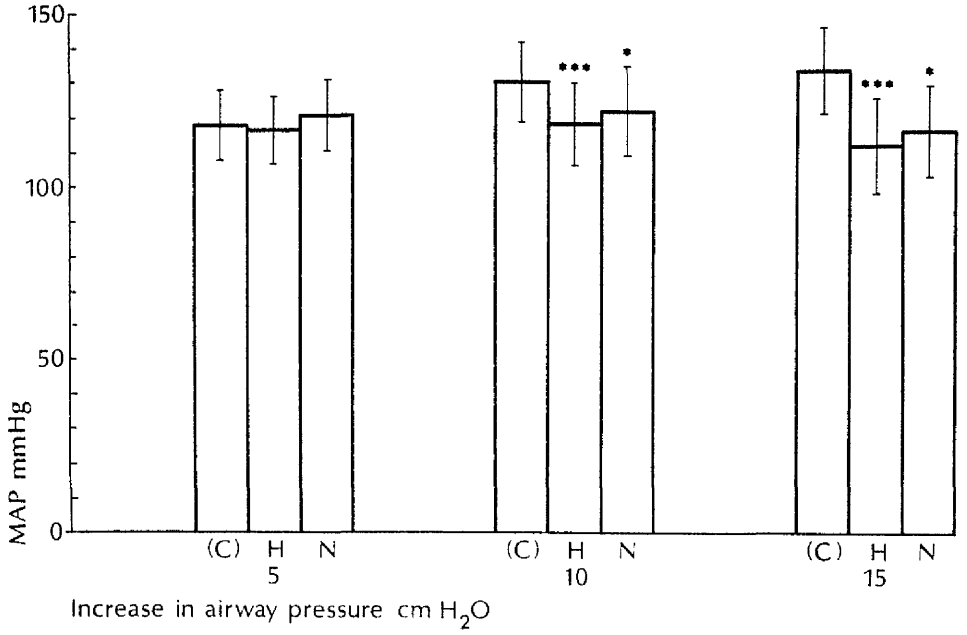

FIGURE 4. Effect of increasing airway pressures on mean arterial pressure (MAP). Each column is the mean of 8 observations ± SEM and each group of columns consists of control (C), hypocarbic (H) and normocarbic (N) observations. Significant differences from control observations. *$P < 0.05$, ***$P < 0.001$.

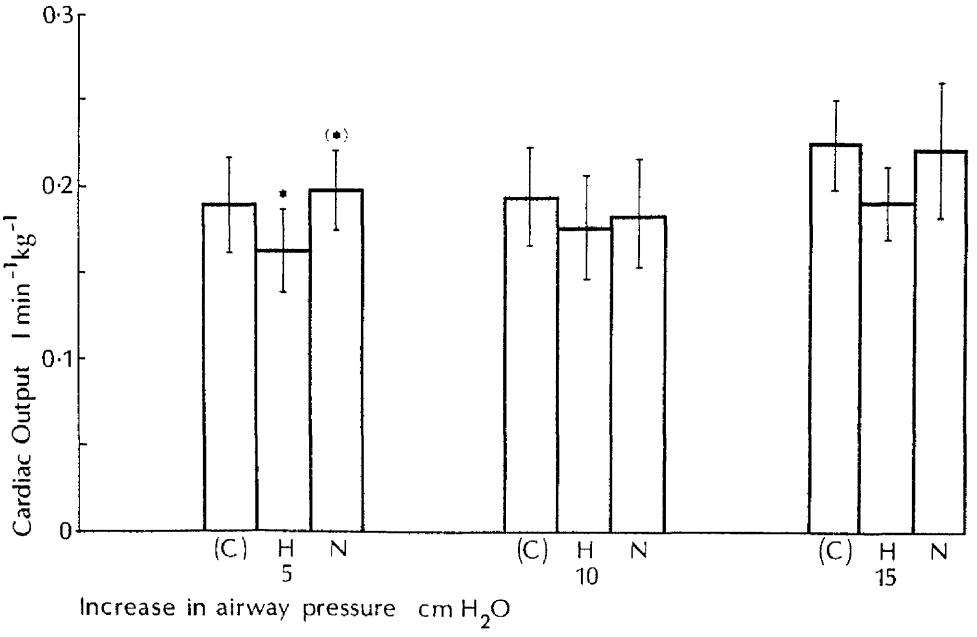

FIGURE 5. Effect of increasing airway pressure on cardiac output (l/min/kg body wt). Each column is the mean of 8 observations ± SEM and each group of columns consists of control (C), hypocarbic (H) and normocarbic (N) observations. Significant differences from control observations: *P < 0.05; and from hypocarbia (*) P < 0.05.

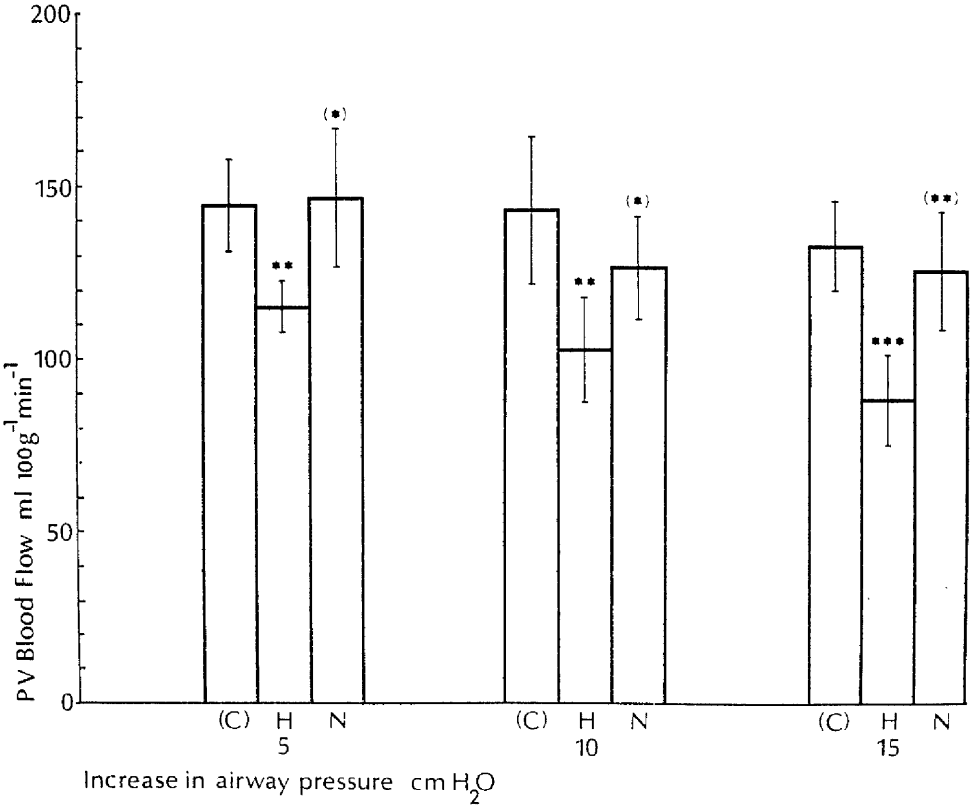

FIGURE 6. The effect of increasing airway pressure on portal venous blood flow in mls/min/100g liver wt. Each column is the mean of 8 observations ± SEM and each group of columns consist of control (C), hypocarbic (H) and normocarbic (N) observations. Significant differences from control observations ** $P < 0.01$, *** $P < 0.001$; from hypocarbia (*) $P < 0.05$, (**) $P < 0.01$.

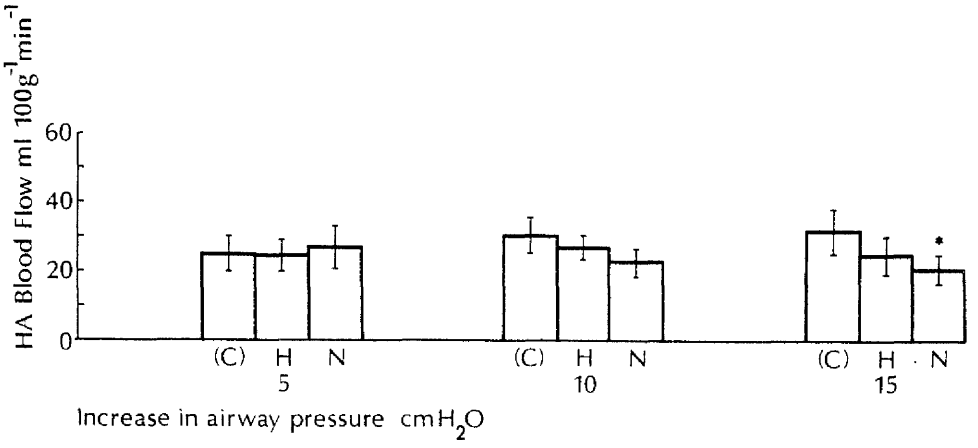

FIGURE 7. The effect of increasing airway pressure on hepatic arterial blood flow in mls/min/100g liver wt. Each column is the mean of 8 observations ± SEM and each group of columns consist of control (C), hypocarbic (H) and normocarbic (N) observations. Significant differences from control observations *P < 0.05.

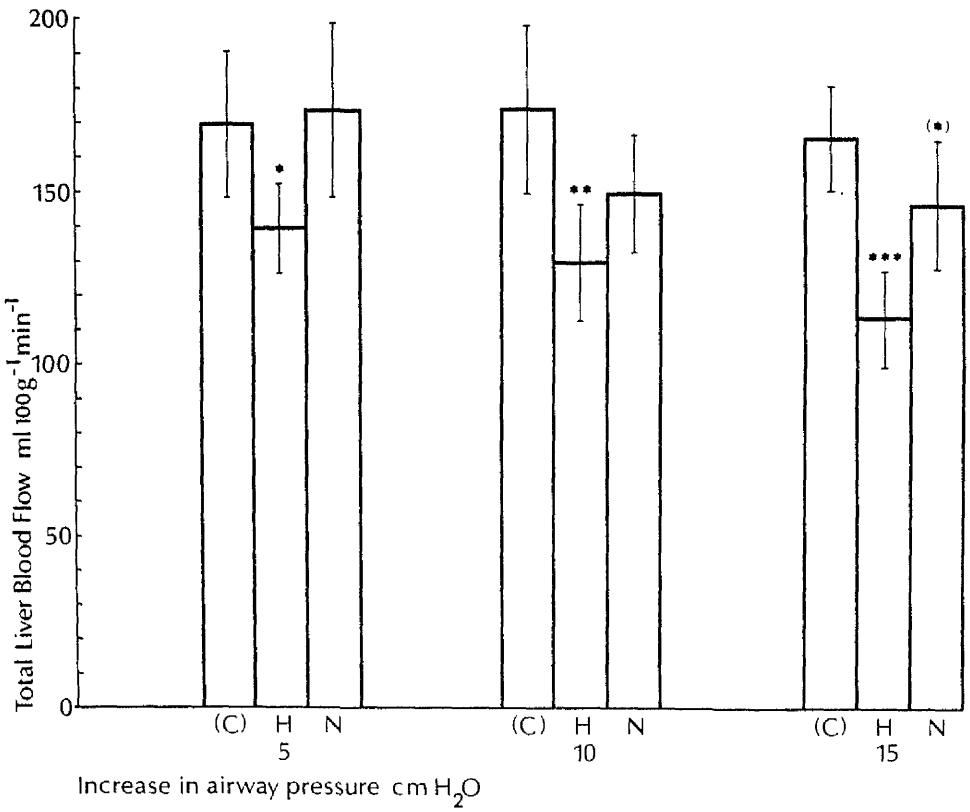

FIGURE 8. The effect of increasing airway pressure on total liver blood flow in mls/min/100g liver wt. Each column is the mean of 8 observations ± SEM and each group of columns consist of control (C), hypocarbic (H) and normocarbic (N) observations. Significant differences from control observations *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$; from hypocarbia (*)$P < 0.05$.

TABLE V.

	Hepatic O_2 Consumption (ml/min /100g liver wt).	Splenic Blood flow (ml/min/ kg body wt).	Portal Venous pressure (mm Hg)	Hepatic Venous Pressure (mm Hg)	Carbon dioxide Tension (mm Hg)
Control	5.51 ±0.61	4.42 ±0.1	7.91 ±1.18	0.48 ±0.29	41.6 ±1.3
Hypocarbia 5cm H_2O raised AP	5.98 ±0.82	3.42 ±0.72*	7.91 ±1.19	0.25 ±0.46	30.7 ±1.4
Normocarbia	6.53 ±0.78	3.66 ±0.92	8.53 ±1.38***	0.56 ±0.79	40.4 ±0.7
Control	6.98 ±1.21	3.71 ±0.8	8.2 ±1.02	0.23 ±0.51	38.6 ±0.5
Hypocarbia 10cm H_2O raised AP	6.23 ±1.13	2.79 ±0.62*	9.0 ±0.99*	1.05 ±0.41*	22.7 ±1.1
Normocarbia	6.25 ±1.1	3.0 ±0.72	9.75 ±0.88***(*)	1.17 ±0.33	38.2 ±1.2
Control	6.64 ±0.7	3.1 ±0.68	9.14 ±0.92	0.16 ±0.49	38.9 ±0.36
Hypocarbia 15cm H_2O raised AP	5.42 ±0.87	2.28 ±0.68*	10.46 ±1.11*	2.18 ±0.56*	17.3 ±1.72
Normocarbia	7.03 ±0.87(*)	3.54 ±0.91**	10.78 ±1.31*	1.34 ±0.55*	39.2 ±1.34

The effect of hypocarbia and raised airway pressure (AP) upon hepatic oxygen consumption, splenic blood flow, portal and hepatic venous pressure and $PaCO_2$. Values are mean ± SEM *$P < 0.05$; ***$P < 0.001$ relative to control; (*)$P < 0.05$ relative to the hypocarbic measurements.

TABLE VI.

	Peripheral Resistance mm Hg/l/min	Hepatic Arterial Resistance mm Hg/ml/min	Portal Venous Resistance mm Hg/ml/min x10^5	Mesenteric Resistance mm Hg/ml/min
Control	27.9 ±3.42	1.22 ±0.38	102.8 ±14.3	0.15 ±0.08
Hypocarbia	32.8 ±4.5*	1.09 ±0.31	126.6 ±15.7*	0.18 ±0.021*
5 cm H_2O raised AP				
Normocarbia	28.3 ±4.7(*)	1.23 ±0.41	113.8 ±16.1(*)	0.15 ±0.021(*)
Control	27.5 ±4.2	0.79 ±0.14	125.6 ±18.9	0.17 ±0.023
Hypocarbia	28.2 ±4.3	0.84 ±0.19	161 ±22.4**	0.21 ±0.028*
10 cm H_2O raised AP				
Normocarbia	28.2 ±5.1	1.24 ±0.4	146.2 ±21	0.17 ±0.021
Control	26.4 ±5.1	1.22 ±0.35	147.7 ±25.1	0.19 ±0.027
Hypocarbia	22.0 ±2.7	1.16 ±0.35	191.2 ±25.1*	0.24 0.042*
15 cm H_2O raised AP				
Normocarbia	22.3 ±3.5	1.14 ±0.22	159.7 ±31.5(**)	0.18(**) ±0.37

The effect of hypocarbia and raised airway pressure (AP) upon vascular resistance. Values are mean ± SEM *P < 0.05; **P < 0.01 relative to control (*)P < 0.05, (**)P < 0.01 relative to hypocarbic measurements.

repeated. This sequence, was repeated at airway pressures of 10 and 15 cms H_2O above control. These resulted in $PaCO_2$ tensions of 22.7 ± 1.1 mm Hg and 17.3 ± 1.7 mm Hg (Table V).

To investigate whether the effects seen on returning $PaCO_2$ to normal were due to time, three further dogs were hyperventilated for 40 minutes, without the addition of CO_2 at each airway pressure studied, returning to control between measurements. Measurements of the indices under study were made at 20 and 40 minutes after each period of hyperventilation began.

Results

The mean baseline airway pressure was 10.9 ± 2.2 cms H_2O. The $PaCO_2$ tensions obtained with each airway pressure are detailed in Table V.

When the airway pressure was raised by 10 and 15 cms from baseline, the mean arterial pressure decreased significantly, increasing towards the control value when normocarbia was restored, but still remaining significantly depressed (Fig. 4).

Cardiac output (Fig. 5) decreased at each level of raised airway pressure, significantly at 5 cm H_2O. When carbon dioxide was added the cardiac output increased to control or an even higher level.

Portal venous (PV) blood flow decreased significantly (Fig. 6) with each increase in airway pressure but when normocarbia was restored the flow increased significantly to near control values.

The hepatic arterial (HA) blood flow decreased with each rise in airway pressure (Fig. 7), a further small decrease being seen

when carbon dioxide was added, this was significant at the 15 cm H_2O raised airway pressure. The effect on total liver blood flow (Fig. 8) obtained by adding the HA and PV blood flows was similar to that seen in PV blood flow.

Total peripheral resistance (Table VI) increased significantly at a raised airway pressure of 5 cm H_2O, returning to control with the addition of carbon dioxide, however, it remained unchanged at the two higher raised airway pressures. Portal venous and mesenteric vascular resistance increased significantly with each increase in airway pressure, decreasing significantly towards control at each pressure when carbon dioxide was added (Table VI). Hepatic arterial resistance did not change significantly at any time (Table VI). Portal venous pressure (Table V) increased significantly with raised airway pressures of 10 and 15 cms H_2O increasing further with the addition of carbon dioxide. Hepatic venous pressure increased significantly at raised airway pressures of 10 and 15 cms H_2O (Table V).

Hepatic oxygen consumption (Table V) decreased at 10 and 15 cms H_2O raised airway pressure in parallel with liver blood flow and increased significantly at the 15 cm raised airway pressure with the restoration of normocarbia. Hepatic venous oxygen content was unchanged.

Splenic venous blood flow decreased significantly at all levels of raised airway pressure, increasing significantly to above control levels at 15 cms H_2O raised airway pressure when carbon dioxide was added (Table V).

In the three further dogs in which hypocarbia was maintained for 40 mins, there were no significant differences

between any of the measurements made at 20 and 40 minutes, suggesting the changes detailed above were not due to the passage of time.

Discussion

It was seen in these investigations that portal venous blood flow decreased progressively with each increase in airway pressure but returned towards control levels when normocarbia was restored. The portal pressure was seen to rise with increased airway pressure and to rise still further when carbon dioxide was added. It has been shown that increases in hepatic venous pressure result in passive increases in portal venous pressure with a passive decrease in portal venous blood flow (Hanson and Johnson, 1966; Lutz, Peiper and Bauereisen, 1968). As described in the previous chapter carbon dioxide increases portal venous blood flow, i.e. by producing splanchnic vasodilatation, in a progressive manner when hypercarbic $PaCO_2$ tensions are produced. This relationship between carbon dioxide tension and portal venous blood flow was shown in this series of investigations to be maintained at sub-normal carbon dioxide tensions, in that with decreasing $PaCO_2$ portal venous blood flow decreased and portal venous and mesenteric vascular resistance increased.

It has been shown by several authors that hyperventilation with uncompensated hypocarbia results in a decrease in portal venous blood flow (Goldstein, Simmons and Tashkin, 1972; Johnson, 1975, and Scholtholt and Shiraishi, 1970). However, the only attempt to separate the effects of I.P.P.V. (intermittent positive pressure ventilation) and hypocarbia has been by Johnson (1975)

who showed no difference in portal venous blood flow between a group of dogs hyperventilated and made normocarbic and a group of dogs which remained hypocarbic, findings which suggested that the changes seen in portal venous blood flow were due to I.P.P.V. alone and that the blood carbon dioxide tension plays no role. However, she only studied the effects of extreme hyperventilation (tidal volume 40ml/Kg and a $PaCO_2$ of approximately 8 mm Hg), producing a 3 mm Hg rise in hepatic venous pressure. The arterial PCO_2 tensions achieved in the present study were 30, 22 and 17 mm Hg (Table V) at +5, 10 and 15 cms H_2O airway pressure respectively, with a maximal rise in hepatic venous pressure of 2 cms H_2O at an airway pressure of +15 cm H_2O and it is noticeable that recovery of portal venous blood flow on changing to normocarbic hyperventilation is less complete at the higher airway pressures. It is suggested therefore that the rise in hepatic venous pressure produced by extreme hyperventilation is too great an impediment to portal venous blood flow for the splanchnic vasodilator effect of carbon dioxide to overcome but that at the lesser degree of hyperventilation seen in this study the addition of carbon dioxide to the inspired gas, to restore normocarbia, can largely reverse the reduction in portal venous blood flow produced by intermittent positive pressure ventilation and hypocarbia. Two other important differences between the studies were that Johnson's dogs were ventilated at a frequency almost twice that of this series and she does not state what species of dogs she studied. It was decided to confine the experiments described in this thesis to greyhounds, as it was found in preliminary experiments that there was a wide variability in the cardiovascular responses to various stimuli

between different breeds of dog.

The changes seen in hepatic arterial blood flow were small. However, at 10 and 15 cm H_2O raised airway pressures, there was a decrease with the restoration of normocarbia; these changes were both significant at 15 cms H_2O raised airway pressure. The changes seen in hepatic arterial resistance were variable and not significant; it is said that the interpretation of vascular resistance changes in the presence of a varying mean arterial pressure is difficult (Green, Lewis, Nickerson, et al, 1944; Mundschau, Zimmerman, Gildersleeve, et al, 1966).

As discussed in connection with the hypercarbia experiments, hepatic arterial blood flow is thought to be regulated by an intrinsic myogenic mechanism (Hinshaw, Reins and Wittmers, 1965; Hanson and Johnson, 1966; and Lutz, Peiper and Bauereisen, 1968). This could explain the effects seen in these experiments, that is the increase in hepatic venous pressure would produce an increase in hepatic arteriolar pressure and a decrease in hepatic arterial blood flow. The further decrease in hepatic arterial blood flow seen when carbon dioxide is added, could be expected from this mechanism, as the rise in portal venous blood flow produced, would result in more pressure being reflected back to the hepatic arterioles. This decrease in hepatic arterial blood flow has been seen with hypercarbia in the experiments described in the previous chapter. The pattern of the decrease in hepatic arterial blood flow was similar to that described in the previous chapter; that is, with the addition of carbon dioxide there was an immediate large decrease in hepatic arterial blood flow, with an increase towards control by 20 mins.

Hepatic oxygen consumption fell, although not significantly, during hyperventilation, returning to control levels with a significant increase at the 15 cms H_2O raised airway pressure, with the addition of carbon dioxide. This was accompanied by an unchanged hepatic venous oxygen content. These results suggest that a reduction in aerobic metabolism takes place in the liver during hypocarbic alkalosis. This would agree with the finding of hyperlactatemia during hypocarbia in dogs by some authors (Berry and Scheur, 1967; Zborowska-Sluis and Dosseter, 1967). This hyperlactataemia is a compensation for the respiratory alkalosis (Eichenholz, Mulhausen, Anderson, et al, 1962), but may be primarily of extrahepatic origin (Goldstein, Tashkin and Simmons, 1972).

It was seen that splenic venous blood flow decreased significantly with hypocarbic hyperventilation but a recovery to control levels was seen only when normocarbia was restored at a raised airway pressure of 15 cms H_2O. This suggests that the rise in portal pressure recorded with hyperventilation also affects splenic venous tone with a resultant decrease in flow. The slight effect of carbon dioxide on splenic blood flow confirms the studies previously described upon the effect of moderate hypercarbia on splenic blood flow. However, Ramlo and Brown (1959) showed that severe hypercarbia produces splenic contraction and it would seem that the stimulus produced by the large increase in inspired concentration of carbon dioxide needed to restore normocarbia at a raised airway pressure of 15 cms H_2O is sufficient to elicit this response.

While there have been conflicting results regarding the

effects of hypocarbia on cardiac output and mean arterial pressure, both in the dog and man (Rowe, Castillo and Crumpton, 1962; Kontos, Mauck, Richardson, et al, 1965; Cooperman, Warden and Price, 1968) the results in this series of experiments confirm several previous observations both in animals and man (Prys-Roberts and Kelman, 1966; Theye, Milde and Michenfelder, 1966; Morgan, Crawford, Hornbein, et al, 1967; Moster, Reier, Gardier, et al, 1969), in that hypocarbia and intermittent positive pressure ventilation both have separate effects on cardiac output and mean arterial pressure. It is possible that different background anaesthetic techniques, ventilatory patterns and in one case the substitution of positive negative ventilation for intermittent positive pressure ventilation may explain their varying results. It was decided in the series described above to use a ventilatory pattern that is commonly used in clinical practice and that allowed stepwise increases in airway pressure to be made.

In the greyhound therefore, it was found that hyperventilation with hypocarbia accompanied by moderately raised airway pressures, produced a large decrease in portal venous blood flow and small decrease in hepatic arterial blood flow with a possible reduction in aerobic metabolism. These undesirable effects are largely reversed if normocarbia is produced by the addition of carbon dioxide and it would seem therefore that intermittent positive pressure ventilation at normal $PaCO_2$ tensions at the pressures seen in routine clinical practice has little deleterious effect upon the liver.

CHAPTER 7.

THE EFFECT OF HYPEROXIA UPON LIVER BLOOD FLOW AND OXYGEN CONSUMPTION

Experimental Protocol

Six greyhounds were prepared surgically as previously described.

The PaO_2 was continuously monitored using an intra-arterial polarographic electrode (IBC differential oxygen analyser) the readings of which were confirmed by arterial blood gas analysis (Corning 165) before experimental measurements were made.

Approximately three hours after the induction of anaesthesia baseline values were determined. The PaO_2 was then increased to 200 mm Hg (26.6 kPa) by increasing the inspired oxygen concentration and decreasing the inspired nitrogen concentration thus maintaining the ventilatory minute volume and therefore $PaCO_2$ at control values (40 mm Hg). Measurement of liver blood flow and mean arterial pressure were made continuously. All the indices under study were measured after twenty minutes of hyperoxia. The PaO_2 was then returned to control of 100 mm Hg (13.3 kPa) and after the animal had stabilised the baseline measurements were repeated. This sequence was repeated at PaO_2 tensions of 300 mm Hg (39.9 kPa) and 400 mm Hg (53.2 kPa), returning to control between each increased tension.

Results

The results are presented in Table VII. No significant changes in mean arterial pressure, cardiac output, portal venous blood flow, hepatic arterial blood flow or total liver blood flow

TABLE VII

	Control	200 mm Hg	Control	300 mm Hg	Control	400 mm Hg
MAP (mm Hg)	108.6 ± 9.3	113.7 ± 10.1	116 ± 10.3	116.5 ± 10.5	117 ± 9.4	119 ± 10
Cardiac Output (litre/min/kg)	0.218 ±0.02	0.212 ±0.028	0.216 ±0.029	0.199 ±0.029	0.197 ±0.039	0.197 ±0.041
PVBF (ml/100g/min)	103.4 ± 12.6	97.9 ±10.3	96.7 ± 8.9	95.4 ±10.0	89.9 ± 7.7	93.8 ± 9.0
HABF (ml/100g/min)	30.1 ± 4.2	30.3 ± 3.4	26.3 ± 3.1	26.3 ± 3.7	25.4 ± 3.0	23.9 ± 2.75
TLBF (ml/100g/min)	133.5 ± 16.3	128.2 ± 13.1	122.9 ± 11.1	121.7 ± 13.0	115.3 ± 9.8	117.7 ± 10.8

The effect of increasing arterial tensions of oxygen (PaO_2) upon mean arterial pressure, cardiac output, portal venous blood flow (PVBF), hepatic arterial blood flow (HABF) and total liver blood flow (TLBF) 20 min after increasing the PaO_2. The values are ± SEM.

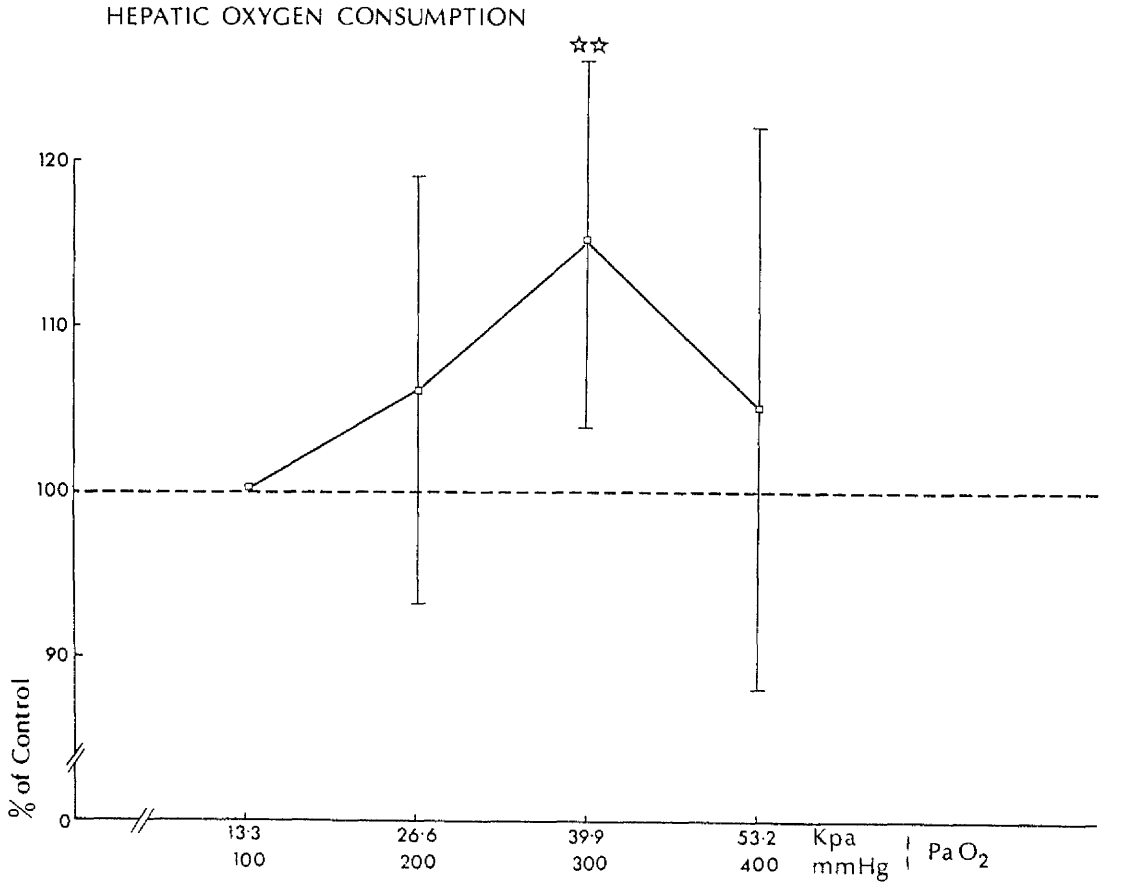

FIGURE 9. The effect of three increased arterial tensions of oxygen (PaO_2) upon hepatic oxygen consumption measured 20 min after increasing PaO_2. The values are expressed as percentages of each preceding control (each control equals 100%). Bars indicate ± SEM ** indicate significance of $P < 0.01$ (the analysis was performed upon the absolute values obtained).

were noted at any of the hyperoxic tensions studied. However, hepatic oxygen consumption rose at all three PaO_2 tensions, from the initial control value of 4.7 mls/100 g/min, significantly at a PaO_2 of 300 mm Hg (Fig. 9).

Discussion

It has previously been shown that 100% oxygen breathing at hyperbaric atmospheric pressure reduces myocardial contractility (Smith and Ledingham, 1972) and that small but significant reductions in cardiac output and regional perfusion are seen both in animals and man with 100% oxygen breathing at normal atmospheric pressures (Eggers, Paley and Leonard, 1962; Murray, Fukud and Jacob, 1964; Bergovsky and Bertun, 1966). The effects seen at normal atmospheric pressures were slight however, and at the lesser degrees of hyperoxia seen in this study no changes were evident. Similarly these degrees of hyperoxia produced no effects on either portal venous blood flow or hepatic arterial blood flow. Galindo (1965) has shown that hyperbaric oxygen has no effect upon liver blood flow and it is not surprising therefore, that levels of hyperoxia seen in routine clinical practice also have no effect.

Small increases in hepatic oxygen consumption (at 300 mm Hg) were seen in this investigation. This suggests that in the anaesthetised greyhound the oxygen supply to the liver at a normal PaO_2 of 100 mm Hg is marginally inadequate.

CHAPTER 8.

THE EFFECT OF HYPOXIA UPON LIVER BLOOD FLOW AND OXYGEN CONSUMPTION

Experimental Protocol

Seven greyhounds were prepared surgically in the routine manner described.

As in the hyperoxia experiments, the PaO_2 was continuously monitored using an IBC differential oxygen analyser.

After surgery was completed and the preparation had stabilised, baseline measurements were determined at a PaO_2 of 100 mm Hg (13.3 kPa). The PaO_2 was then lowered to 70 mm Hg (9.3 kPa) by decreasing the inspired oxygen concentration and increasing the nitrogen concentration, thus maintaining the ventilatory minute volume and the $PaCO_2$ at the control of 40 mm Hg (5.3 kPa). As in previous experiments, liver blood flow and mean arterial pressure were measured continuously, while measurements of these and the other indices under study were repeated 20 min after the start of the hypoxic period. The inspired gases were then returned to control concentrations, and after the animal had stabilised the baseline measurements were repeated. This sequence, returning to control PaO_2 of 100 mm Hg between each decreased tension was repeated at PaO_2 of 55 mm Hg (7.3 kPa), 40 mm Hg (5.3 kPa) and 25 mm Hg (3.3 kPa).

Results

It was found at each hypoxic tension that mean arterial

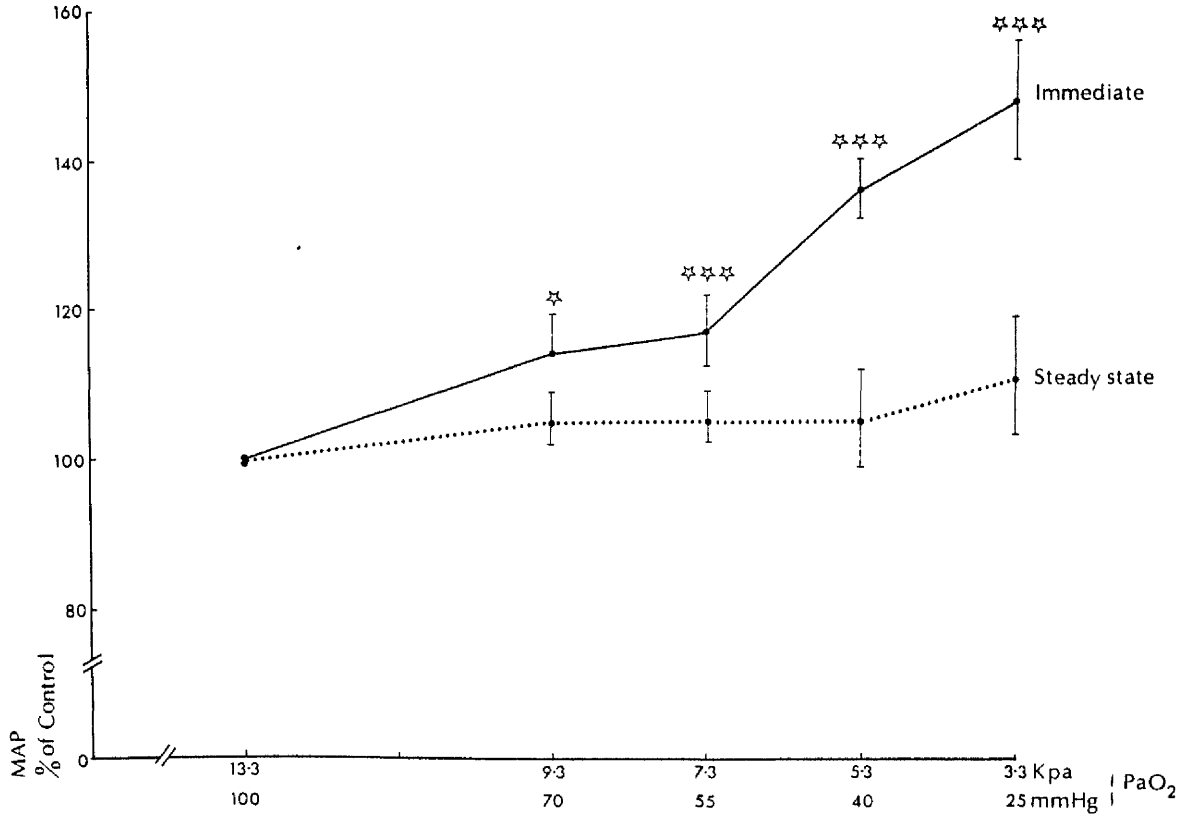

FIGURE 10. The effect of four decreased arterial tensions of oxygen (PaO_2) upon mean arterial pressure (MAP) both immediately and 20 min after decreasing PaO_2. The values are expressed as percentages of each preceding control (each control equals 100%). Bars indicate ± SEM. * indicates significance of $P < 0.05$, ***$P < 0.001$ (the analysis was performed upon the absolute values obtained).

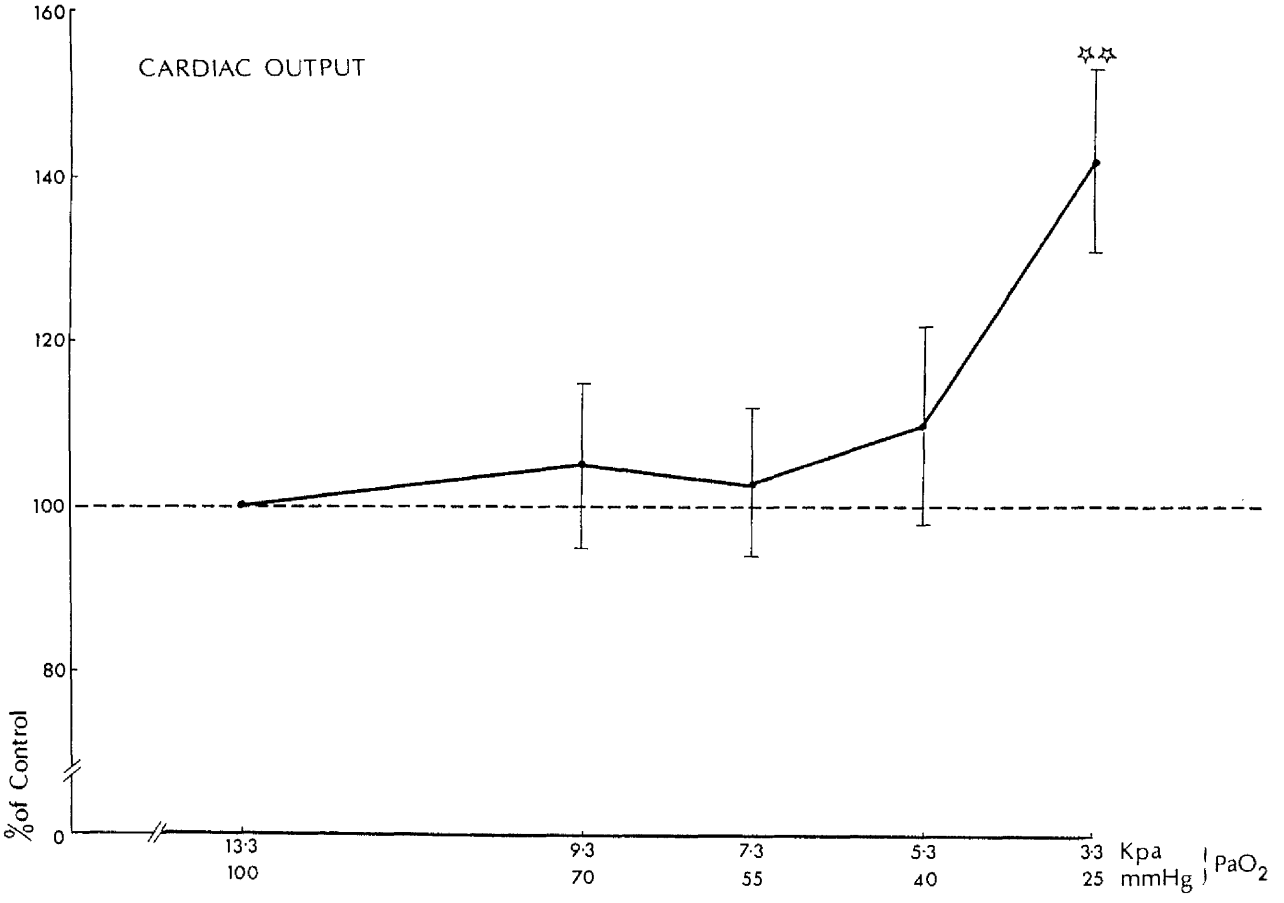

FIGURE 11. The effect of four decreased arterial tensions of oxygen (PaO_2) upon cardiac output 20 min after decreasing PaO_2. The values are expressed as percentages of each preceding control (each control equals 100%). Bars indicate $\pm$ SEM. ** indicate significance of $P < 0.01$ (the analysis was performed upon the absolute value obtained).

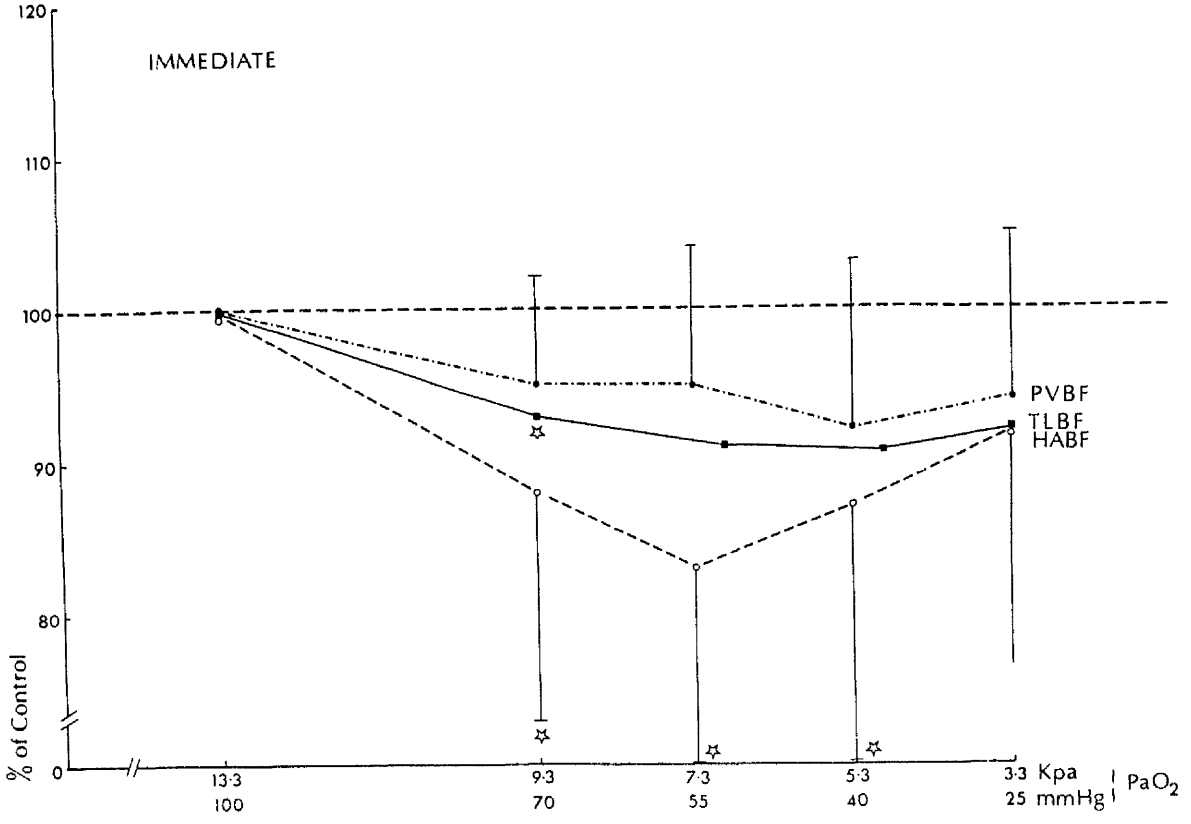

FIGURE 12. The effect of four decreased arterial tensions of oxygen (PaO_2) upon total liver blood flow (TLBF), portal venous blood flow (PVBF) and hepatic arterial blood flow (HABF) immediately after decreasing PaO_2. The values are expressed as percentages of each preceding control (each control equals 100%). Bars indicate $\pm$ SEM. * indicates significance of $P < 0.05$ (the analysis was performed upon the absolute values obtained.

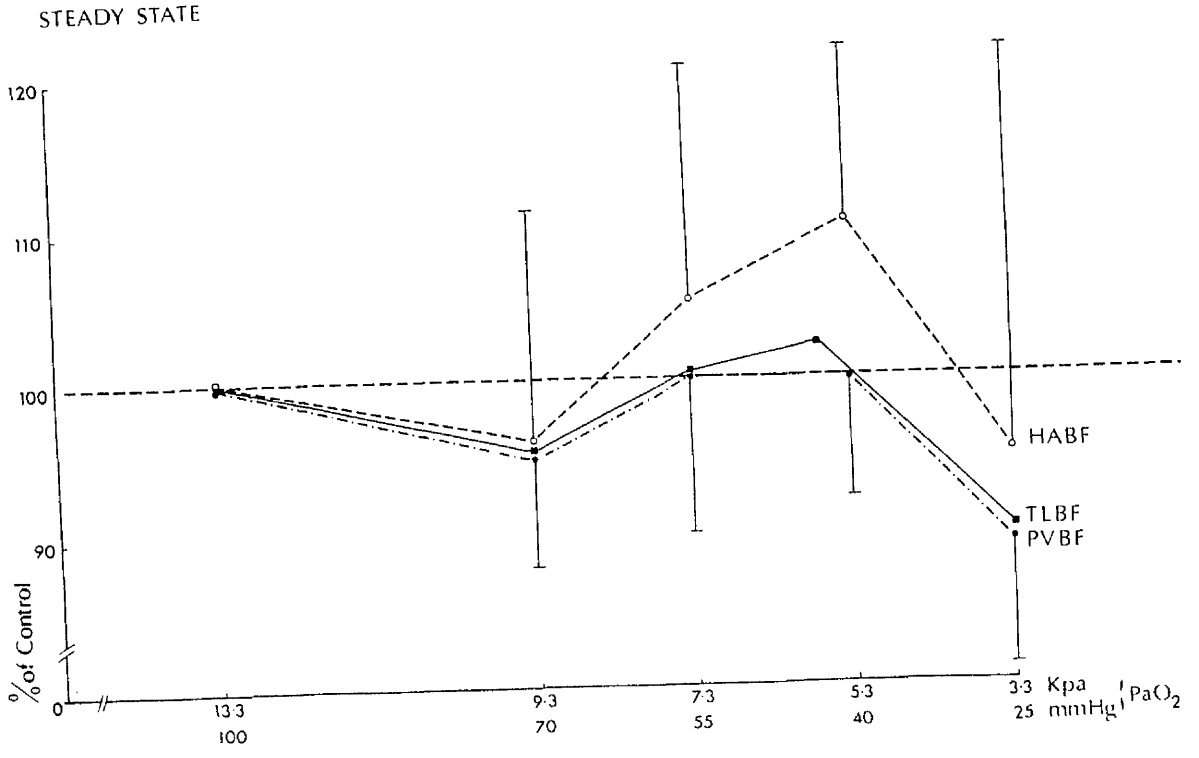

FIGURE 13. The effect of four decreased arterial tensions of oxygen (PaO_2) upon total liver blood flow (TLBF), portal venous blood flow (PVBF) and hepatic arterial blood flow (HABF) 20 min after decreasing PaO_2. The values are expressed as percentages of each preceding control (each control equals 100%). Bars indicate ± SEM.

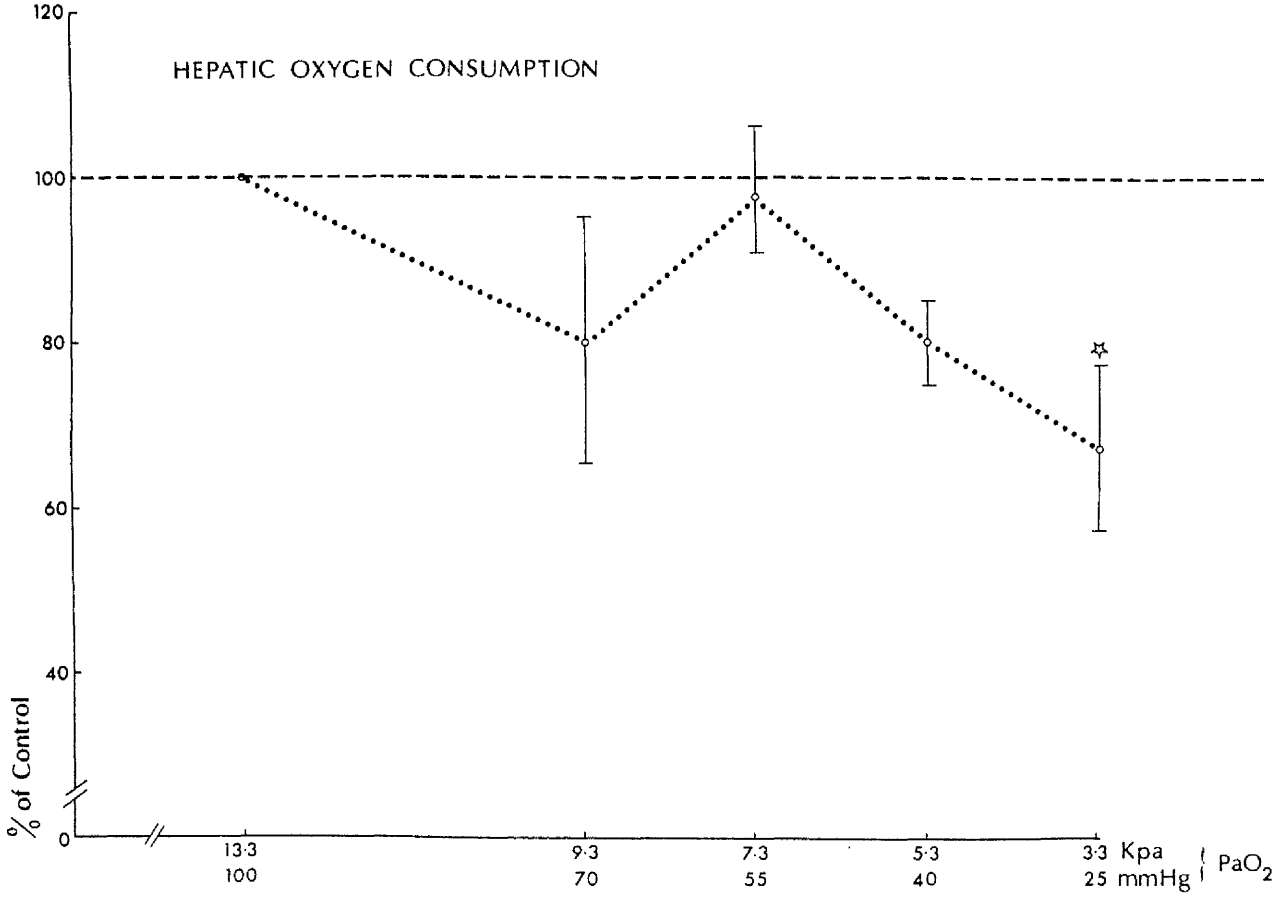

FIGURE 14. The effect of four decreased arterial tensions of oxygen (PaO_2) upon hepatic oxygen consumption measured 20 min after decreasing PaO_2. The values are expressed as percentages of each preceding control (each control equals 100%). Bars indicate ± SEM. * indicates significance of $P < 0.05$ (the analysis was performed upon the absolute values obtained).

	Control	70 mm Hg	Control	55 mm Hg	Control	40 mm Hg	Control	25 mm Hg
H.A.R.	0.52 ±0.07	0.65* ±0.09	0.52 ±0.08	0.77* ±0.13	0.49 ±0.11	0.78* ±0.20	0.45 ±0.07	0.81* ±0.17
M.V.R.	0.169 ±0.017	0.197* ±0.019	0.182 ±0.021	0.217** ±0.02	0.176 ±0.012	0.270* ±0.036	0.176 ±0.016	0.282* ±0.044

TABLE VIII

The immediate effect of four decreased arterial oxygen tensions (PaO_2) upon hepatic arterial resistance (HAR) and mesenteric vascular resistance (MVR) (mm Hg per ml per min). The values are ± SEM. *indicates a significance of $P < 0.05$; ** $P < 0.01$.

TABLE IX

	Control	70 mm Hg	Control	55 mm Hg	Control	40 mm Hg	Control	25 mm Hg
Hepatic Venous Pressure (mm Hg)	1.03 ±1.3	0.71 ±1.5	0.92 ±1.3	0.78 ±1.5	1.1 ±1.2	1.05 ±0.9	1.8 ±0.95	2.0 ±1.2
Portal Venous Pressure (mm Hg)	6.3 ±1.2	7.0 ±1.1	7.8 ±1.3	8.0 ±1.3	7.8 ±1.2	9.1 ±1.23	7.7 ±1.3	8.6 ±1.1
Splenic Blood Flow (mls/min/kg body wt)	5.64 ±0.78	5.04 ±0.69	4.86 ±0.56	4.76 ±0.8	4.46 ±0.81	4.27 ±0.71	5.4 ±0.87	4.91 ±0.58
Hepatic Venous Oxygen Content (mls/100mls)	12.65 ± 0.83	13.3 ± 0.83	14.1 ± 0.66	11.6*** ± 0.62	14.1 ± 0.53	9.4* ±0.72	14.7 ± 0.83	3.2*** ±0.71

The effect of four decreased arterial oxygen tensions (PaO_2) upon hepatic and portal venous pressure, splenic blood flow and hepatic venous oxygen content, twenty minutes after hypoxia was instituted. The values are ± SEM. * indicates a significance of $P < 0.05$ *** $P < 0.001$.

TABLE X.

Mean Arterial Blood Pressure	110.5 mm Hg
Cardiac Output	0.177 litres/min/kg body wt.
Portal Venous Blood Flow	122 mls/min/100g liver wt.
Hepatic Arterial Blood Flow	49.5 mls/min/100g liver wt
Hepatic Oxygen Consumption	4.7 mls/min/100g liver wt.

The initial control values for mean arterial pressure, cardiac output, portal venous blood flow, hepatic arterial blood flow and hepatic oxygen consumption, preceding the hypoxia experiments.

pressure increased significantly immediately after the introduction of the hypoxic gas mixture but returned to control values by the time 20 min had passed (Fig. 10). Cardiac output, measured 20 min after the start of each hypoxic period, was significantly increased at the 25 mm Hg PaO_2 tension (Fig. 11).

No significant changes were seen in portal venous blood flow at any PaO_2 tension studied, either immediately or in the steady state (Figs. 12 and 13). Hepatic arterial blood flow decreased significantly at all tensions except 25 mm Hg immediately hypoxia commenced (Fig. 12) but returned to control values or above by 20 min (Fig. 13). Total liver blood flow which was obtained by adding the hepatic arterial and portal venous blood flows, decreased immediately after hypoxia commenced (Fig. 12) but returned to control values at all except a PaO_2 of 25 mm Hg. This decrease was only significant at the 70 mm Hg PaO_2 tension. The response of hepatic arterial and portal venous blood flow was variable at 25 mm Hg. Hepatic arterial and mesenteric vascular resistances both increased significantly at all PaO_2 tensions studied, immediately after introduction of the hypoxic gas mixture (Table VIII).

A small decrease, which was not significant, was seen in splenic venous blood flow at each PaO_2 after 20 min hypoxia (Table IX). Hepatic oxygen consumption measured after 20 min hypoxia, decreased at all tensions (Fig. 14) only significantly at a PaO_2 of 25 mm Hg. Hepatic venous oxygen content decreased significantly at PaO_2 tensions of 55 mm Hg and below (Table IX).

There were no significant changes in hepatic and portal venous pressures (Table IX). The initial control values for

mean arterial pressure, cardiac output, portal venous blood flow, hepatic arterial blood flow and hepatic oxygen consumption are stated in Table X.

Discussion

There have been a considerable number of studies upon the effects of hypoxia upon hepatic arterial and portal venous blood flow over the last few years (Fischer, Takacs and Molnar, 1960; Matsuno, 1969; Scholtholt and Shiraishi, 1970; Tashkin, Goldstein and Simmons, 1972; Ishikawa, Matsui, Fukumura, et al, 1974; Larsen, Krarup and Munck, 1976; Meyer, Berkman and Dutton, 1977). The majority of these reported no significant changes but those which showed changes appear to contradict each other. This may be because "hypoxia" was a single arbitrary arterial oxygen tension ranging from a moderate to a very severe level in these studies. Another important feature in almost all these reports is that the authors did not continuously measure flow but took measurements at one time only, usually after 30 min hypoxia. The experiments carried out in this series confirm the previous reports that portal venous blood flow is unchanged, with the exception of the study by Meyer, et al, 1977 which reported a decrease in portal venous blood flow. However, although the small immediate decrease in portal venous flow seen in the present investigation was not significant, it was accompanied by a significant increase in mesenteric vascular resistance soon after hypoxia was instituted.

A larger significant decrease was seen in hepatic arterial blood flow accompanied by an increase in hepatic arterial resistance immediately the PaO_2 was reduced. This had returned to or above

control, by the time 20 min had elapsed. Similar observations of a transient decrease in hepatic arterial blood flow have been made in cats by Larsen, Krarup and Munck (1976) while in the dog Fischer, Takacs and Molnar (1959), using a rotameter, showed a rapid irreversible decrease in hepatic arterial blood flow with hypoxia (this may have been due to the measurement technique). The other reports all demonstrate a rise or non significant change by 30 min. It has been demonstrated (Mundschau, Zimmerman, Gildersleeve, et al, 1966; Lautt, 1977) that the hepatic artery rapidly escapes a centrally mediated vasoconstriction in the dog and this is the possible cause of the effect seen in this series. Indeed, since the dog, unlike man, (Cunningham, Aldrete and Mays, 1976) cannot survive ligature of the hepatic artery such an escape mechanism would be necessary for the animal's survival. The most likely explanation for the hepatic arterial vasoconstriction seen in this series is that it is merely involved in the chemoreceptor mediated, general vasoconstrictor response to hypoxia (Krasney, 1971). The rise in mesenteric vascular resistance seen would lend support to this hypothesis. An alternative mechanism could be provided by the similar transient increase in pulmonary vascular resistance with hypoxia which has been described previously (Malik and Kidd, 1973; Tucker and Reeves, 1975) producing back pressure upon the hepatic veins and therefore arterioles and provoking the myogenic vasoconstriction discussed in the carbon dioxide experiments. The observation that the hepatic venous pressure was unchanged in this series makes this mechanism unlikely.

Splenic venous blood flow was little affected by hypoxia even

at a PaO_2 of 25 mm Hg. In this it reacted in the same way as portal venous blood flow. It was of interest to note that if the PaO_2 was allowed to fall below 25 mm Hg there was an acute, large rise in systemic arterial pressure, followed by cardiovascular collapse. The spleen contributed to this stress response with a large increase in outflow. At the same time a large rise in hepatic arterial blood flow was seen, possibly due to local mechanisms overriding the central stress response.

Hepatic oxygen consumption decreased only significantly at a PaO_2 of 25 mm Hg. Other workers have shown in the cat (Lutz, Henrich and Bauereisen, 1975; Larsen, Krarup and Munck, 1976) that, under hypoxic conditions extraction of oxygen by the liver can approach 100% and it has been shown in the guinea pig and mouse that hypoxia must be severe before hepatic excretory function is affected (Shorey, Schenker and Combes, 1969). The liver of the anaesthetised greyhound also extracts oxygen very efficiently, the mechanism only failing at very low PaO_2 tensions. It was seen that at a PaO_2 of 25 mm Hg hepatic venous oxygen content was only 20% of control.

Hypoxia, even of a mild degree, produced a significant rise in mean arterial pressure but by the time steady state measurements were taken 20 min later, it had returned to control values. This pressor effect has been well documented in paralysed ventilated dogs (Kontos, Mauck, Richardson, et al, 1965; Krasney, 1971) but these workers do not appear to have studied the hypoxic effects for more than 10 min. However, it has been shown in cats (Larsen, Krarup and Munck, 1976) that hypoxaemia causes an immediate increase in systemic arterial blood pressure which lasts about 10 min, then

returning to or below control levels.

Cardiac output, measured after 20 min, was only seen to increase at a PaO_2 of 25 mm Hg. This is in keeping with the findings of Kontos, et al (1965) who showed no increase at a PaO_2 of 33 mm Hg and Krasney (1971) who showed a significant increase at a PaO_2 of 24 mm Hg.

In conclusion, in these experiments it was seen that even mild hypoxia produced a marked transient rise in systemic arterial pressure accompanied by a rise in hepatic arterial resistance, and a smaller rise in mesenteric vascular resistance. It was also seen that the liver maintains oxygen consumption and presumably normal function until severe hypoxia occurs.

CHAPTER 9.

THE EFFECT OF METABOLIC ACIDOSIS UPON LIVER BLOOD FLOW AND OXYGEN CONSUMPTION

Experimental Protocol

Eight greyhounds were prepared surgically as previously described.

After the completion of surgery and the preparation had stabilised, baseline control values were determined at a PaO_2 of 100 mm Hg (13.3 kPa) and a $PaCO_2$ of 40 mm Hg (5.3 kPa). The base deficit was maintained at 4 mequivs/litre as this appears to be the normal value for dogs (Zweens, Frankena, Kampen, et al, 1977).

A molar solution of lactic acid was infused intravenously at a rate of 0.1 ml/kg/min by means of a syringe pump. Repeated, frequent blood gas and pH measurements were made and the base deficit calculated. The end tidal CO_2 concentration was measured continuously by means of a capnograph and kept stable by adjustment of the tidal volume. Liver blood flows and mean arterial blood pressure were measured continuously. Measurements of the other indices under study were repeated when a base deficit of 5, 10 and 15 mequivs/litre relative to control was achieved.

Results

With a base deficit of 5 and 10 mequivs/litre there was a small but significant rise in mean arterial blood pressure which returned towards control of 130 mm Hg by the time 15 mequivs/litre

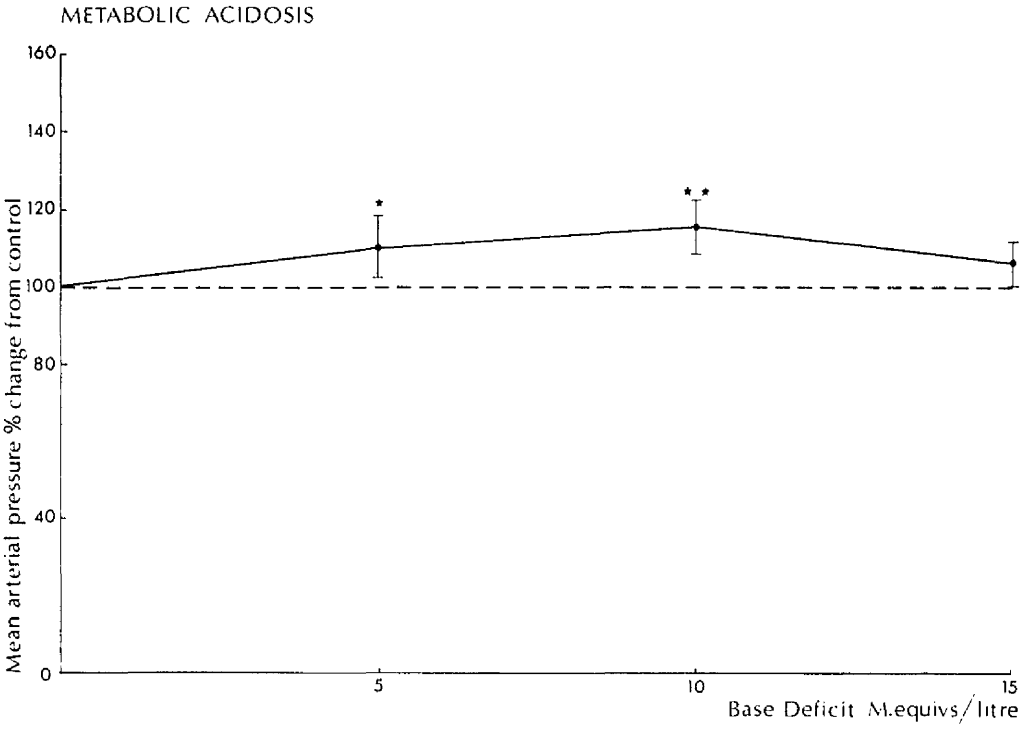

FIGURE 15. The effect of a base deficit of 5, 10 and 15 mequivs/litre upon mean arterial blood pressure. The values are expressed as percentages of the control (control equals 100%). Bars indicate ± SEM. * indicates significance of $P < 0.05$ **$P < 0.01$, (the analysis was performed upon the absolute values obtained).

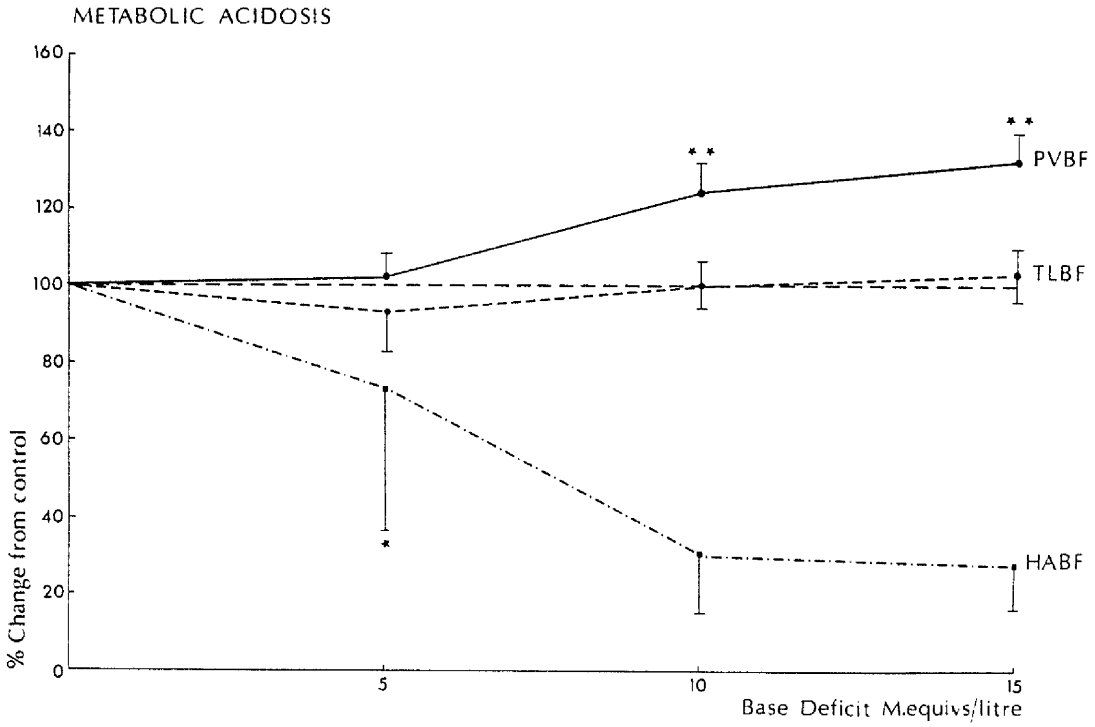

FIGURE 16. The effect of a base deficit of 5, 10 and 15 mequivs/litre upon portal venous blood flow (PVBF), hepatic arterial blood flow (HABF) and total liver blood flow (TLBF). The values are expressed as percentages of the control (control equals 100%). Bars indicate ± SEM. * indicates significance of $P < 0.05$, ** $P < 0.01$ (the analysis was performed upon the absolute values obtained).

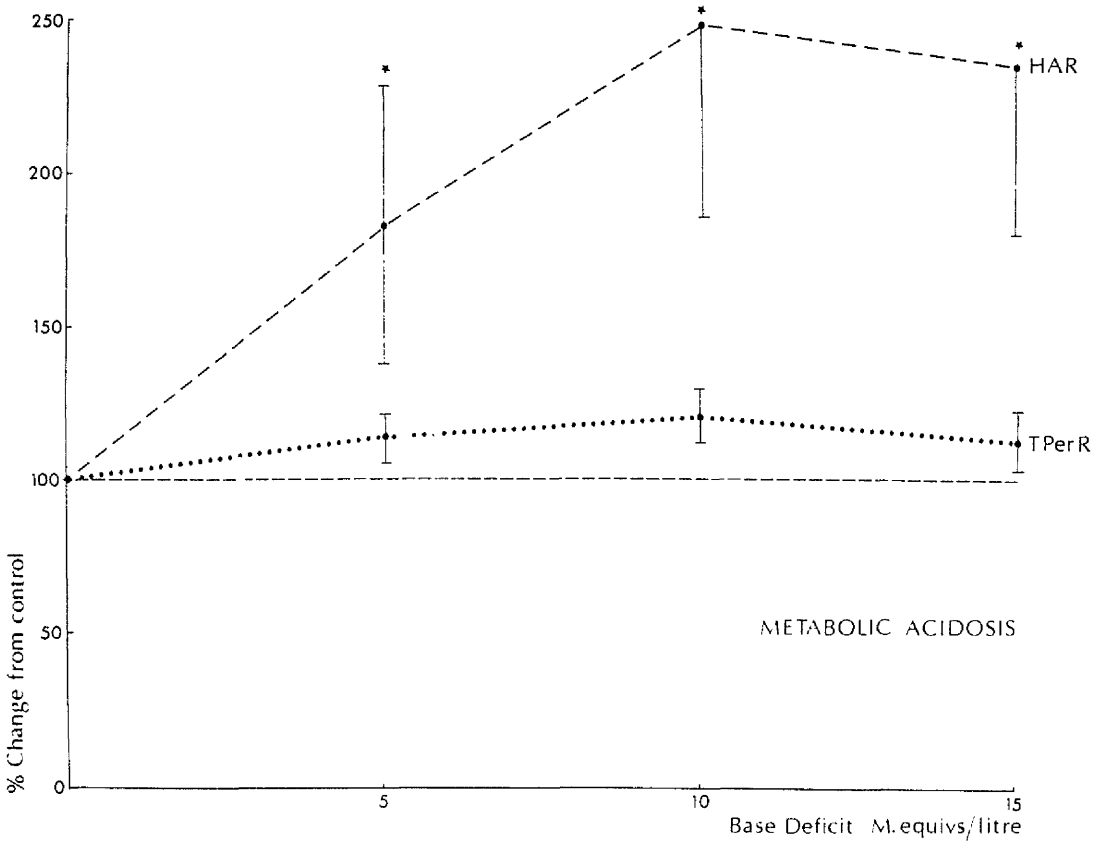

FIGURE 17. The effect of a base deficit of 5, 10 and 15 mequivs/litre upon hepatic arterial resistance (HAR) and total peripheral resistance (T Per R). The values are expressed as percentages of the control (control equals 100%). Bars indicate ± SEM. * indicates significance of $P < 0.05$ (the analysis was performed upon the absolute values obtained).

TABLE XI

	Control	5 mequivs/litre	10 mequivs/litre	15 mequivs/litre
Cardiac Output (litres/min/kg body wt)	0.125 ±0.017	0.110 ±0.008	0.110 ±0.008	0.114 ±0.012
Splenic Venous Blood Flow (mls/min/kg body wt)	5.64 ±0.9	5.31 ±0.87	5.49 ±0.87	4.78 ±0.73
Portal Venous Pressure (mm Hg)	7.08 ±0.59	8.78** ±0.75	11.2*** ± 0.87	11.6*** ± 1.33
Hepatic Venous Pressure (mm Hg)	2.28 ±0.76	2.33 ±0.54	2.7 ±0.64	3.05 ±0.87
Hepatic Oxygen Consumption (ml/min/100g liver wt)	3.92 ±0.59	4.13 ±0.95	4.96 ±0.67	5.1 ±0.67
Hepatic Venous Oxygen Content (ml/100ml)	12.2 ± 0.74	10.6* ± 0.82	9.93* ±0.74	9.13* ±0.31

The effect of a base deficit of 5, 10 and 15 mequivs/litre upon cardiac output, splenic venous blood flow, portal venous pressure, hepatic venous pressure, hepatic oxygen consumption and hepatic venous oxygen content. The values are ± SEM. * indicates a significance of $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$.

was achieved (Fig. 15). There were no significant changes in cardiac output (Table XI).

There was a significant increase in portal venous blood flow (PVBF) from the control value of 94.2 mls/100g liver wt/min at the 10 and 15 mequiv/litre base deficits (Fig. 16). Hepatic arterial blood flow (HABF) decreased at all three base deficits studied from the control value of 35.2 mls/100g liver wt/min, significantly at 5 mequivs/litre (Fig. 16). Total liver blood flow was unchanged at all three base deficits (Fig. 16).

There were no significant changes in total peripheral resistance at any base deficit but hepatic arterial resistance increased significantly at all three base deficits (Fig. 17). There were no significant changes in portal venous resistance or mesenteric vascular resistance. Portal venous pressure rose significantly at all three base deficits while there were no significant changes in hepatic venous pressure (Table XI).

There was an increase in hepatic oxygen consumption, failing to reach significance at each base deficit studied. However, there was a significant decrease in hepatic venous oxygen content at each base deficit (Table XI).

There were no significant changes in splenic venous blood flow (Table XI).

Discussion

Metabolic acidosis is a common clinical problem resulting from circulatory failure, as in shock (Schumer, 1966; Wiener and Spitzer, 1974; Garcia-Barreno and Balibrea, 1978), ventilatory

failure (Broder and Weil, 1964) and sometimes spontaneously (Huckabee, 1971).

There is little information available upon the effects of metabolic acidosis on liver blood flow. It has been shown in cats (McGinn, Mendel and Perry, 1967) that an infusion of hydrochloric acid produced no change in superior mesenteric arterial blood flow. However the $PaCO_2$ in these experiments was less than 25 mm Hg. In Chapter 6 of this thesis, it was shown that hypocarbia produces a decrease in portal venous blood flow and it is possible that in McGinn, et al's experiments, this balanced the effect of the metabolic acidosis resulting in unchanged portal blood flow. In the rat (Yudkin, Cohen and Slack, 1976) metabolic acidosis produced by the oral administration of ammonium chloride resulted in a reduction in estimated hepatic blood flow. In a small series of dogs (Goldstein, Simmons and Tashkin, 1972) variable effects on liver blood flow were produced by an infusion of hydrochloric acid, but when the acidosis was corrected, hepatic arterial blood flow increased markedly.

In the greyhound, with normocarbia it appears that metabolic acidosis produced by an infusion of lactic acid results in an increase in portal venous blood flow, accompanied by a marked decrease in hepatic arterial blood flow, resulting in an unchanged total liver blood flow. The reduction in hepatic arterial blood flow was accompanied by a large increase in hepatic arterial resistance in the presence of a virtually unchanged peripheral resistance (Fig. 17). This suggests that the effect seen in the hepatic artery is a local phenomenon. It has been shown that a rise in hepatic sinusoidal pressure results in an increase in tone

in hepatic arterioles possibly by a myogenic mechanism (Hanson and Johnson, 1966; Lutz, Peiper and Bauereisen, 1968). In this series of experiments a significant increase in portal venous pressure and by inference sinusoidal pressure was seen at each base deficit studied (Table XI). This could partly be explained by the significant increase in portal venous blood flow at the larger base deficits (Fig. 16), but another mechanism, possibly an increase in tone in one of the several hepatic outlet sphincters which have been described (Knisely, Harding and Debacker, 1957) must also be involved. This interaction between portal venous and hepatic arterial circulations appears similar to that already described in hypercarbic greyhounds.

An increase in hepatic oxygen consumption which was not significant was accompanied by a significant decrease in hepatic venous oxygen content showing an increased oxygen extraction in the presence of an unchanged liver blood flow. This may be due to the increased lactic acid being presented to the liver in these experiments as it has been shown that the liver deals with this aerobically unless marked hypotension occurs (Ballinger, Vollenweider and Montgomery, 1961; Bashour and McLelland, 1967). This decrease in hepatic venous oxygen content is also due to a larger proportion of the unchanged total liver blood flow being poorly oxygenated portal venous blood.

In this study, it was seen that metabolic acidosis produced by a slow infusion of molar lactic acid produced a small but significant increase in mean arterial blood pressure at 5 and 10 mequivs/litre base deficit, although this was returning towards control by the time 15 mequivs/litre base deficit was achieved

(Table XI). Cardiac output however, tended to decrease, although this was not significant. Previous studies upon anaesthetised ventilated dogs have shown that metabolic acidosis has little effect upon mean arterial blood pressure (Smith and Corbascio, 1966; Goldstein, Simmons and Tashkin, 1972) but may reduce cardiac output (Carson, Chorley, Hamilton, et al, 1965; Smith and Corbascio, 1966). This depressant effect is especially seen if a fast infusion of acid is given and it may be that there is a critical infusion rate needed to produce myocardial depression. Indeed, it was noteable in this series of experiments that if a much faster infusion rate than 0.1 ml/kg/min of lactic acid was used cardiovascular collapse could be provoked in the dogs.

In conclusion, metabolic acidosis in the greyhound results in no overall change in liver blood flow but a reduced supply of oxygen to the liver and possibly increased extraction by the liver. This suggests that in low flow conditions, metabolic acidosis is disadvantageous to the liver.

CHAPTER 10.

THE EFFECT OF METABOLIC ALKALOSIS UPON LIVER BLOOD FLOW AND OXYGEN CONSUMPTION

Experimental Protocol

Seven greyhounds were prepared surgically in the standard manner described.

After the completion of surgery and the preparation had stabilised, baseline values were determined at a PaO_2 of 100 mm Hg (13.3 kPa), a $PaCO_2$ of 40 mm Hg (5.3 kPa) and a base excess of -4 mequivs/litre. A molar infusion of sodium bicarbonate was infused at a rate of 0.1mls/kg/min by means of a syringe pump. Repeated, frequent blood gas and pH measurements were made and the base excess calculated. The end tidal CO_2 concentration was measured continuously by means of a capnograph and kept stable by adjustment of the tidal volume. Hepatic arterial and portal venous blood flow and mean arterial pressure were measured continuously. Measurements of the other indices under study were repeated when a base excess of 5, 10 and 15 mequivs/litre relative to control was achieved.

Results

There were no significant changes in mean arterial pressure or cardiac output at any base excess studied (Table XII).

There was an increase in portal venous blood flow from the control level of 111.7 mls/100g liver wt/min, significant at a base excess of 10 and 15 mequivs/litre (Fig. 18). Hepatic

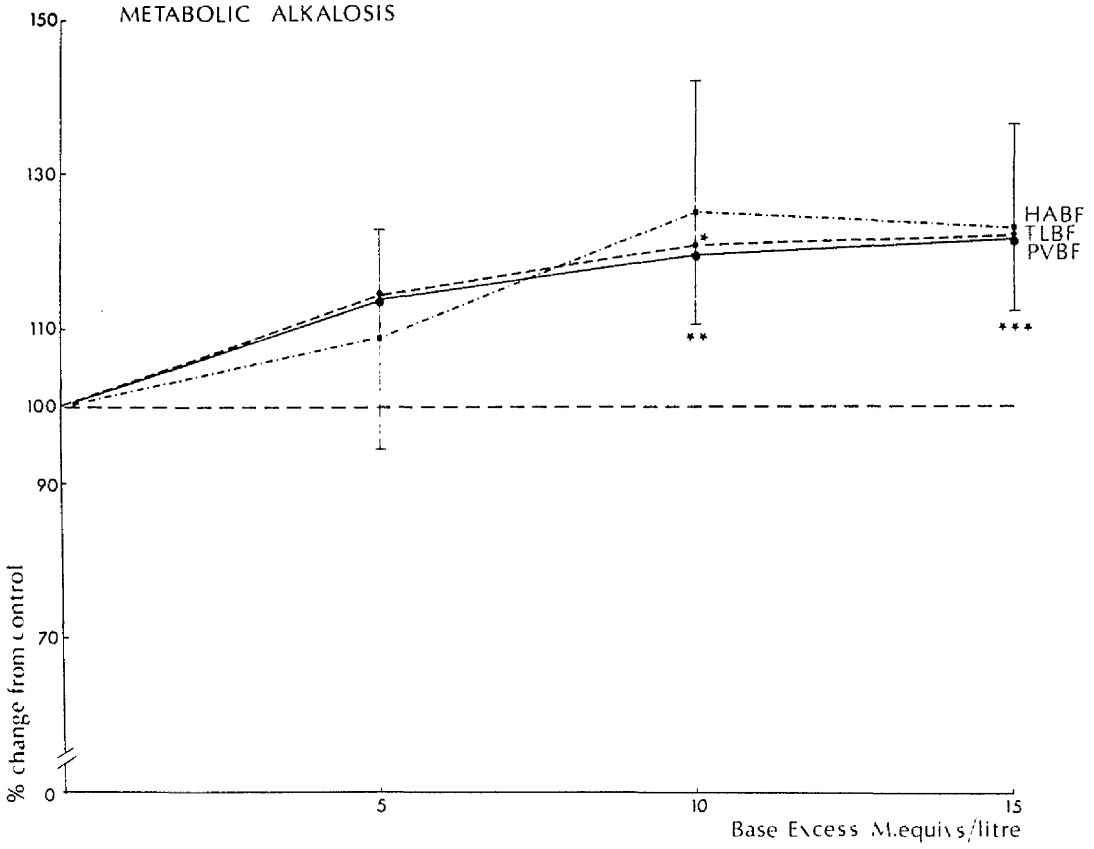

FIGURE 18. The effects of a base excess of 5, 10 and 15 mequivs/litre upon portal venous blood flow (PVBF), hepatic arterial blood flow (HABF) and total liver blood flow (TLBF). The values are expressed as percentages of the control (control equals 100%). Bars indicate ± SEM. * indicates significance of $P < 0.05$, ** $P < 0.01$ and *** $P < 0.001$ (the analysis was performed upon the absolute values obtained).

TABLE XII.

	Control	5 mequivs/litre	10 mequivs/litre	15 mequivs/litre
Mean Arterial Pressure (mm Hg)	111.4 ± 7.8	121.3 ± 9.1	121.7 ± 7.9	119.1 ± 8.4
Portal Venous Pressure (mm Hg)	7.37 ±0.78	7.25 ±0.88	7.25 ±0.86	7.58 ±0.86
Hepatic Venous Pressure (mm Hg)	3.58 ±0.5	3.45 ±0.45	3.24 ±0.58	3.94 ±0.61
Hepatic Oxygen Consumption (ml/min/100g liver wt)	5.76 ±0.84	6.33 ±0.73	7.29 ±1.6	5.93 ±1.02
Cardiac Output (litres/kg body wt/min)	0.146 ±0.012	0.154 ±0.011	0.144 ±0.006	0.153 ±0.009
Splenic Venous Blood Flow (mls/kg body wt/min)	4.31 ±0.49	4.65 ±0.71	4.89 ±0.94	4.45 ±0.74

The effect of a base excess of 5, 10 and 15 mequivs/litre upon mean arterial pressure, portal venous pressure, hepatic venous pressure, hepatic venous oxygen content, cardiac output and splenic venous blood flow. The values are ± SEM.

arterial blood flow increased in a similar manner from the control level of 39.7 mls/100g liver wt/min, but not significantly (Fig. 16). Total liver blood flow increased significantly at 10 and 15 mequivs/ litre base excess (Fig. 18).

There were no significant changes in peripheral resistance, hepatic arterial resistance, portal venous resistance and mesenteric vascular resistance. There were no significant changes in hepatic venous pressure or portal venous pressure (Table XII).

Hepatic oxygen consumption did not change significantly at any base excess nor did splenic venous blood flow (Table XII).

Discussion

Metabolic alkalosis is seldom a serious clinical problem but can, on occasion, prove life threatening (Abouna, Veazey and Terry, 1974).

Small but significant increases in portal venous blood flow and total liver blood flow were seen with metabolic alkalosis (Fig. 17). Goldstein, Simmons and Tashkin (1972) showed an increase in portal venous blood flow in the dog with metabolic alkalosis. This was associated with a non-significant decrease in hepatic arterial blood flow. This decrease however, may have been associated with the moderate hypoxia produced in their experiments as it has been shown in the experiments on hypoxia in this thesis that this produces a reduction in hepatic arterial blood flow. It is noteable that portal venous pressure did not rise with metabolic alkalosis and there was no decrease in hepatic arterial blood flow, providing further evidence for the proposition that the decrease in hepatic arterial blood flow associated with

metabolic and respiratory acidosis is related to an increase in sinusoidal pressure and that this increase is due, at least in part, to hepatic venous outlet constriction.

It has been shown that metabolic alkalosis produces an increase in whole body oxygen consumption (Karetzky and Cain, 1969). This effect was small and does not appear to involve the liver.

Metabolic alkalosis produced by an infusion of sodium bicarbonate produced no significant changes in mean arterial blood pressure or cardiac output. Previous reports of myocardial depression produced by metabolic alkalosis were following rapid bolus infusions of sodium bicarbonate (Clancy, Cingolani, Taylor, et al, 1967; Ng, Levy and Zieske, 1967; Bello, Bianco, Velorde, et al, 1977) and the effects may have been due to the use of hyperosmotic solutions (Wildenthal, Adcock, Crie, et al, 1975) or to the intracoronary infusion technique used.

In conclusion, the increase in liver blood flow seen with metabolic alkalosis, accompanied by the lack of significant changes in hepatic oxygen consumption suggests that metabolic alkalosis may be marginally beneficial to the liver.

CHAPTER 11.

THE EFFECTS OF ENFLURANE AND HALOTHANE UPON LIVER BLOOD FLOW AND OXYGEN CONSUMPTION

Introduction

Having established the effects of varying blood gas tensions and acid base status upon liver blood flow and oxygen consumption, it was thought that it would be of value to investigate the effects of the two main volatile anaesthetic agents in use in this country upon liver blood flow and oxygen consumption. These are halothane ($CF_3CHCl\ Br$) and enflurane (ethrane) (CF_2HOCF_2CFClH). Halothane has been in widespread use as a volatile general anaesthetic drug since its introduction in 1956 (Raventos, 1956). However, over the past few years there has been increasing suspicion that it produces dose related "halothane hepatitis" possibly due to a metabolite of the drug (Cousins, Gourlay, Sharp, et al, 1978; Inman and Mushin, 1978). Enflurane has been available since 1966 (Virtue, Lund, Phelps, et al, 1966) but only since 1978 in the U.K.

Since no cases of "enflurane hepatitis" have been reliably documented (Black, 1979) it has been suggested that this drug should substitute for halothane in these cases where repeated inhalational anaesthetics are necessary or where any suspicion of compromised liver function exists.

Accordingly, it would seem desirable that a detailed study of the comparative effects of halothane and enflurane upon liver blood flow and oxygen consumption should be made.

In this study, four concentrations of each drug were studied. It has been suggested that the minimum alveolar concentration (MAC) required to prevent gross movement in response to painful stimulus might serve as a means of comparing potency of different anaesthetics (Eger, Saidman and Brandstater, 1965). MAC has been shown to be 0.87% halothane (Eger, Brandstater, Saidman, et al, 1965) and approximately 2% enflurane (Merin, Kumazawa and Luka, 1976) in dogs. Therefore the effects of halothane and enflurane upon the variables under study have been compared graphically at approximately equipotent anaesthetic concentrations over the range of concentrations used in clinical practice.

It will be seen that a more anaesthetically potent (2%) concentration of halothane was studied than that of enflurane (3%). This is because it proved impossible to study higher concentrations of enflurane without provoking cardiovascular collapse.

Methods

Twelve greyhounds were prepared surgically in the routine manner described.

After surgery was completed, the preparation was allowed to stabilise and baseline measurements were determined at a PaO_2 of 100 mm Hg (13.3 kPa) and a $PaCO_2$ of 40 mm Hg (5.3 kPa). Splenic blood flow was not measured in these experiments.

In six of the greyhounds, halothane was added to a mixture of 70% N_2 and 30% O_2 by means of a Fluotec Mk II (Cyprane) temperature compensated vaporiser at concentrations of ½%, 1%, 1½% and 2%. Each concentration was given for 30 minutes.

Hepatic arterial blood flow, portal venous blood flow and mean arterial pressure were measured continuously and measurements of these and all the other indices under study were taken after thirty minutes administration of halothane. The concentration of halothane was then increased and measurements repeated after a further thirty minutes. The preparation was not returned to control between each halothane administration. Arterial blood samples were taken after each 30 min halothane administration and analysed for blood halothane using gas liquid chromatography by the method of Allott, Steward and Mapleson (1971). In the second group of six greyhounds, enflurane (ethrane) was administered by means of an Enfluratec (Cyprane) temperature compensated vaporiser at concentrations of 1%, 1.5%. 2% and 3%. A similar protocol to the halothane experiments was followed, i.e. enflurane was given at each increasing concentration for thirty minutes, not returning to control between each concentration. Arterial blood samples were taken at the end of each 30 min period of administration and analysed for blood enflurane concentration by a solvent extraction method similar to that used in the halothane experiments. The statistical analysis was performed upon absolute values relative to control.

Results

Halothane Experiments

Mean arterial blood pressure decreased in a linear fashion from the control level of 122 mm Hg with increasing concentrations of halothane (Fig. 19).

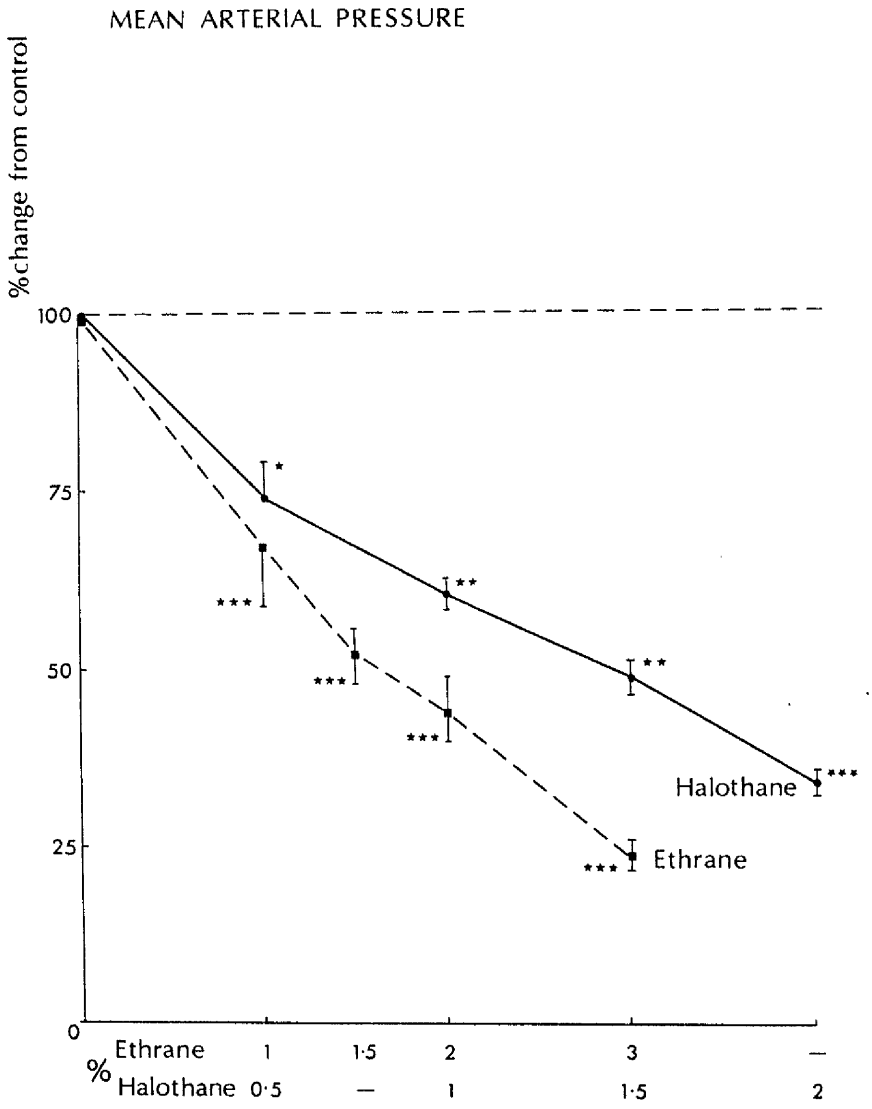

FIGURE 19. The effect of equipotent concentrations of halothane and enflurane (ethrane) upon mean arterial blood pressure. The values are shown as percentages of the control; bars indicate ± SEM. *P < 0.05, **P < 0.01, ***P < 0.001.

Cardiac output decreased in a similar manner from the control figure of 0.155 litres/kg body weight (Fig. 20).

Portal venous blood flow decreased significantly with each concentration of halothane from the control level of 137 mls/100 g liver weight to a minimum value of 45% of control with 2% halothane (Fig. 21).

There was a greater percentage decrease in hepatic arterial blood flow from control of 38 mls/100 g liver weight to a value 35% of control with 2% halothane (Fig. 22). Total liver blood flow decreased in a similar manner to portal venous blood flow (Fig. 23).

There were small decreases in peripheral resistance (Fig. 24) which were not significant. Hepatic arterial resistance did not change significantly with any concentration of halothane (Fig. 25). There were no significant changes in mesenteric vascular resistance (Table XIII).

There was a small decrease in hepatic oxygen consumption with each concentration of halothane which did not reach significance (Table XIII). There were no significant changes in hepatic venous or portal venous pressure (Table XIII).

The blood halothane concentrations achieved after each 30 minute administration are stated in Table XIV.

Enflurane Experiments

Mean arterial pressure decreased from control of 122 mm Hg to 24% of control with 3% enflurane (Fig. 19).

Cardiac output decreased linearly to 51% of the control

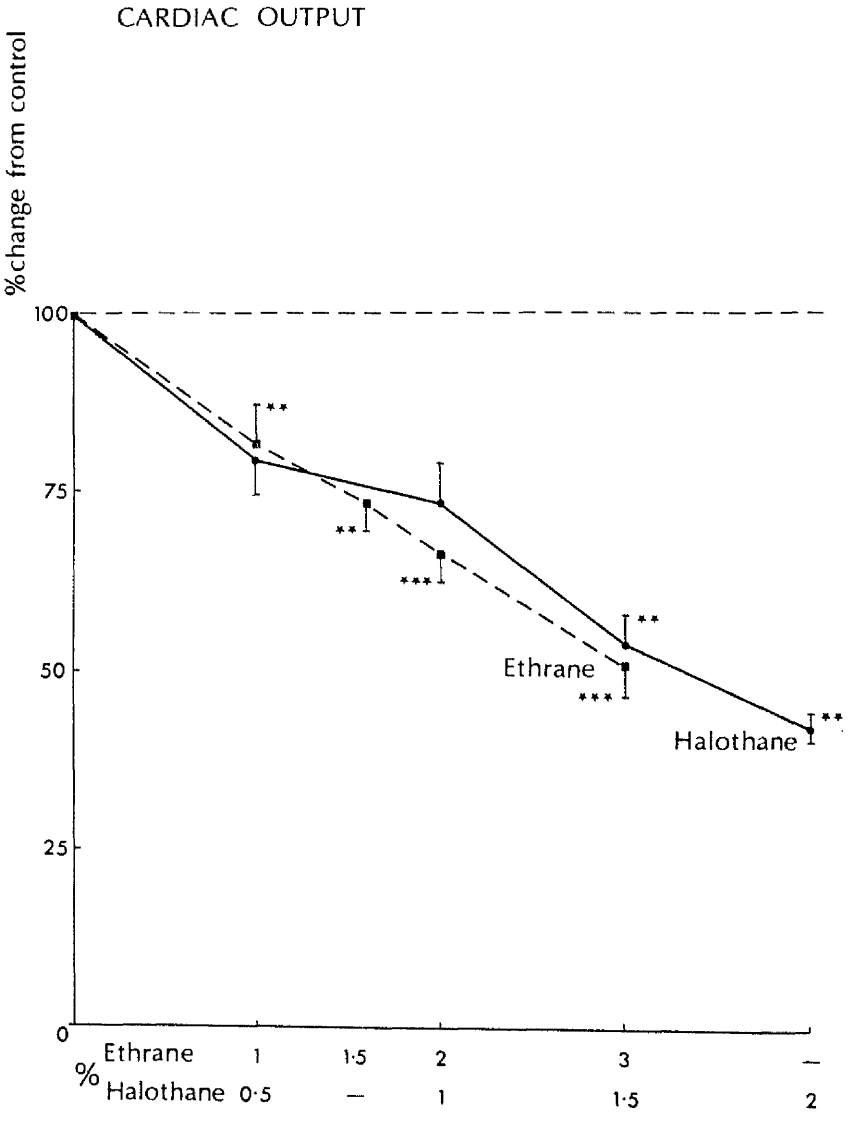

FIGURE 20. The effect of equipotent concentrations of halothane and enflurane (ethrane) upon cardiac output. The values are shown as percentages of the control; bars indicate ± SEM. $^{**}P < 0.01$, $^{***}P < 0.001$.

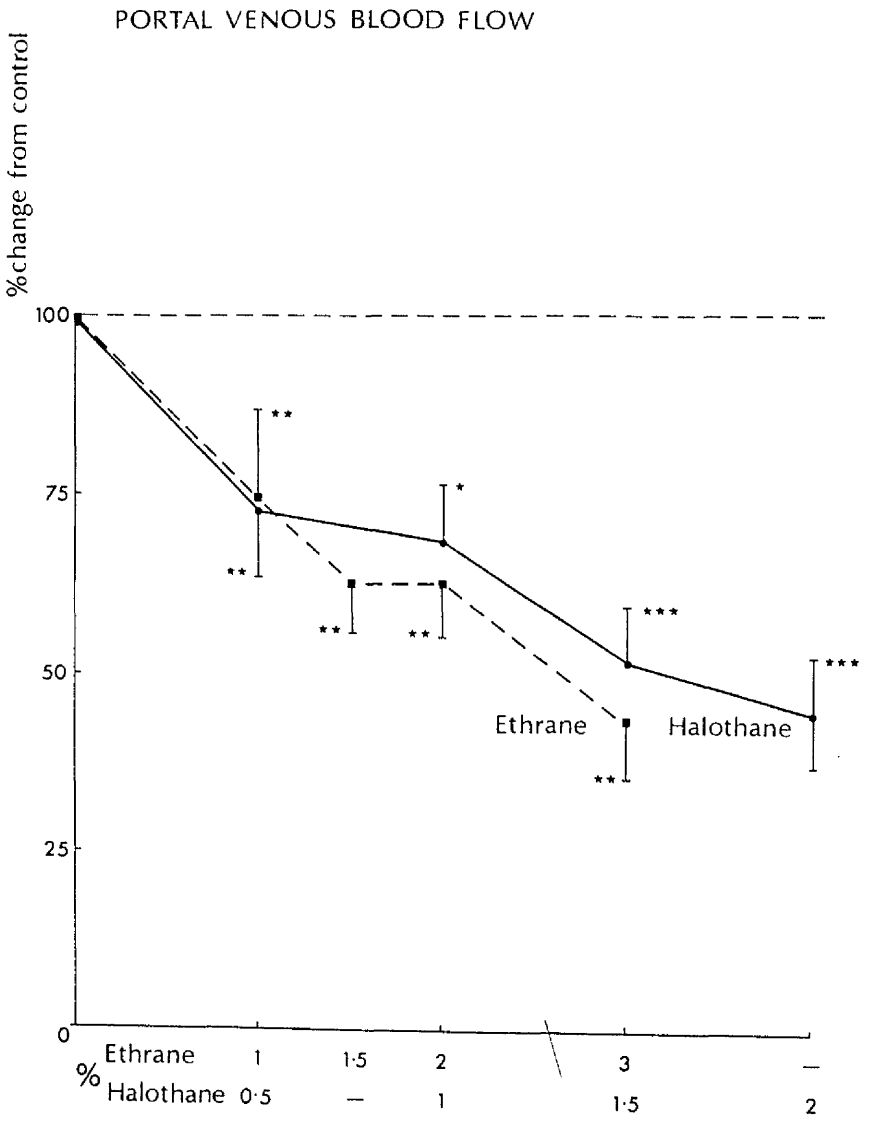

FIGURE 21. The effect of equipotent concentrations of halothane and enflurane (ethrane) upon portal venous blood flow. The values are shown as percentages of the control, bars indicate ± SEM. *P < 0.05, **P < 0.01, ***P < 0.001.

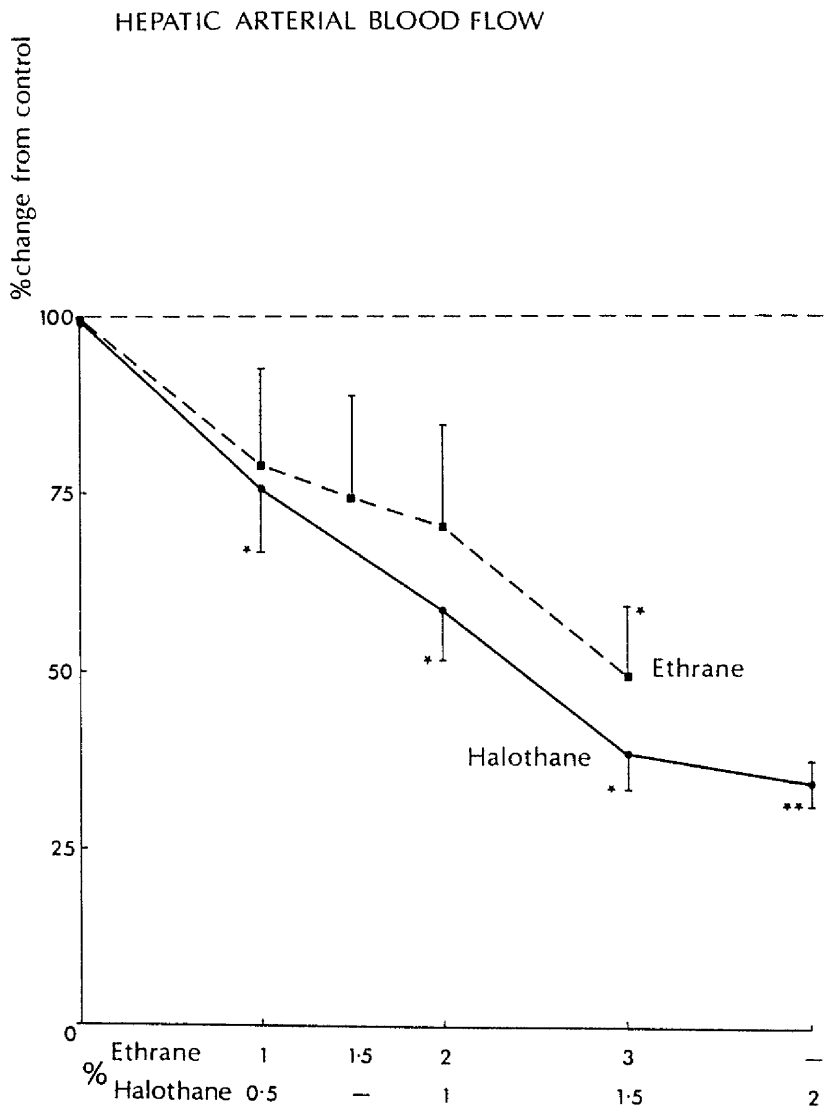

FIGURE 22. The effect of equipotent concentrations of halothane and enflurane (ethrane) upon hepatic arterial blood flow. The values are shown as percentages of the control, bars indicate ± SEM, *P < 0.05, **P < 0.01.

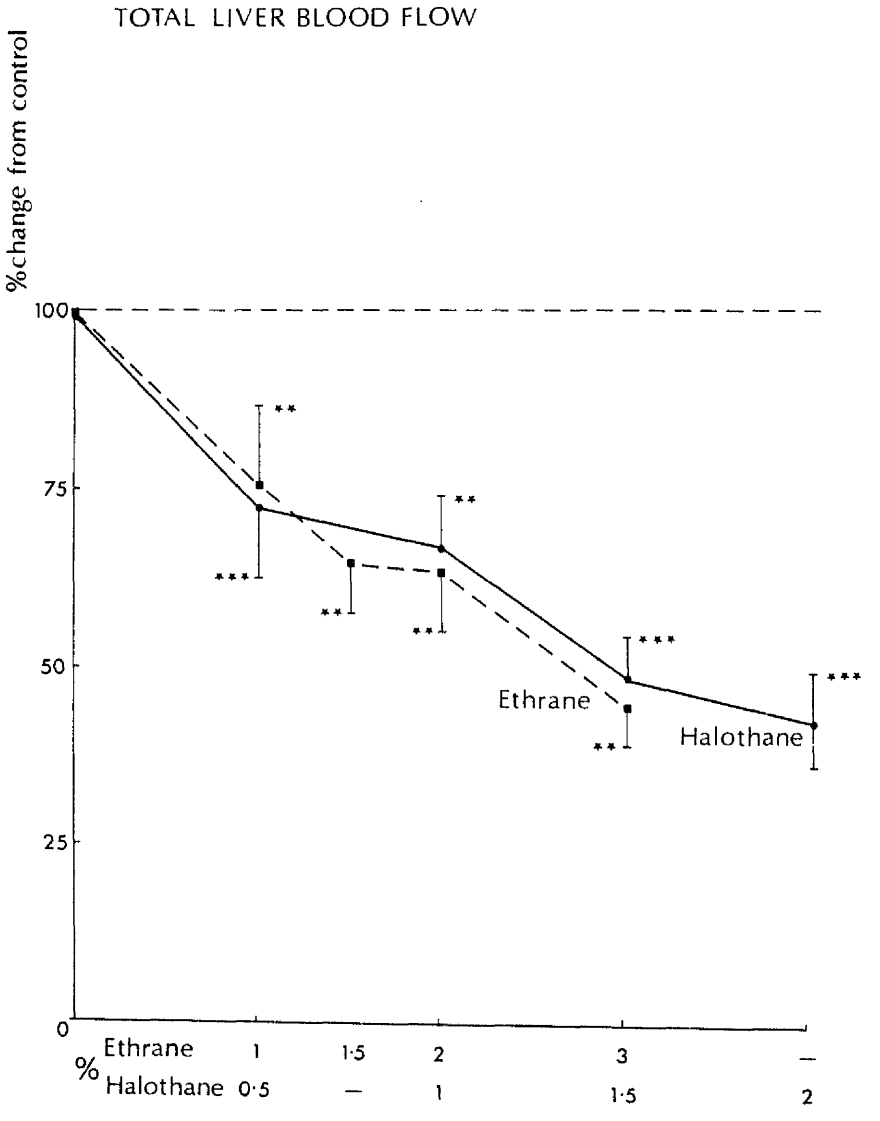

FIGURE 23. The effect of equipotent concentrations of halothane and enflurane (ethrane) upon total liver blood flow. The values are shown as percentages of the control, bars indicate ± SEM, **P < 0.01, ***P < 0.001.

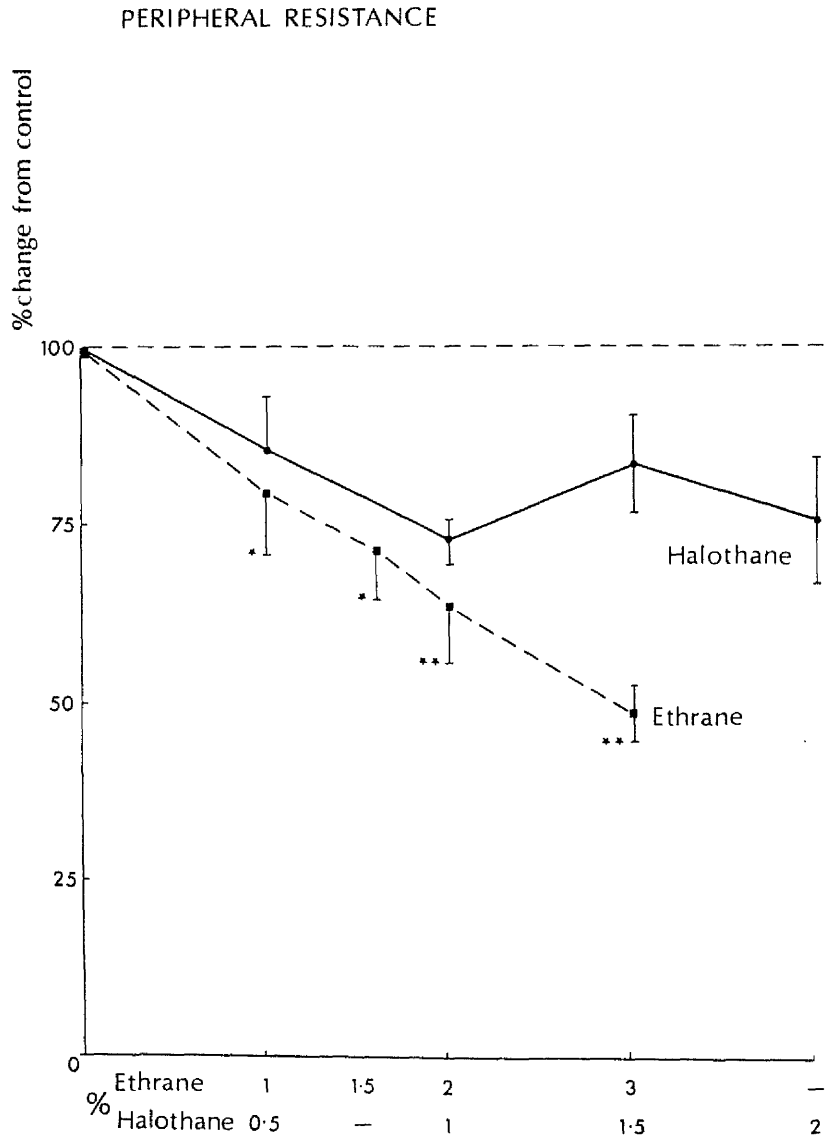

FIGURE 24. The effect of equipotent concentrations of halothane and enflurane (ethrane) upon total peripheral resistance. The values are shown as percentages of the control, bars indicate ± SEM, *P < 0.05, **P < 0.01.

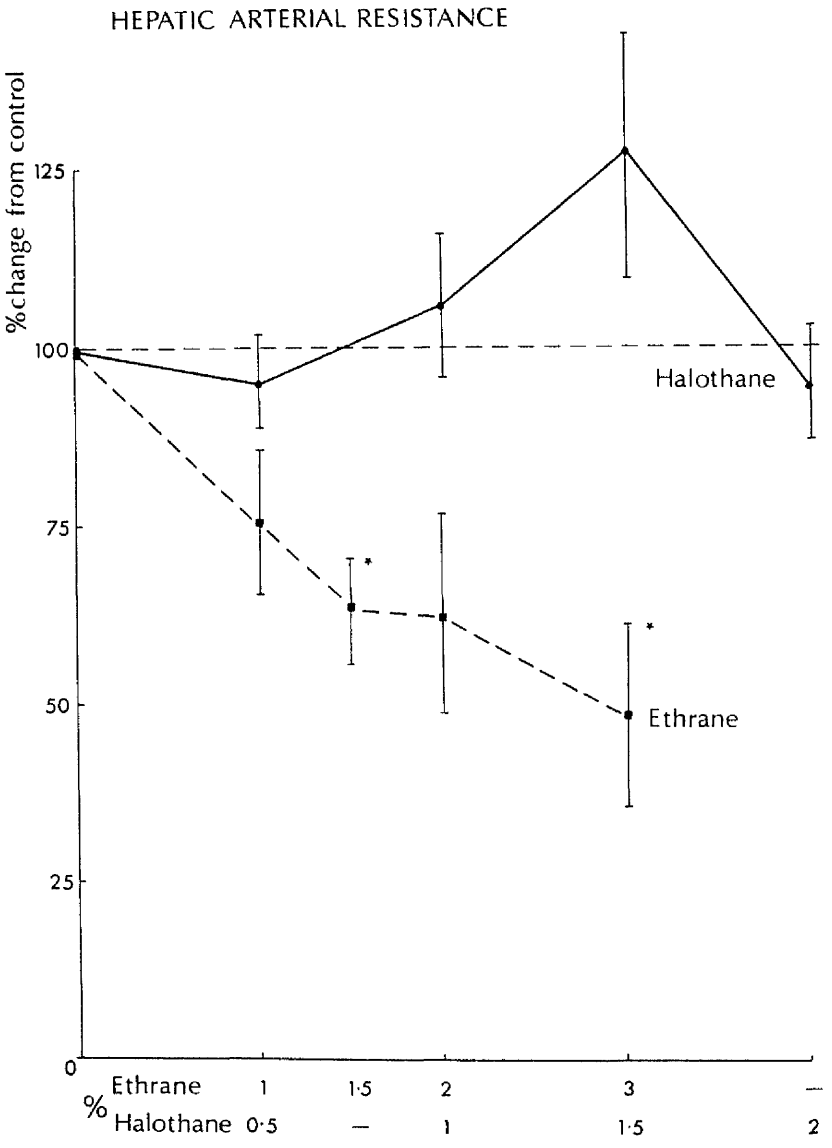

FIGURE 25. The effect of equipotent concentrations of halothane and enflurane (ethrane) upon hepatic arterial resistance. The values are shown as percentages of the control, bars indicate ± SEM, *$P < 0.05$.

TABLE XIII.

	Control	0.5%	1%	1.5%	2%
Hepatic Oxygen Consumption (mls/min/100g liver wt)	5.0 ±0.87	4.18 ±0.48	4.57 ±0.74	4.19 ±0.65	4.42 ±0.42
Mesenteric Vascular Resistance (mm Hg/ml/min)	0.151 ±0.011	0.158 ±0.014	0.139 ±0.019	0.150 ±0.026	0.116 ±0.017
Hepatic Venous Pressure (mm Hg)	3.05 ±1.01	2.91 ±1.13	3.36 ±0.74	3.05 ±1.08	3.7 ±0.74
Portal Venous Pressure (mm Hg)	7.73 ±1.23	7.25 ±1.23	7.38 ±1.34	6.5 ±1.38	6.86 ±1.48

The effect of four concentrations of halothane upon hepatic oxygen consumption, mesenteric vascular resistance, hepatic venous pressure and portal venous pressure. Values are ± SEM.

TABLE XIV.

	Control	0.5%	1%	1.5%	2%
Arterial Halothane (mg/100mls)	0	10.72 ± 2.72	17.52 ± 2.24	23.98 ± 2.65	29.23 ± 4.7

Arterial halothane concentrations after each thirty minute administration of 0.5%. 1%. 1.5% and 2% halothane. Values are ± SEM.

value of 0.139 litres/Kg body weight with 3% enflurane (Fig. 20).

Portal venous blood flow decreased significantly with each concentration of enflurane from the control level of 112 mls/100g liver weight to a minimum value of 44% of control with 3% enflurane (Fig. 21).

Hepatic arterial blood flow decreased significantly only at the 3% enflurane concentration from a control of 27.1 mls/100g liver weight (Fig. 22). Total liver blood flow decreased in a similar manner to portal venous blood flow (Fig. 23).

Peripheral resistance decreased significantly with each concentration of enflurane (Fig. 24). Hepatic arterial resistance decreased significantly with 1.5 and 3% enflurane (Fig. 25). Mesenteric vascular resistance decreased significantly with 2 and 3% enflurane (Table XV).

There were no significant changes in hepatic oxygen consumption with any concentration of enflurane (Table XV). There were no significant changes in portal venous pressure or hepatic venous pressure (Table XV). The blood enflurane concentrations achieved after each 30 min administration are stated in Table XVI.

Comparison of effects of halothane and enflurane

The effects of halothane and enflurane have been graphed together to allow comparison. Minimum alveolar concentrations (MAC) have been plotted together to allow comparison of equipotent anaesthetic doses. There were no significant differences between the control enflurane and halothane values. However, there was

TABLE XV.

	Control	1%	1.5%	2%	3%
Hepatic Oxygen Consumption (mls/min/100g liver wt)	3.67 ±0.52	3.74 ±0.59	3.64 ±0.25	3.79 ±0.53	3.13 ±0.36
Mesenteric Vascular Resistance (mm Hg/ml/min)	0.196 ±0.026	0.178 ±0.032	0.160 ±0.025	0.128* ±0.016	0.099** ±0.014
Hepatic Venous Pressure (mm Hg)	1.78 ±0.73	1.8 ±0.56	2.25 ±0.68	2.5 ±0.49	3.42 ±0.57
Portal Venous Pressure (mm Hg)	4.75 ±0.85	4.55 ±0.63	3.85 ±0.56	3.95 ±0.64	4.08 ±0.59

The effect of four concentrations of enflurane upon hepatic oxygen consumption, mesenteric vascular resistance, hepatic venous pressure and portal venous pressure. *$P < 0.05$ **$P < 0.01$.
Values are ± SEM.

	Control	1%	1.5%	2%	3%
Arterial Enflurane Conc. (mg/100mls)	0	15.97 ± 0.99	21.47 ± 0.99	29.42 ± 1.8	40.59 ± 0.71

TABLE XVI.

Arterial enflurane concentrations after each thirty minute administration of 1%, 1.5%. 2% and 3% enflurane.
Values are ± SEM.

a large, though not significant difference between the control hepatic arterial blood flow values and therefore hepatic arterial resistance.

There was a significant difference ($t = 3.85$) between the mean arterial pressure achieved with 2% enflurane and 1% halothane and 3% enflurane and 1.5% halothane ($t = 8.06$) (Fig. 19). There were no significant differences between portal venous, hepatic arterial and total liver blood flows at equipotent concentrations.

There was a significant difference in peripheral resistance between halothane 1.5% and enflurane 3% ($t = 5.15$) (Fig. 24).

There were large differences, which failed to reach significance between the effects of enflurane and halothane upon hepatic arterial resistance.

These analyses have been made using an unpaired 't' test and absolute values.

Discussion

In this study, four concentrations of each drug were studied. To ensure that wide variations in concentrations of each drug were not occurring due to potential leaks or vaporiser malfunction, arterial concentrations were analysed and these showed only a small standard deviation over the experiments. These arterial concentrations are thought to be representative of the partial pressure of the anaesthetic in the brain (Eger and Bahlman, 1971).

As stated in the introduction a more potent (2%) concentration of halothane was studied than that of enflurane (3%) because it proved impossible to study higher concentrations of enflurane

without provoking cardiovascular collapse.

A comparison of halothane and enflurane in spontaneously breathing patients showed no difference between the cardiovascular effects of the two drugs (Ascorve, Criado, Peral, et al, 1976). However, studies of enflurane in both man (Calverley, Smith, Prys-Roberts, et al, 1978b) and the dog (Moran, Prys-Roberts, Hamilton, et al, 1977; Merin, Kumazawa and Luka, 1976) during controlled ventilation with normocarbia showed greater cardiovascular depression was produced by enflurane than by halothane. In the experiments described in this chapter, there was little difference between the depressant effects of the two drugs on cardiac output but a significant difference between the effects on mean arterial blood pressure and therefore peripheral resistance. Halothane as previously described in man (Prys-Roberts, Lloyd, Fisher, et al, 1974) had an insignificant effect on peripheral resistance while 3% enflurane reduced peripheral resistance to 50% of control.

There have been a number of previous reports of the effects of halothane both upon total liver blood flow (Ahlgren, Aronsen, Erisson, et al, 1967; Deutsch, 1967; Juhl and Einer-Jensen, 1974). These all demonstrated progressive reductions in liver blood flow in parallel with cardiac output. Previous studies on the effect of halothane on portal venous and hepatic arterial blood flow at mean arterial halothane concentrations of 20-24 mg/100 mls (produced by 30 minute administration of approximately 1.5% halothane) showed similar decreases of approximately 50-60% in both blood flows (Thulin, Andreen and Irestedt, 1975; Andreen, Irestedt and Zetterstrom, 1977). The small, insignificant increase in hepatic arterial resistance is similar to that seen by Thulin and co-workers

in 1975, although in their second series in 1977 they demonstrated a much larger increase in resistance.

The decrease in portal venous blood flow should have, if the myogenic mechanisms previously described were active, resulted in a decrease in hepatic arterial resistance and a relative preservation or autoregulation of hepatic arterial blood flow. Halothane, however, appears to abolish the reciprocal relationship between hepatic arterial and portal venous blood flow at all the concentrations studied.

The effects seen with four concentrations of enflurane (approximately 0.5 to 1.5 MAC) were similar to these described by Irestedt and Andreen (1979) with 2.2% enflurane. That is, there were dose related decreases in both hepatic arterial and portal venous blood flows. However, in contrast to halothane, hepatic arterial resistance did decrease significantly with enflurane. There appears therefore, in the dog, to be a difference between the effects of halothane and enflurane on hepatic arterial blood flow. This could be due to a local interference by halothane with the relaxation of the hepatic arterioles following reduced portal blood flow. However, in view of the different effects of the two drugs on total peripheral resistance and on mesenteric vascular resistance, it seems likely that this is a generalised phenomenon. Halothane would appear to produce its hypotensive effect by producing myocardial depression while enflurane produces greater cardiovascular depression by both an effect on the myocardium and blood vessels. It must be emphasised that these results were obtained in the artificially ventilated,normocarbic dog and that if the animals had been allowed to breathe the inhalational anaesthetics spontaneously, the result

would have been respiratory depression and hypercarbia. Hypercarbia would have been expected to increase cardiac output thus opposing the drug effects (Price, 1960; Calvery, Smith, Prys-Roberts, et al, 1978a).

Halothane was seen as in previous studies, to produce a small but insignificant decrease in hepatic oxygen consumption (Theye, Kuster and Dawson, 1972; Andreen, Irestedt and Thulin, 1975). Enflurane had no effect on hepatic oxygen consumption, producing only a small decrease which was not significant with the 3% concentration. This was similar to the effect seen by Irestedt and Andreen (1979) with 2.2% enflurane. It was seen therefore that neither drug significantly depresses hepatic aerobic metabolism with enflurane having no effect at all except the highest concentration studied.

In conclusion, at equipotent anaesthetic concentrations enflurane appears in the greyhound to have a marginally advantageous effect over halothane on hepatic arterial blood flow and hepatic oxygenation. However, it is doubtful whether this effect counterbalances the greater cardiovascular depression produced by enflurane.

CHAPTER 12.

CONCLUDING DISCUSSION

Anaesthetic Technique

The extensive dissection necessary to allow the various measurements made in these experiments necessitated the use of general anaesthesia throughout the procedure. All the experiments detailed were acute experiments, the dogs were not allowed to recover consciousness and were sacrificed after the measurements were made.

Anaesthesia was induced with thiopentone sodium (20 mg/kg). This dose is much larger than that used in man but is that recommended to produce anaesthesia in dogs (Hall, 1966). While it has been shown that thiopentone is metabolised more slowly in dogs than man (Brodie, Mark, Papper et al, 1950) these authors have also shown that, in the dog, as in man, there is a rapid redistribution of thiopentone away from organs such as the brain towards neutral fat stores. This results in rapid recovery of consciousness and the reversal of any cardiovascular depression.

Pentobarbitone sodium (30 mg/kg) was used to maintain anaesthesia. This again is the dose recommended by Hall (1966). This dose has been shown to produce stable cardiovascular conditions with no change in mean arterial blood pressure accompanied by a small decrease in cardiac output (Gilmore, 1965). Several groups of workers have agreed that pentobarbitone produces only transient effects upon liver blood flow in dogs (Fisher, Russ, Selker, et al, 1956; Gilmore, 1958; Evringham, Brenneman

and Horvath, 1959) although Ericsson (1971) utilising the microsphere technique showed small decreases in liver blood flow 30 min after induction of anaesthesia with pentobarbitone.

In the greyhound, it proved unnecessary to give any supplements of pentobarbitone during the experiments described, thus the cardiovascular stability of the preparation was maintained.

Pancuronium bromide (0.15 mg/kg), a non-depolarising muscle relaxant was given at the commencement of the procedure to allow abdominal relaxation and facilitate surgical access. This drug was not given again during the experiment. Pancuronium, in this dose, has been shown to produce minimal cardiovascular effects in the pentobarbitone anaesthetised greyhound (Gibbs, Tait and Sykes, 1976) and as the experimental measurements were not made until at least 3 hours after administration of the drug it would seem unlikely that it interfered with these measurements.

Ideally, the experiments described in this thesis would have been carried out in the unanaesthetised dog. However, it would have proved impossible to carry out these measurements with currently available equipment, in an acceptable manner in the conscious dog. It has also been shown by Fisher, et al (1956) that in the conscious dog, during periods of restlessness, the relationship between cardiac output and liver blood flow is not stable. It would be extremely difficult therefore, in such a dog, to assess whether changes seen in experimental variables were due to stress, the experimental variable being studied, or a combination of both.

The other major departure from normal physiology involved in these experiments was that the dogs were artificially ventilated.

This produces a number of alterations in cardiovascular physiology due to changes in intrathoracic pressure interfering with venous return. However, providing high intrathoracic pressure is not produced and an adequate expiratory phase is allowed, these changes are not large (Mushin, Rendell-Baker, Thompson, et al, 1969). Artificial ventilation was unavoidable in these experiments to allow the study of changes in blood gases and acid base status without attempted respiratory compensation by the dog. In the studies upon halothane and enflurane profound respiratory depression occurs in the spontaneously breathing subject with the higher concentrations of these drugs and it would not be possible to separate the effects of the drugs from the accompanying hypercarbia. An additional reason for using intermittent positive pressure ventilation in these studies was that a major purpose of them was to help develop anaesthetic techniques most beneficial to the liver during major surgery. Such patients would, as routine, be artificially ventilated and the ventilatory pattern used was one commonly seen in clinical practice.

As discussed in the chapter on hypocarbia, these experiments were all performed in greyhounds as preliminary experiments demonstrated a wide variability in cardiovascular responses between different breeds of dog. Greyhounds also have the advantage that they are readily available and are usually in good condition.

Measurement of liver blood flow and vascular resistance

As stated in Chapter I. of this thesis, it is only the introduction of electromagnetic flowmeters with non occlusive

zeroing and the synchronisation of excitation currents when more than one meter is used, that has allowed continuous accurate recording of flow to be made in the hepatic artery and portal vein. The flow probes used were precalibrated by the manufacturer (Statham) but as the values obtained were central to this thesis, the accuracy of the probes was checked in the laboratory. Details of the principles of the Statham SP 2202 electromagnetic flowmeter and the calibration experiments are included in the appendix to this thesis.

The measurement of hepatic arterial and portal venous blood flow allowed hepatic arterial and portal venous resistance to be calculated. However, portal venous resistance calculations produced results which are difficult to interpret as small errors in pressure measurement produce very large changes in that particular calculation (equation p 30).

Summary and Discussion of Changes in Liver Blood Flow during Experiments

In summary, the effects of the various experimental situations upon liver blood flow and hepatic arterial resistance were as follows:-

1. Respiratory acidosis (hypercarbia) produced an increase in portal venous blood flow (PVBF) and a decrease in hepatic arterial blood flow (HABF) accompanied by an increase in hepatic arterial resistance (HAR).
2. Respiratory alkalosis (hypocarbia) produced a decrease in PVBF accompanied by a small decrease in HABF and no significant change in HAR. Intermittent positive pressure ventilation had no independent effect apart from a decrease in HABF with extreme hyperventilation.

3. Hyperoxia had no effect on these variables.

4. Hypoxia had no effect on PVBF but produces an immediate reduction in HABF, which later returned to control and an immediate increase in HAR.

5. Metabolic acidosis produced an increase in PVBF, a decrease in HABF and an increase in HAR.

6. Metabolic alkalosis produced an increase in PVBF, an insignificant increase in HABF and no change in HAR.

7. Enflurane produced a decrease in PVBF, a decrease in HABF and a decrease in HAR.

8. Halothane produced a decrease in PVBF, a decrease in HABF and no change in HAR.

Burton Opitz (1911a.) found that hepatic arterial blood flow in the anaesthetised dog increased about 15% when portal inflow was shunted into the renal vein. More recently Ternberg and Butcher (1965) demonstrated an increase in hepatic arterial blood flow when portal venous blood flow was decreased which they ascribed to removal of the mechanical impediment of the slower portal venous blood flow.

However, both Hanson and Johnson (1966) and Lutz, Peiper and Bauereisen (1968) felt the evidence supported a myogenic mechanism regulating hepatic arterial blood flow, i.e. pressure sensitive smooth muscle present in the hepatic arterial resistance vessels which respond to an increase in pressure by constricting. Both Hanson and Johnson (1966) and subsequently Folkow and Neil (1971) suggest that one would expect to find a metabolic mechanism, as in voluntary muscle, regulating hepatic arterial blood flow.

However, if this were so, one would expect that an increase in hepatic venous pressure, resulting in pooling of "vasodilator metabolites" would result in a decrease in hepatic arterial resistance. In fact the opposite was seen to occur by both Hanson and Johnson (1966) and Lutz, Peiper and Bauereisen (1968).

Takeuchi, Kubo, Tone, et al (1969) failed to show this "reciprocity response" between hepatic arterial and portal venous blood flow in the denervated liver, but the review by Rappaport and Schneiderman (1976) states that this response has been seen in all intact preparations. This would suggest a neural component to the response but Hanson (1973) has demonstrated that it is abolished by the smooth muscle relaxant papaverine and not significantly affected by autonomic blocking agents. This would indicate that adrenergic mechanisms are not directly involved and the data has been used to support the myogenic hypothesis.

The hepatic artery is surrounded by a thick coat of nerves from the coeliac plexus, the vagi and the phrenic nerves (Rappaport and Schneiderman, 1976). Greenway and Oshiro (1972) showed that unlike the cat, the hepatic artery of the dog did not escape the vasoconstriction caused by continuous stimulation of the hepatic nerves over a ten minute period. However, Mundschau, Zimmermann, Gildersleeve, et al (1966) showed in the dog, that the hepatic artery readily escaped from the general increase in vasomotor tone produced by sino-aortic denervation or haemorrhage. It would seem therefore that most of the available evidence suggests local mechanisms are most important in the control of hepatic arterial blood flow.

There is no evidence that pressure induced autoregulatory

responses occur in the intrahepatic portal vessels or that stimulation of the hepatic nerve plexus affects portal venous blood flow (Greenway and Stark, 1971).

Do the changes seen in hepatic arterial and portal venous blood flow seen in the experiments detailed in this thesis, match the conclusions of these previous studies?

Both metabolic and respiratory acidosis produced an increase in portal venous blood flow and pressure, accompanied by an increase in hepatic arterial resistance and a decrease in hepatic arterial blood flow. These findings are fully in agreement with the theory of myogenic regulation of hepatic arterial blood flow discussed above.

Respiratory alkalosis produced a decrease in portal venous blood flow. This was accompanied by an insignificant decrease in hepatic arterial blood flow rather than the increase one might expect from the "reciprocity response". This decrease was presumably caused by the increase in hepatic venous pressure and therefore sinusoidal pressure resulting from the hyperventilation used to produce hypocapnia and it was noteable that the increase in sinusoidal pressure resulting from the restoration of normocarbia, was accompanied by a further decrease in hepatic arterial blood flow as theoretically expected.

Hypoxia resulted only in transient systemic hypertension accompanied by a decrease in hepatic arterial blood flow. The hepatic artery rapidly escaped from this vasoconstriction but whether this was a local or a generalised phenomenon cannot be answered without simultaneous measurement of other organ blood flows. Hyperoxia produced no effects.

Metabolic alkalosis resulted in a small increase in portal venous blood flow accompanied by an insignificant increase in

hepatic arterial blood flow. No changes in portal venous pressure were seen so again one would not expect to see a reciprocity response.

Finally, the two anaesthetic agents studied despite having many similarities had different effects on liver blood flow. Enflurane produced a reduction in portal venous blood flow, and pressure and the theoretically expected reduction in hepatic arterial resistance. However, halothane while producing a decrease in portal venous blood flow and pressure, produced a slightly increased hepatic arterial resistance. This was, unlike enflurane, accompanied by an unchanged peripheral vascular resistance, suggesting that the hepatic artery participated in a generalised response. Millar and Biscoe (1966) showed that halothane produced an increase in post ganglionic sympathetic nervous activity in the rabbit and this may also occur in the dog.

In conclusion therefore, with the exception of halothane, all the experimental conditions studied produced changes in hepatic arterial blood flow compatible with the myogenic theory of flow regulation.

Hepatic Oxygen Consumption

Before discussing the results obtained from the hepatic oxygen consumption calculations, a critique of the methodology involved is necessary. Analysis of blood oxygen content was performed using the Lex-O_2-Con analyser which, as stated in the introduction, has been shown by different groups of workers to correlate well with results obtained by use of the Van Slyke technique. This was confirmed in preliminary experiments in this laboratory.

To produce accurate results it is necessary to sample hepatic venous blood from a site which is receiving blood draining from all the lobes of the liver but is not so near the junction with the

inferior vena cava that reflux of blood from the inferior vena cava occurs. Ideally, the catheter should be some 4-5 cm from this junction (Shoemaker, Walker, Van Itallie, et al, 1959), and every attempt was made to ensure this was so in these experiments. However, the only way to ensure a completely mixed sample is either to create surgically a reservoir for hepatic venous blood (Ballinger, Haupt, Hering, et al, 1959) from the inferior vena cava or to obstruct intermittently the inferior cava with a balloon catheter below the junction of the inferior vena cava and hepatic vein (Goldstein, Tashkin and Simmons, 1971). Both methods have various objections, the first the major surgery necessary to create the reservoir, unacceptable in an acute preparation and the second that hypotension occurred when the inferior vena cava was obstructed. Therefore, it was felt that there was no acceptable alternative to the method used in these experiments to sample hepatic venous blood but bearing in mind that sampling errors might be occurring.

The most notable feature of these studies of hepatic oxygen consumption is its stability. Indeed only marked hypocarbia and hypoxia produced significant decreases in this measurement. It has since been shown in these laboratories that neither does haemorrhagic hypotension reduce hepatic oxygen consumption (Smith, Mathie, Hughes, et al, 1979). Therefore it appears that aerobic metabolism only fails in the liver in extreme circumstances.

Measurement of Splenic Blood Flow

It has been shown that the spleen plays a major role in the cardiovascular responses of the dog to various forms of stress,

a role it does not appear to have in man (Vatner, Higgins, Millard, et al, 1974; Ffoulkes-Crabbe, Creighton, Volgyesi, et al, 1976). Theoretically, to allow the results in these experiments to be applied to human clinical problems, a case could be made to perform splenectomy in these dogs. However, as the spleen was seen to provide some 10-15% of portal venous blood flow in the greyhound, it was decided to measure this flow and examine whether it differed from the responses of total portal venous blood flow. In fact the spleen appeared to play little role in any of the changes in portal blood flow seen in these experiments. It was only with severe hypoxia and severe hypercarbia, that is very stressful situations, that any significant changes in splenic blood flow were seen. The conclusion that can be drawn from this aspect of these studies is that, only during experiments which are extremely stressful to the greyhound is it of material importance to a study of liver blood flow whether splenectomy is carried out or not.

Clinical Applications

The question which must be asked is how applicable is this information, obtained in anaesthetised greyhounds to the human clinical situation? The general cardiovascular responses measured during the various experimental conditions studied have been similar to those quoted during the same conditions in man. The notable exception was that mild to moderate hypercarbia in the greyhound results in hypotension unlike in man, where hypertension occurs. This hypotension is due to a reduction in peripheral resistance, greater than that seen in man where this reduction is more than

compensated for by an increase in cardiac output. That this occurs in an animal as muscular as the greyhound, is not surprising and it would be of interest to study whether equally athletic human subjects have a similar response to hypercarbia.

The dog possesses hepatic venous outlet sphincters which have not been demonstrated in man. These have been shown to constrict in response to a variety of stressful situations thus affecting hepatic arterial blood flow as described earlier. It may prove therefore that the hepatic artery in man does not respond to such stimuli in a similar manner to the dog. However, until a reliable, safe and easily utilisable method of measuring the separate hepatic arterial and portal venous blood flows is developed in man, this must remain a matter for conjecture.

With these reservations in mind, some points of clinical relevance can be made. Hypercarbia appears to be, if anything, potentially beneficial to the liver. Hypocarbic hyperventilation is potentially harmful to the liver but this effect is largely reversed by hyperventilating the animal at normal $PaCO_2$ tensions. Hyperoxia at normal atmospheric pressure has no effect but hypoxia, even of a mild degree results in a transient reduction of hepatic arterial blood flow. Metabolic alkalosis may be mildly advantageous but metabolic acidosis by reducing the oxygen supply to the liver would appear to be harmful.

In these experiments enflurane was seen to result in a reduction in hepatic arterial resistance thus allowing some compensation for the reduced portal venous blood flow. Halothane had no such effect and would seem potentially harmful to a liver with an already compromised blood supply. However, the theoretical

advantage of enflurane in this respect may be outweighed in most situations by the greater general cardiovascular depression produced by enflurane.

Finally, what course should future investigations into this subject take? Hopefully electromagnetic flowprobes may soon become cheap and reliable enough to allow implantation chronically into dogs, thus facilitating the study of liver blood flow in unanaesthetised animals. Ultimately it is hoped that progress will be made towards developing safe and accurate methods of studying the dual circulation to the liver in man.

APPENDIX

The Statham SP2202 Electromagnetic Flowmeters

Principle of Operation

Measurement of blood flow by the electromagnetic method is based on Faraday's Law of Electromagnetic Induction, i.e.

$$E = (MLV) \times 10^{-8}$$

where E is the electromotive force (volts) (emf), M is the magnetic field (gauss), L is the diameter of the lumen (cm) and V is the velocity of the liquid (cm/sec). This induced emf can be obtained by permitting a conductive liquid such as blood to flow through a magnetic field and generate an emf in a direction at right angles to both the magnetic field and the direction of motion of the blood flow.

It was shown by Kolin (1936) that, if blood is passed through a magnetic field a linear relationship existed between the velocity of the blood and the resulting induced emf. This holds true for both laminar and turbulent blood flow. The blood does not need to be in direct contact with the platinum recording electrodes as long as the tube through which it is flowing is electrically conductive such as an artery, vein or porous vascular prosthesis. The sensitivity of this recording is unaffected by the thickness of the vessel wall provided the diameter of the vessel remains constant. This means that recordings obtained at low flows, when the vessel

has collapsed must be viewed with caution; this occurred in these experiments during the halothane and enflurane studies when splenic venous blood flow was impossible to measure.

The electromagnetic flowprobes used in these experiments were of a standard design, that is, they encircle the vessel being studied and have a slotted gate which allows the vessel to be slid inside the probe; the gate is then shut and the vessel is encircled. The probe contains the electromagnets and platinum recording electrodes. In the Statham SP2202 series flowmeters used in this series of experiments, the magnets were excited by a pulsed square wave electrical current with alternate positive and negative pulses and an interval between each pulse, equal in time to the pulse (Fig. 26). This allows up to four flowmeters to be used at the same time without interference. It also allows electronic zeroing to take place during the zero current interval. In these experiments the electronic zero facility was checked from time to time by occluding the vessels distally with balloon occluders (Rhodes Medical Instruments). This revealed a stable zero error in both hepatic arterial and portal venous flowprobes which was subtracted from readings made.

A number of precautions were taken to ensure the accuracy of the flow recordings. The probes were cleaned after each experiment with pumice on pipe cleaners. Prior to each experiment they were placed in a beaker of saline for at least ten minutes. The vessels being studied were meticulously cleared of all adventitia. A further reason for choosing greyhounds from 20-30 kg to study was that the hepatic artery and portal veins are of fairly consistent size, ensuring the probes used fitted the vessels securely.

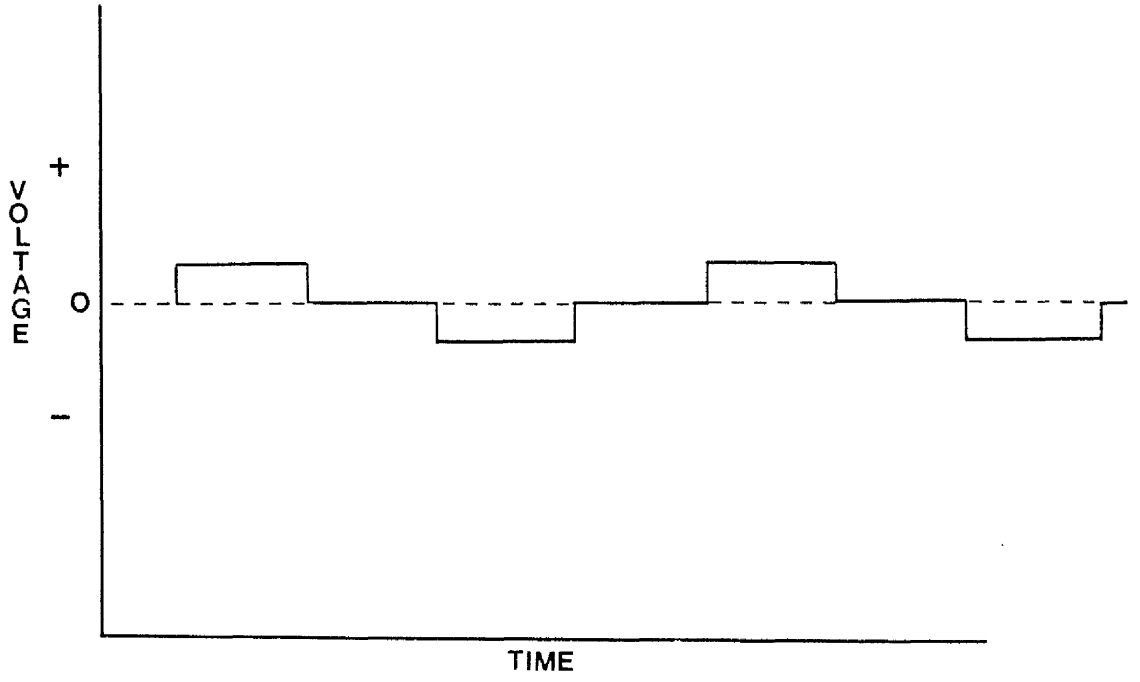

FIGURE 26. Diagramatic illustration of the alternate positive and negative pulses exciting the electromagnetic flowprobes.

Calibration Experiments

In order to check the factory calibration of the flowprobes used on the hepatic artery and portal vein, an in vivo calibration was carried out.

Methods

Three mongrels of approximately 20 kg body weight were anaesthetised in the manner described previously. An incision was made in both thighs and the femoral arteries and femoral veins were exposed for approximately twenty cms. All side branches were exposed and tied off. The haematocrit was determined to ensure it was between 45% and 55%, as variations above and below this level will affect the flow signal obtained. The dog was heparinised with 4,000 units of heparin and one litre of blood was slowly drained from a femoral artery into a heparinised plastic infusion bag. The femoral arteries and veins were both tied off proximally and distally. Plastic cannulae were inserted proximally and distally and secured in place in all the vessels. Flowprobes were placed on the vessel, between the insertion of the proximal and distal cannulae. The femoral artery was used to calibrate the 3 mm flowprobe and the femoral vein to calibrate the 6 mm flowprobe. As both femoral arteries and veins were used in each dog, a total of six calibration experiments were performed. The blood previously collected was infused through a pulsatile pump, through the vessel being studied and collected in a plastic measuring cylinder. Flows over the range 50 mls/min to 350 mls/min were studied in the femoral artery and 100 mls/min to 1,000 mls/min in the femoral vein.

Results

The factory determined sensitivity factor was found to be correct in the 3 mm probe and a small adjustment was necessary with the 6 mm flowprobe. This having been done, a correlation coefficient of 0.995 between actual flow and the electromagnetic flowmeter reading was obtained with the 3 mm probe (Fig. 27) and a correlation coefficient of 0.998 between actual flow and the electromagnetic flowmeter was obtained with the 6 mm probe (Fig. 28).

Conclusion

The electromagnetic flowprobes were found to produce very accurate results over the range of hepatic arterial and portal venous blood flows studied in all the experiments described in this thesis.

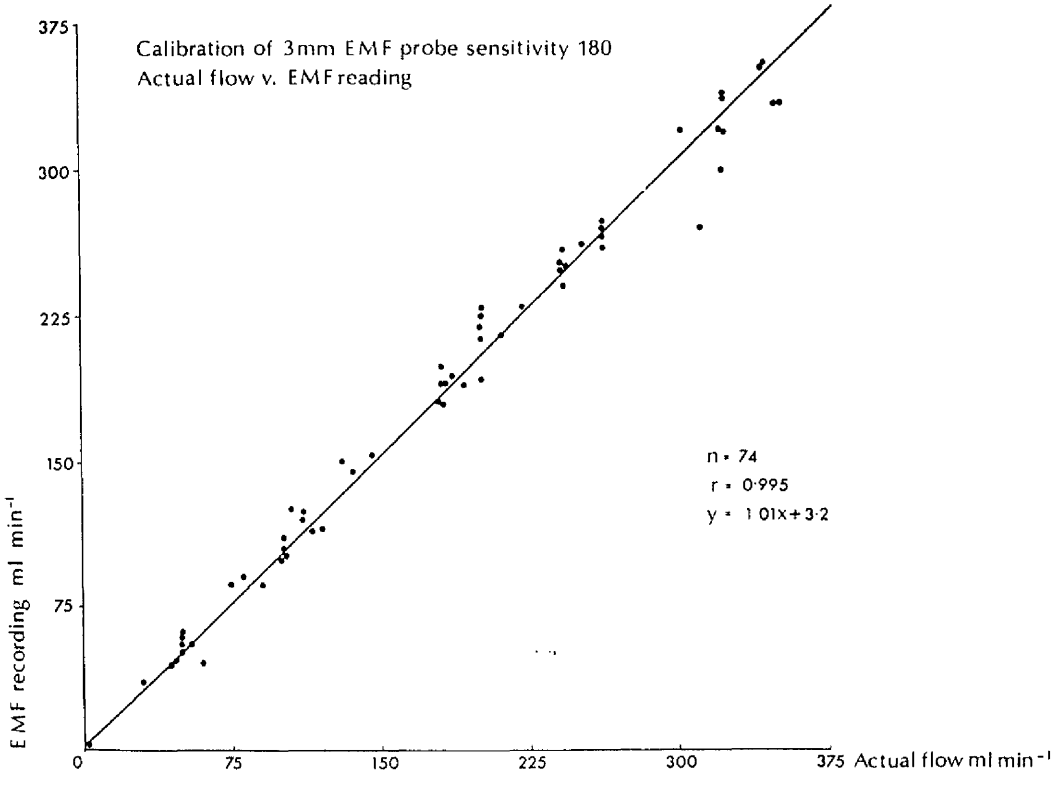

FIGURE 27. Comparison of actual VS recorded blood flow in six experiments using a 3 mm Statham electromagnetic flowprobe (74 readings).

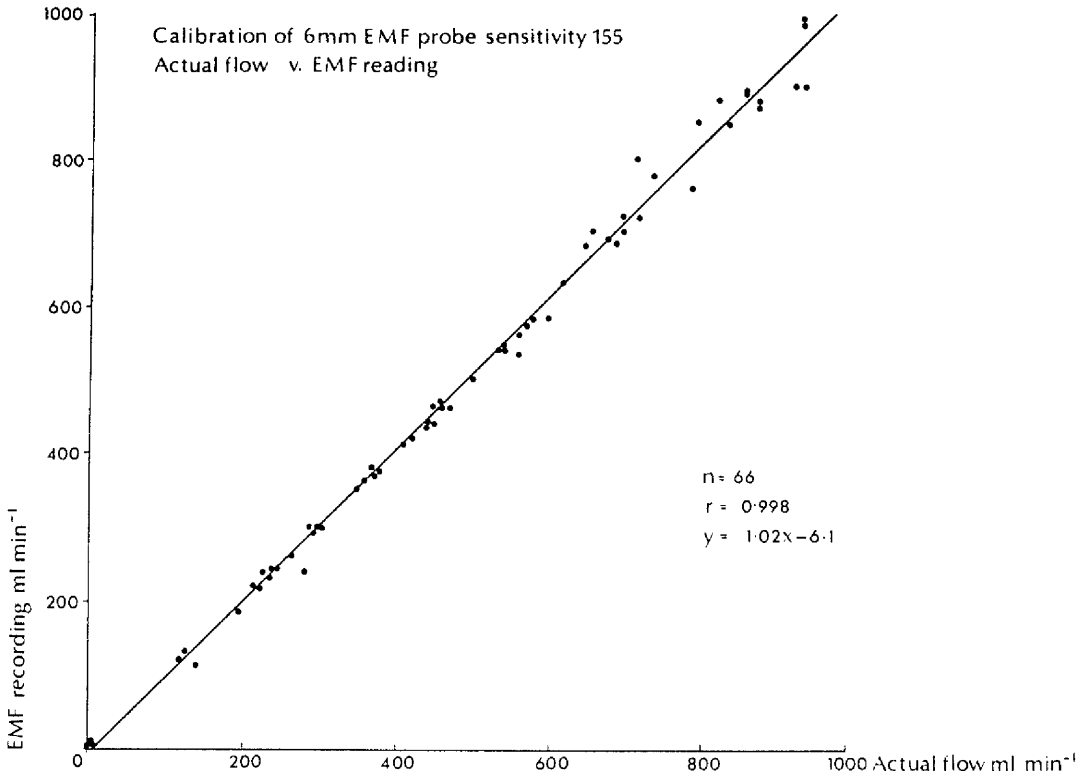

FIGURE 28. Comparison of actual VS recorded blood flow in six experiments using a 6 mm Statham electromagnetic flowprobe (66 readings).

PUBLICATIONS RESULTING FROM WORK INCLUDED IN THIS THESIS AS OF NOVEMBER, 1979

1. The effect of hypercarbia on liver blood flow in the greyhound.
Hughes, R.L., Mathie, R.T., Campbell, D. and Fitch, W.
British Journal of Anaesthesia (1978) 50, 632-633P.

2. The effect of hypercarbia on hepatic blood flow and oxygen consumption in the greyhound.
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6. The effects of enflurane and halothane upon liver blood flow and oxygen consumption in the greyhound.
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7. Liver blood flow and blood gases in the greyhound.
Hughes, R.L.
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PUBLICATIONS RESULTING FROM RELATED WORK

NOT INCLUDED IN THIS THESIS

1. Experimental study of a ^{133}Xenon clearance method for measurement of liver blood flow.
Mathie, R.T., Hughes, R.L., Harper, A.M. and Blumgart, L.H.
Gut (1978) 19, A454.

2. A comparative study of liver blood flow using ^{133}Xenon clearance and electromagnetic flowmeter measurements.
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