STUDIES ON CANINE MYOCARDIAL BLOOD FLOW RELATED TO ANAESTHESIA.

An examination of the effects of changes in blood gas tensions and blood pressure.

A thesis for the degree of Doctor of Medicine

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by

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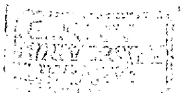

CONTENTS

SUMMARY OF THESIS

The contents of this thesis describe experiments which attempt to determine the responses of blood flow and oxygen consumption in the myocardium along with those of systemic haemodynamic variables to certain of the physiological changes which are imposed by or encountered by anaesthetists in their daily work with patients. The experiments were carried out on closed-chest anaesthetised dogs and the responses to the following conditions have been examined:

1. hypocapnia, induced firstly by increasing minute ventilation of the lungs and secondly, by the withdrawal of carbon dioxide gas which had previously been added to the inspired gas mixture of the hyperventilated animal.

2. hypotension induced by three dose levels of halothane.

3. the combination of halothane-induced hypotension and hypocapnia.

4. hypercapnia induced by the addition of carbon dioxide gas to the inspired gases.

5. hypoxia induced by reduction of the inspired oxygen concentration.

6. hypotension induced by haemorrhage of two different grades of severity (moderate and severe).

All experiments were carried out under light general anaesthesia which was usually induced with thiopentone and maintained with trichloroethylene. In 2 and 3 above (i.e. those experiments involving halothane) anaesthesia was induced with pentobarbitone.

Catheters were positioned in the left coronary artery, the coronary sinus, the ascending aorta and the right atrium under radiographic control using an image intensifier. Myocardial blood flow was measured by estimating the rate of clearance of the radioactive isotope ^{133}Xenon which was injected, in solution, into the coronary artery. Xenon clearance was estimated using a scintillation counter suspended externally over the praecordial area. The clearance was displayed as a curve from which the half time of the clearance was calculated and the half time, when substituted in an equation which was derived on the basis of the Fick principle, allowed the calculation of myocardial blood flow.

Blood oxygen content was calculated from blood oxygen tension. Myocardial oxygen consumption was calculated as the product of the measured blood flow and the arterial-coronary sinus oxygen content difference.

Hypocapnia of moderate degree (arterial carbon dioxide tension 25 mmHg) caused a significant reduction in myocardial blood flow with an associated increase in myocardial oxygen extraction so that oxygen consumption of the myocardium was unaltered. This degree of hypocapnia did not cause significant systemic haemodynamic changes nor were any metabolic changes observed in the myocardium.

Hypotension induced with halothane caused a dose-related reduction in myocardial blood flow and oxygen consumption along with corresponding reductions in heart rate and cardiac output. The higher doses of halothane (1.0% and 1.5%) were associated with increases in myocardial vascular resistance.

The decremental effects of halothane-induced hypotension and hypocapnia on myocardial blood flow were additive when the two conditions were produced simultaneously. During recovery from halothane-induced hypotension, arterial blood pressure gave a poor indication of returning myocardial function. Hypercapnia caused a marked but poorly sustained increase in myocardial blood flow along with a considerable but also poorly sustained reduction in myocardial oxygen consumption. Systemic haemodynamic changes were unremarkable. Similar changes occurred when metabolic acidosis was artificially produced by the infusion of lactic or hydrochloric acid. The responses to hypercapnia were unaffected by beta adrenergic blockade or partial parasympathetic blockade.

Hypoxia did not cause changes in myocardial blood flow until the arterial oxygen tension fell to less than 35 mmHg when a brisk increase in flow occurred. Oxygen consumption was unaffected if hypoxia was sustained for less than 20 minutes. However oxygen consumption fell when hypoxia was sustained for longer periods. Hypoxia was associated with increased blood pressure, increased or decreased heart rate, frequent cardiac arrhythmias and, when sustained, with metabolic acidosis.

The responses to hypoxia were not affected by beta adrenergic blockade or partial parasympathetic blockade.

Haemorrhagic hypotension was associated with considerable reductions in myocardial blood flow. Severe haemorrhage was accompanied by a marked fall in myocardial vascular resistance and also by respiratory and metabolic acidosis. Myocardial oxygen consumption was reduced and oxygen extraction increased, the latter especially so during moderate haemorrhage.

INTRODUCTION

Anaesthesia is a highly abnormal, drug-induced condition and as such, it is frequently associated with gross departures from the normal physiological state, particularly in relation to respiration and circulation. However, by the judicious use of anaesthetic drugs and techniques, the anaesthetist may turn some of these physiological upsets to the advantage of his patient, for example by the lowering of blood pressure to reduce blood loss during surgery or by producing a lowered arterial carbon dioxide tension (hypocapnia) which is thought to diminish the requirements for certain anaesthetic drugs such as analgesic agents and muscle relaxants.

Outwith the operating theatre, the anaesthetist is frequently asked to advise on or assist in the management of patients suffering from acute respiratory problems. Many of these problems, for example severe thoracic injuries, are invariably associated with lowered arterial oxygen tension (hypoxia) and often also with raised arterial carbon dioxide tension (hypercapnia). Many such patients also suffer from haemorrhagic hypotension. It is now well established that such alterations in blood gas tensions and blood pressure as those mentioned above may be associated with profound changes in blood flow in certain tissues, for example hypocapnia causes a reduction in cerebral blood flow (Kety and Schmidt, 1946; Wollman, Smith, Stephen, Colton, Gleaton and Alexander, 1968) and hypercapnia causes an increase in cerebral blood flow (Harper, Glass and Glover, 1961; Reivich, 1964).

Notwithstanding the importance of the myocardial circulation, information relating to it regarding the effects of such changes in respiratory and circulatory homeostasis is scanty or conflicting and furthermore, most of the work which had previously been done in this area had been carried out on open-chest preparations with artificially perfused coronary arterial systems or on isolated heart preparations. Although these had yielded a certain amount of valuable information, they had obvious limitations particularly in the amount of associated systemic haemodynamic data which they could render. In addition, the older work was done before methods of estimation of blood gas tensions and pH were available. Since these are currently the standard methods of assessment of the extent of respiratory and acid-base upsets, it seemed important to re-examine the myocardial blood flow responses to certain of these commonly occurring respiratory and circulatory disturbances using current methods of measurement of blood gases and pH.

For the above reasons therefore, and because of the writer's background in anaesthesia, a series of experiments was devised to examine in the anaesthetised dog, the responses of myocardial blood flow, myocardial oxygen consumption and systemic haemodynamics to the following:-

1. hypocapnia
2. hypotension induced with halothane
3. the combination of halothane induced hypotension and hypocapnia
4. hypercapnia

5. hypoxia

6. haemorrhagic hypotension.

A radioactive inert gas clearance method using ^{133}Xenon was employed for the estimation of myocardial blood flow. This technique was chosen because of its convenience and because it required only the minimum of surgical manipulation and trauma. Experiments could thus be carried out on closed-chest, virtually intact animals so that valid systemic haemodynamic measurements could be made simultaneously with blood flow measurements.

CHAPTER 1

HISTORICAL BACKGROUND

As far back as the time of the ancient Greeks, ideas concerning circulation of the blood existed. Aristotle himself had ideas relating to the pulsation of the heart and the movement of the blood and the early Greeks also suspected some form of mixing of air and blood within the chest although their ideas of why this should happen were quite divorced from the physiological truth. In the 2nd century B.C., Erasitratos of Alexandria described the valves of the heart and also gave a systematic though inaccurate description of a circulation. He postulated that the blood was transferred from the right ventricle to the left ventricle through pores in the interventricular septum. This idea was strengthened by Galen the great Roman physician and the Galenical theory persisted until the middle ages. The celebrated Belgian anatomist, Andreas Vesalius published his great work 'De Humani Corporis Fabrica' in 1543 and in this was included a description of the coronary vessels. From about this time, ideas concerning the true nature of the movement of the blood began to be advanced but the final elucidation had to await the work of William Harvey who, in his major work 'Exercitatio anatomica de motu Cordis et Sanguinis in Animalibus' described the heart as a pump and the manner in which it caused the blood to circulate. He included in this work, published in 1628, a description of the function of the coronary vessels. In the 18th century the part played by pathological conditions of the coronary arteries in cardiac disease

began to be appreciated and in the 19th century the effects of experimental coronary artery ligation were frequently observed.

As the physiological importance of blood supply to tissues began to be appreciated, attempts to measure blood flow were made and have become increasingly refined and more accurate up till the present time. Undoubtedly, one of the most important contributions in the field of blood flow measurement was made by Adolf Fick (1870). Fick showed that the output of the heart could be calculated by dividing the total amount of oxygen taken up by the body in unit time by the amount of oxygen given up by unit volume of blood (i.e. the arteriovenous oxygen content difference). This meant that only arterial and mixed venous blood oxygen content had to be known in addition to total body oxygen uptake. Although Fick was concerned with the estimation of cardiac output, the principle which he stated is applicable to any mass of tissue and is valid for most indicators. It forms an important part of the theory underlying methods of blood flow measurement utilising inert gases.

Almost all methods of flow measurement have, at some time or other, been applied to the coronary circulation, including artificial perfusion in the isolated heart (Langendorff, 1899) and measurement of coronary venous effluent by collection via a cannula (Morawitz and Zahn, 1914). In 1927 Rein applied a thermostromuhr to a coronary artery and measured, for the first time, arterial inflow in the non-artificially perfused heart. Since then, the thermostromuhr has been supplanted by the electromagnetic flow meter and this device has been widely and successfully used in experimental coronary blood flow work.

In 1945 Kety and Schmidt used the inert gas nitrous oxide to measure cerebral blood flow and this method has been used subsequently to measure blood flow in the myocardium (Eckenhoff, Hafkenschiel, Landmesser and Harmel, 1947; Gregg, Longino, Green and Czerwonka, 1951; Goodale and Hackel, 1953). In 1949, Kety demonstrated that blood flow could be measured by externally counting the rate of disappearance of radioactivity after the intramuscular injection of radioactive sodium. With the subsequent ready availability of radioactive isotopes of the inert gases krypton and xenon, the convenience of the methods using measurement of radioactivity and inert gas clearance could be combined. Variations of methods using inert radioactive gas clearance have since been used to measure blood flow in many tissues, for example, in brain (Lassen and Munck, 1955; Høedt-Rasmussen, Sveinsdottir and Lassen, 1966; McDowall and Harper, 1965), in muscle (Lassen, Lindbjerg and Munck, 1964), in skin (Bell and Harper, 1964), in kidney (Bell and Harper, 1965) and in myocardium (Herd, Hollenberg, Thorburn, Kopald and Barger, 1962; Ross, Ueda, Lichtlen and Rees, 1964; Rees, Redding, Ashfield, Gibson and Gavey, 1966; McBride and Ledingham, 1968). In tissues such as brain and myocardium where blood flow is high, the injection of such isotopes into the arterial inflow renders flow estimation very reliable. Such a method is used to measure myocardial blood flow in the experiments to be described herein.

CHAPTER 2.

MATERIALS AND METHODS

All studies were carried out in a laboratory of the Department of Surgery, Western Infirmary, Glasgow. The basic methods used throughout the series of studies are described in this chapter. Variations from, or additions to these basic methods are described at the beginning of the appropriate chapters. A brief description of the functioning of certain of the items of apparatus used is contained in the appendix.

All experiments were carried out on healthy, adult dogs under anaesthesia which was usually induced with a 2.5% solution of sodium thiopentone given intravenously in a dosage of 15-20 mg/kg body weight. This was immediately followed by suxamethonium chloride 50-100 mg and endotracheal intubation was performed. Intermittent positive pressure ventilation was then commenced and maintained using a Palmer respiratory pump, the minute volume from which was adjusted to produce an arterial carbon dioxide tension ($PaCO_2$) of about 40 mmHg. This was facilitated by monitoring expired CO_2 content using an infra-red carbon dioxide analyser. Anaesthesia was usually maintained with trichloroethylene 0.5-1% vaporised from a Tritec vaporiser. The carrier gas for this agent was a mixture of oxygen and nitrogen, the respective volumes of which were adjusted to produce an arterial oxygen tension (PaO_2) of about 100 mmHg. This was facilitated by measuring the inspired oxygen concentration (FIO_2) with a paramagnetic oxygen analyser. An FIO_2 of 23-25% was usually required. Reflex movements were prevented by

the administration of 100 mg doses of suxamethonium chloride given intramuscularly as required. The core temperature of the animal was recorded using a copper-constantan thermocouple passed through the mouth, into the mid-oesophageal region. Under fluoroscopic control using an image intensifier, a No.7 Sones catheter was inserted via the exposed common carotid artery in the neck and manipulated until its tip came to lie a few millimetres within the orifice of one of the two main branches of the left coronary artery - usually the circumflex branch. Heparin 2,500 I.U. was administered at this time and at 2 hourly intervals thereafter. A second catheter was inserted in a similar manner into the external jugular vein and manipulated until its tip lay several centimetres into the coronary sinus. Figure 1 shows a coronary angiogram taken at this stage in the preparation of one of the animals. Other catheters were inserted through the left femoral artery and vein into the descending aorta and right atrium respectively and connected to appropriately calibrated pressure transducers. Blood samples were thus available from the aorta, right atrium and coronary sinus and pressure measurements from the aorta and right atrium.

Myocardial blood flow was measured using a method similar to that described by Herd and associates (1962) and Ross and associates (1964). The dead space of the coronary arterial catheter was filled with 0.5-1 ml of a solution of the radioactive isotope ^{133} Xenon. This was then flushed into the coronary artery using a 3 ml bolus of heparinised normal saline warmed to 37^{o}C. The clearance of the isotope from the myocardial tissue was measured using a scintillation counter suspended externally over the praecordial area. The output from the counter was passed to an Ecko pulse height analyser and

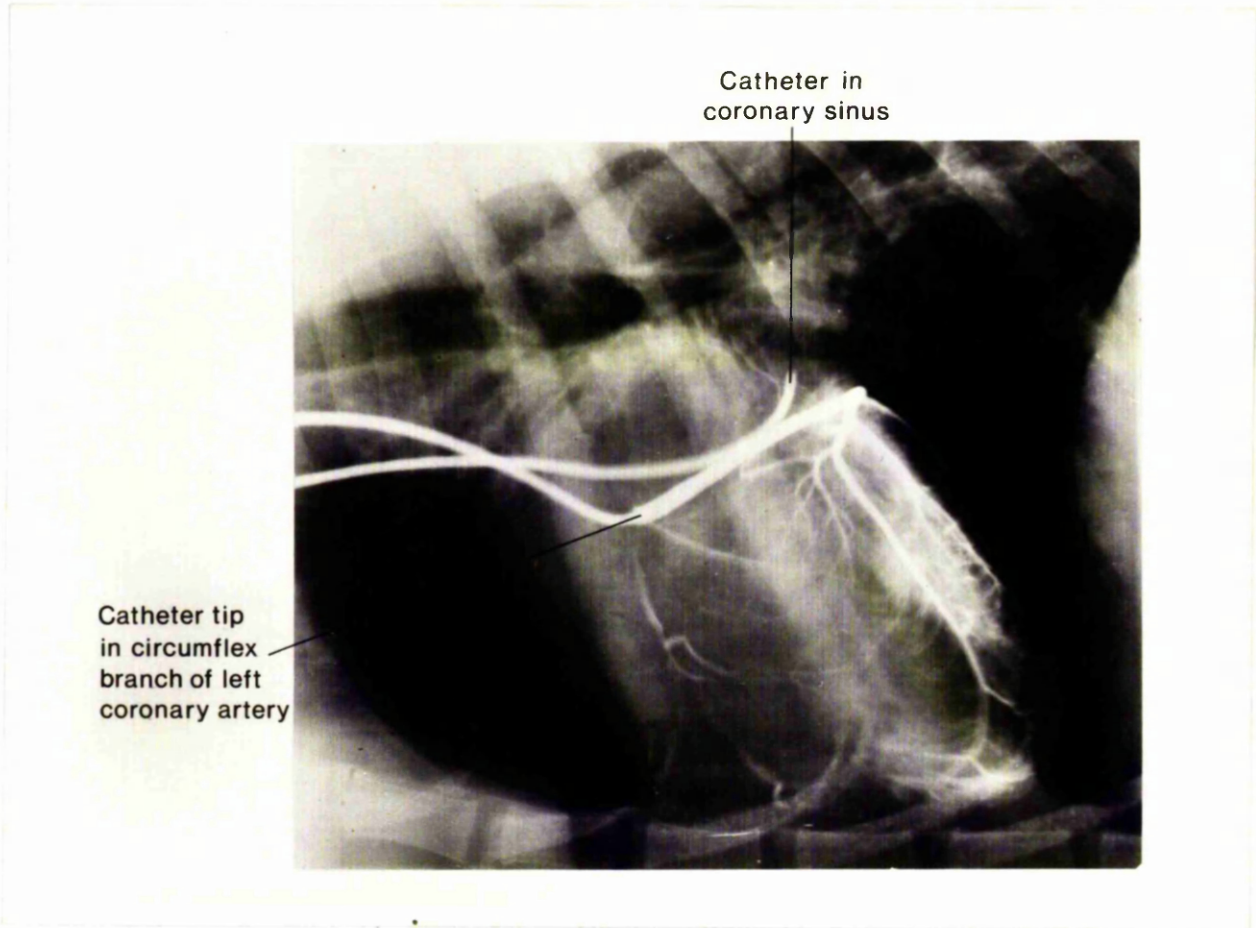

Fig. 1. A coronary angiogram taken during the preparation of one of the animals. The Sones catheter is seen entering the ostium of the circumflex branch of the left coronary artery which is well demonstrated. A small amount of contrast medium has also entered the anterior descending branch. The coronary sinus catheter is also seen in situ.

ratemeter and the clearance was displayed as a curve on a Servoscribe direct writing recorder operating at a paper speed of 120 mm/min. A typical clearance curve is shown in figure 2. The derivation of myocardial blood flow in ml/100g/min from this curve is explained later. The general experimental set-up is seen in the diagram in figure 3 and the photograph in figure 4.

Blood oxygen and carbon dioxide tensions and pH were measured using appropriate electrode systems. 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. The oxygen electrode was covered with a membrane of 20μ polypropylene. Because of the diffusibility characteristics of oxygen through the membrane, a systematic error is introduced into the measurement of PO_2 in blood as compared with that in the gaseous phase (McDowall, Ledingham and Tindal, 1968). To correct this, a blood-gas factor was derived for each experiment using blood which was equilibrated by tonometry in a rotating syringe with oxygen of a known tension (Torres, 1963). This factor was applied to each measurement of oxygen tension. Since the electrodes were maintained constantly at 37^{o}C, all measurements of blood pH, PCO_2 and PO_2 were corrected for any difference in temperature between the animal's mid-oesophagus and the electrodes using the blood gas calculator designed by Severinghaus (1966). This also allowed the calculation of blood oxygen saturation from PO_2 taking into account the blood pH and the animal's temperature. Haemoglobin (Hb) concentration was measured using the cyanhaemoglobin method (see appendix).

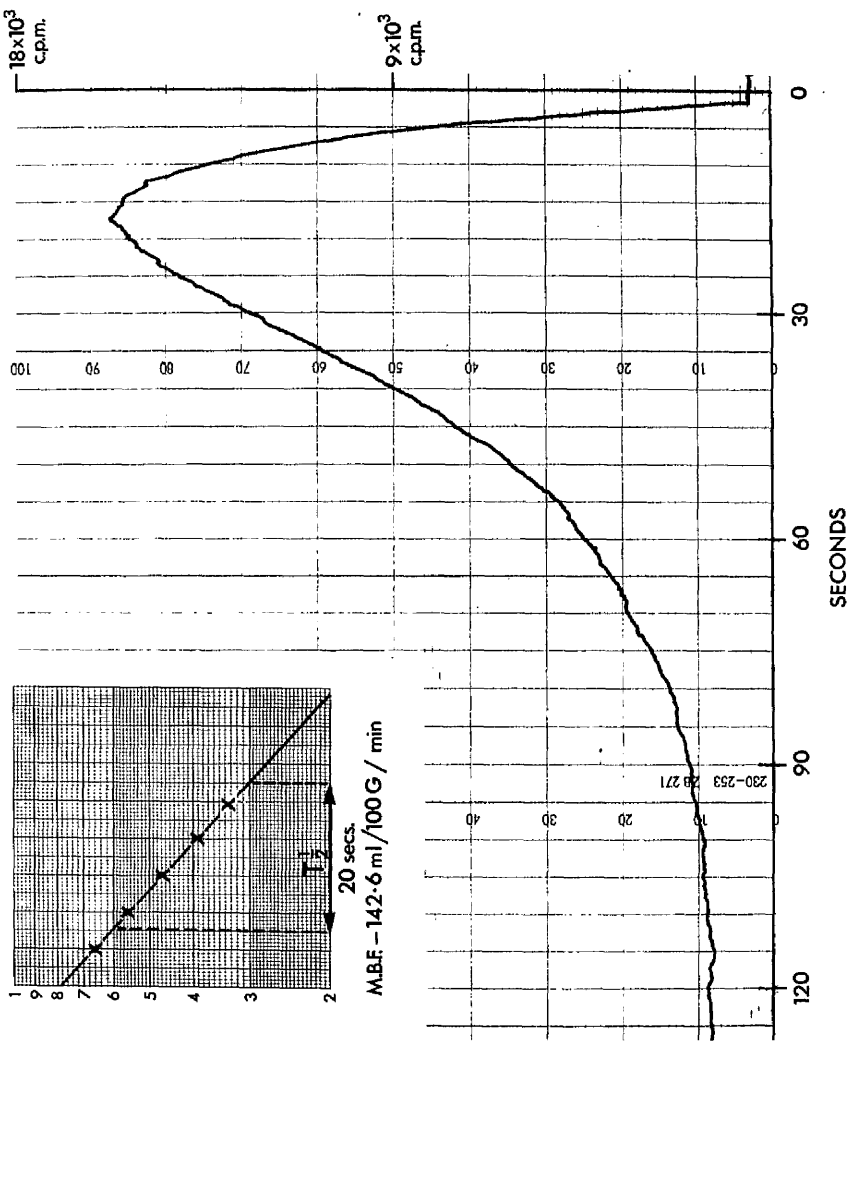

Fig. 2. A typical radioactive clearance curve. The upslope of the curve commencing at 0 sec. represents the phase of entry of the isotope into the myocardium. The downslope is the clearance phase which is mono-exponential for most of its course. The semi-logarithmic plot of this curve is seen in the inset with the derivation of $T\frac{1}{2}$.

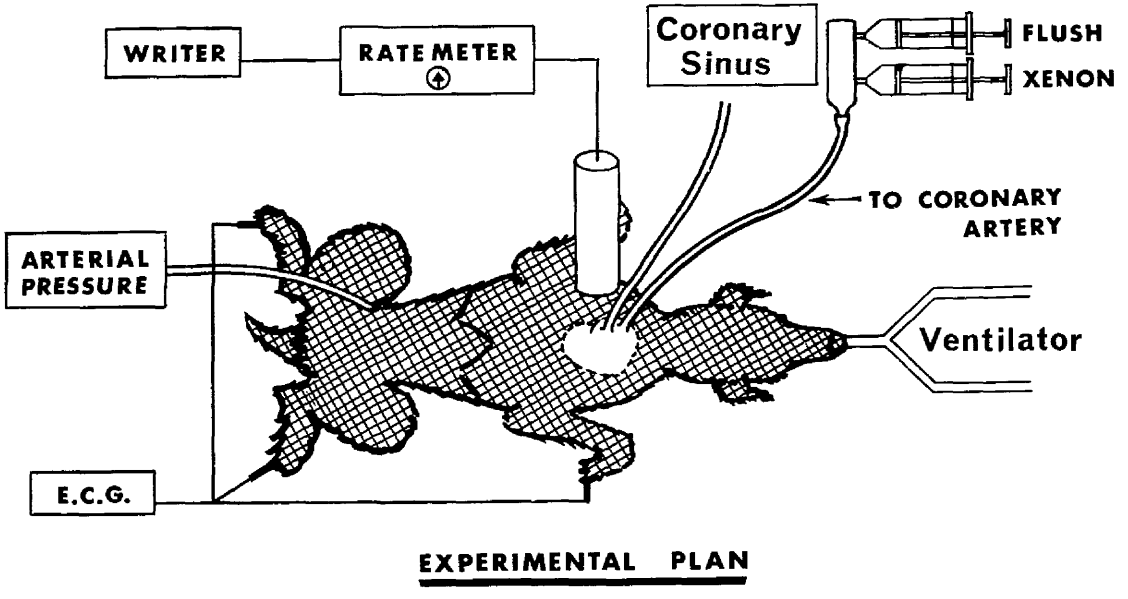

Fig. 3. Schematic diagram of the experimental plan. The scintillation counter is suspended over the praecordial area.

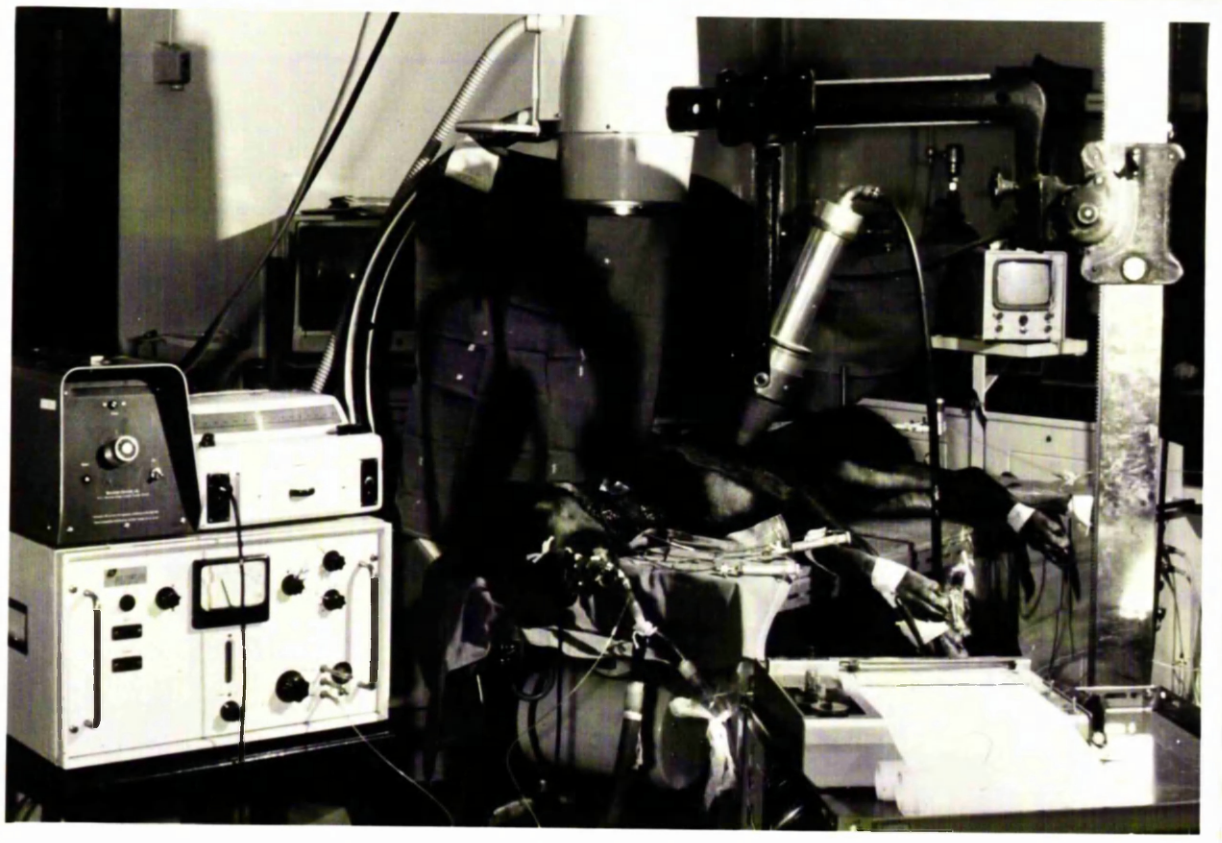

Fig. 4. Photograph of the experimental set-up. The endotracheal tube and thermocouple lead are seen entering the mouth of the animal. The scintillation counter is approximated to the chest wall and in the right foreground is seen the recorder for the clearance curve. The oxygen analyser, temperature recorder and carbon dioxide analyser are in the left foreground. The image intensifier head is visible beneath the table and the viewing screen is in the left-centre background. The oscilloscope for display of E.C.G. and pressure trace is seen in the right background mounted above the ink-jet recorder. The coronary arterial and coronary sinus catheters are seen entering the neck area.

The oxygen content of blood was calculated as follows:-

$$\text{Blood oxygen content (ml/100 ml)} = \text{Hb(g/100 ml)} \times 1.34 \times \frac{\text{\% saturation}}{100} + PO_2\text{(mm Hg)} \times 0.0031$$

The factor 0.0031 is the Bunsen solubility coefficient which indicates the volume of oxygen in ml which dissolves in plasma per mm Hg oxygen tension at $37^{o}C$.

The electrocardiogram (standard limb lead II) was constantly visible on an oscilloscope along with the aortic and right atrial pressure traces and these were recorded, during flow measurements, on a multichannel ink-jet recorder (Elema-Schonander, Mingograf 81). Mean pressures were obtained by integration and the heart rate was counted from the electrocardiogram. Cardiac output was measured using a dye-dilution method. 1 ml of indocyanine green dye was injected into the right atrium and blood containing the diluted dye was withdrawn from the aorta through a cuvette densitometer. The signal from the densitometer was fed to a recorder which displayed the dilution of the dye as a curve from which the output was calculated (see appendix for details).

In certain of the experiments, concentrations of lactate, pyruvate, non-esterified fatty acids (NEFA) and glucose in arterial and coronary sinus blood were measured (for methods see appendix). From the foregoing measurements, the following data were derived (for the purpose of these calculations and later in the presentation

of results, it is assumed that right atrial blood is representative of mixed venous blood although it is appreciated that minor discrepancies may occur due to incomplete mixing of blood in the right atrium).

1. Myocardial O_2 extraction (%) =

$$\frac{\text{arterial-coronary sinus } O_2 \text{ content difference (ml/100 ml)} \times 100}{\text{arterial } O_2 \text{ content (ml/100 ml)}}$$

2. Myocardial O_2 availability (ml/100g/min) =

$$\frac{\text{myocardial blood flow(ml/100g/min)} \times \text{arterial } O_2 \text{ content (ml/100 ml)}}{100}$$

3. Myocardial O_2 consumption (ml/100g/min) =

$$\frac{\text{myocardial blood flow(ml/100g/min)} \times \text{arterial-coronary sinus } O_2 \text{ content difference (ml/100 ml)}}{100}$$

4. Myocardial consumption of lactate, pyruvate, NEFA and glucose were calculated as in 3 above with the appropriate quantity substituted for oxygen.

5. Total body O_2 extraction (%) =

$$\frac{\text{arterial-right atrial } O_2 \text{ content difference (ml/100 ml)} \times 100}{\text{arterial } O_2 \text{ content (ml/100 ml)}}$$

6. Total body O_2 availability (ml/min) =

$$\frac{\text{cardiac output (ml/min)} \times \text{arterial } O_2 \text{ content (ml/100 ml)}}{100}$$

7. Total body O_2 consumption (ml/min) =

$$\frac{\text{cardiac output(ml/min) x arterial-right atrial } O_2 \text{ content difference (ml/100 ml)}}{100}$$

8. Myocardial vascular resistance (arbitrary units) =

$$\frac{\text{mean arterial pressure (mm Hg) minus right atrial pressure (mm Hg) x 100}}{\text{Myocardial blood flow (ml/100g/min)}}$$

9. Systemic vascular resistance (arbitrary units) =

$$\frac{\text{mean arterial pressure (mm Hg) minus right atrial pressure (mm Hg)}}{\text{cardiac output (l/min)}}$$

Results are presented as tables or figures showing mean values $\pm$ the standard error of the mean (SEM). Statistical significance between groups of data was tested using Student's t test for paired data. The P values are indicated where significant changes occurred (i.e. $P < 0.05$).

Theoretical considerations arising from methods.

The method of measurement of myocardial blood flow described requires the injection of a small volume of a solution of the radioactive inert gas ^{133}Xenon directly into the arterial supply of the myocardial tissue. In considering the validity of the method certain assumptions have to be made. It is assumed that:-

1. During the passage of the bolus of radioactive xenon solution through the myocardium, the isotope becomes evenly distributed throughout the volume of tissue perfused by the vessel into which the solution is injected.

2. The blood to tissue distribution of the isotope occurs as a function of the blood/tissue partition coefficient of xenon. The blood/tissue partition coefficient is known as λ and has been shown to have the value 0.72 (Conn, 1961).

3. Recirculation of the isotope is negligible. (Because of the much higher affinity of xenon for air than blood, some 95% of the gas comes out of the blood in a single passage through the lungs (Ueda, Lichtlen, Rees, Ross and Iio, 1963). The amount left for recirculation is therefore very small and when it is borne in mind that only the coronary effluent contains the isotope and that this is diluted by the blood returning to the heart from all other areas of the body then the amount of radioactivity recirculating to the myocardium is indeed negligible.) After the initial passage of the bolus therefore, the arterial blood coming to the myocardium can be considered free of xenon and so the isotope then moves back from the tissue into the blood and is cleared from the myocardium at a rate which is a function of capillary blood flow.

4. A single clearance system is being measured in which capillary flow during the time of measurement is constant. (Ueda et al., (1963) showed that the clearance curve follows a single exponential

until radioactivity declines to less than 20% of peak level. In taking measurements therefore, only points which lie above this level on the curve are used thus ensuring that the clearance may be analysed as a single exponential.)

Calculation of myocardial blood flow.

A single bolus of radioactive xenon solution is introduced into the coronary artery.

Let Ca = concentration of xenon in the artery.
Cv = concentration of xenon in the vein.
Cm = concentration of xenon in the myocardium.
Qm = mass of xenon in the myocardium.
F = blood flow.
t = time.

The rate of change of the amount of xenon in the myocardium is expressed in terms of flow by the Fick principle:

$$\frac{d\,Qm}{dt} = F\,(Ca - Cv)$$

After passage of the bolus of gas solution

$$Ca = 0 \text{ (since recirculation is negligible)}$$

$$\therefore \frac{d\,Qm}{dt} = -\,F\,Cv$$

But at blood/tissue equilibrium, $\lambda = \frac{Cm}{Cv}$

$$\therefore \quad Cv = \frac{Cm}{\lambda}$$

Since $Cm = \frac{Qm}{Vm}$ then $Cv = \frac{Qm}{Vm}$

$$\therefore \quad \frac{d\,Qm}{dt} = -\frac{FQm}{\lambda Vm}$$

This is a standard differential equation which can be solved using the exponential decay expression

$Qm = Qm\,(0)\,e^{-kt}$ where $Qm\,(0)$ is the value of Qm at the commencement of the measured clearance (i.e. when $t = 0$) and e is the base of natural logarithms.

$$\text{The clearance rate constant } k = \frac{F}{\lambda Vm}$$

$$\therefore \quad \frac{F}{Vm} = k\lambda$$

Since the partition coefficient λ has a known value (0.72), the expression means that flow per unit volume of tissue can be found when k, the only other unknown in the equation is calculated. k is calculated from the time required for the exponentially decaying Qm to fall from any value to half of that value.

This is derived as follows:-

In the expression $Qm = Qm\,(0)\,e^{-kt}$, if the time required for $Qm\,(0)$ to fall to half its value is $t_{\frac{1}{2}}$ then

$$\frac{Qm}{2} = Qm\, e^{-kt_{\frac{1}{2}}}$$

$$\therefore \quad \tfrac{1}{2} = e^{-kt_{\frac{1}{2}}}$$

$$\therefore \quad \tfrac{1}{2} = \frac{1}{e^{kt_{\frac{1}{2}}}}$$

$$\therefore \quad e^{kt_{\frac{1}{2}}} = 2$$

$$\therefore \quad kt_{\frac{1}{2}} = \log_e 2$$

$$\therefore \quad k = \frac{\log_e 2}{t_{\frac{1}{2}}}$$

$$\log_e 2 = 0.69315$$

$\therefore$ k can be calculated when $t_{\frac{1}{2}}$ is determined experimentally. $t_{\frac{1}{2}}$ is found by transposing points from the clearance curve at 5 second intervals to semilogarithmic paper. This results in a straight line plot and the time taken for the radioactivity to decline from any level to half of that level is easily determined (see inset - Fig. 4).

The equation $\frac{F}{Vm} = k\lambda$ can now be rewritten as $F = k\lambda Vm$

If a volume of myocardium of 100 ml is selected, then

$$F = k\,\lambda\, 100 \text{ ml/min/100 ml}$$

$$= k\,\lambda\,\frac{100}{\rho} \text{ ml/min/100g}$$

ρ is the density of the myocardium and = 1.05g/ml according to Herd et al. (1962) and λ = 0.72 (Conn, 1961).

$$\therefore \text{Myocardial blood flow} = \frac{k \times 0.72 \times 100}{1.05} \text{ ml/100g/min.}$$

$$= 68.5 \text{ k ml/100g/min.}$$

Practical considerations.

It is important to consider whether the presence of a catheter tip in the orifice of the coronary artery is likely to constitute an obstruction to blood flow. There are several reasons which lead to the conclusion that this is not so. Firstly, the tip of the Sones No.7 catheter is fine and tapered and it is introduced only a few millimetres into the orifice of the coronary artery. Radiography shows the vessel to have a diameter which is usually at least twice that of the catheter for example in figure 3, the diameter of the vessel at its orifice is 3.5 mm whereas that of the catheter is 1.5 mm. The cross sectional area of the vessel is therefore considerably greater than that of the catheter tip (8.5 sq mm as opposed to 1.77 sq mm) and therefore the resistance to flow imposed by the very short segment of catheter in the vessel is likely to be negligible when considered in relation to the total resistance of the left coronary vascular bed. Furthermore, if the catheter is advanced along the artery, visible slowing of clearance of radio-opaque contrast medium can be seen when the catheter reaches a point where the vessel flow is becoming obstructed. At this point, E.C.G. evidence of ischaemia may be seen which is not present when the catheter is satisfactorily sited. Brice, Dowsett and Low (1964)

showed that in experimental and pathological occlusion of the carotid artery some 80-90% of the cross sectional area of the vessel had to be occluded before flow was reduced or the pressure gradient across the obstructed area increased. If a similar type of relationship holds good for the coronary artery, then the catheter, when satisfactorily sited, should not obstruct flow. Finally, and perhaps most convincing of all, when the catheter is withdrawn from the coronary artery during the inscription of a curve, no alteration occurs in the continuity of the curve and thus in the rate of xenon clearance (see Fig. 5).

The other item of methodology that requires some comment regarding its accuracy is the method of estimation of blood oxygen content. Such indirect methods as that used here are open to the criticism that since they involve a number of different measured quantities each of which is liable to inaccuracies, then the reliability of the estimations is questionable. Because of this, in one of the series of animals, a comparison was made between the method of estimation of oxygen content from PO_2 and a direct method of estimation using the technique of Van Slyke and Neill (1924). The result of this comparison is shown in figure 6. There was a close correlation between the two methods and therefore the indirect method of estimation of oxygen content is regarded as satisfactory.

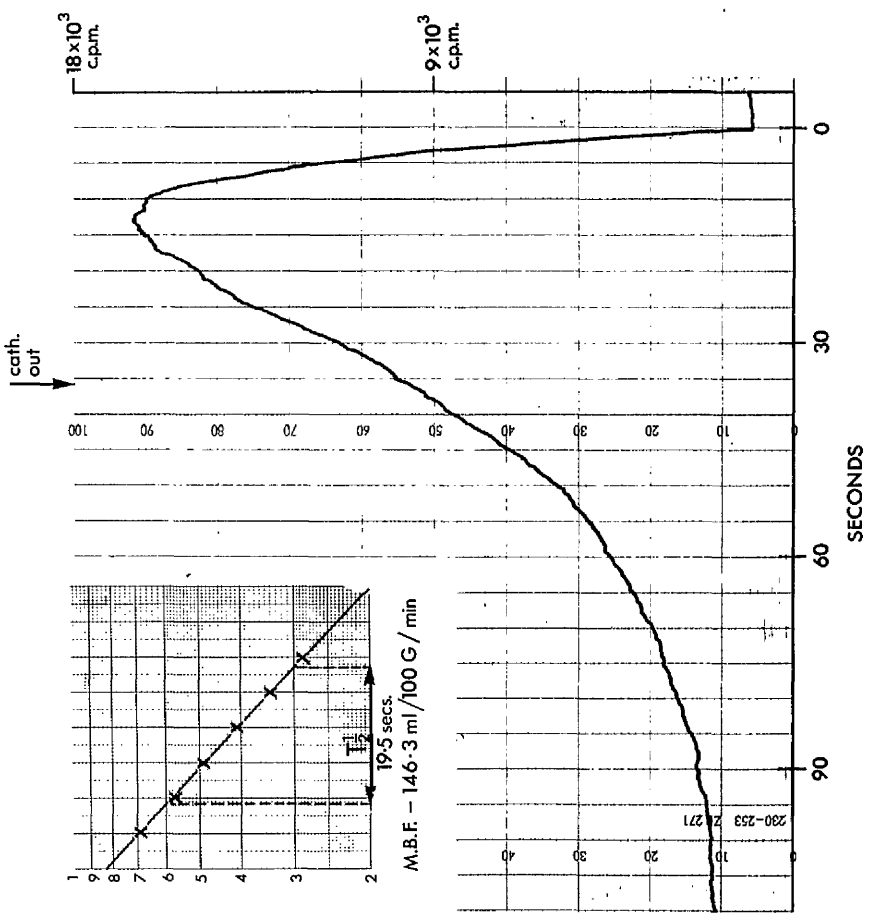

Fig. 5. This clearance curve was obtained a few minutes after that seen in figure 2. The curves are virtually identical with very similar flow rates. At the arrow marked 'cath. out' the coronary arterial catheter was withdrawn from the coronary artery. No discontinuity of the curve is seen indicating no change in flow rate, thus showing that the catheter was not obstructing flow.

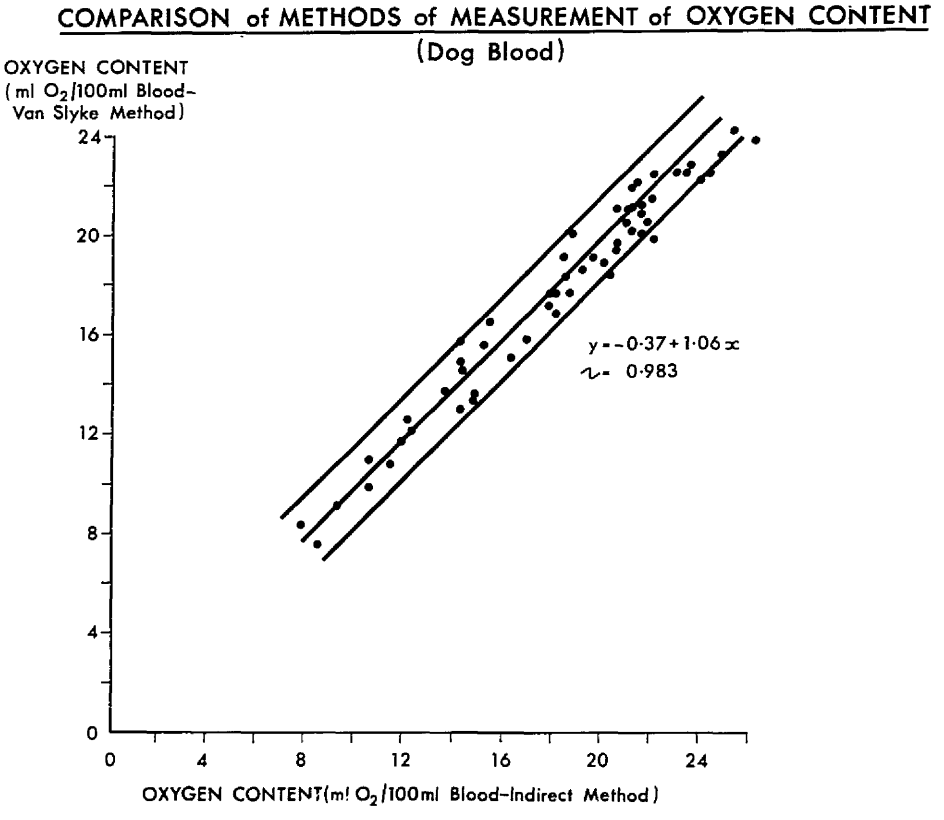

Fig. 6. A comparison of blood oxygen contents derived by calculation from PO_2 (indirect method) and measurement by the Van Slyke method. The close correlation between the two methods is evident.

CHAPTER 3.

RESPONSES OF MYOCARDIAL BLOOD FLOW AND METABOLISM TO HYPOCAPNIA.

Eleven animals were included in this study (weight range 18-25 kg). The technique of anaesthesia and methods of measurement were as described in Chapter 2.

The experiments were carried out in five phases so that hypocapnia was induced by two methods. The five phases were as follows:

1. Control phase - $PaCO_2$ about 40 mm Hg.
2. Hyperventilation by increasing tidal volume - $PaCO_2$ about 25 mm Hg.
3. As phase 2 with CO_2 gas added to the inspired gas mixture - $PaCO_2$ about 40 mm Hg.
4. CO_2 gas withdrawn - $PaCO_2$ about 25 mm Hg.
5. Ventilation returned to control level - $PaCO_2$ about 40 mm Hg.

Haemoglobin concentration was estimated at the commencement of each phase. The duration of phases 1, 2, 3 and 4 was 20-30 minutes while phase 5 was slightly longer (25-35 min).

Two sets of measurements of myocardial blood flow, haemodynamic data, arterial, coronary sinus and mixed venous blood gases and pH were made during each phase after stabilisation of the $PaCO_2$.

Along with the second of each of these sets of measurements, blood samples were withdrawn from the aorta and coronary sinus for estimation of blood glucose, lactate, pyruvate and NEFA. Altogether these samples amounted to some 60 ml of blood during each phase and this was replaced with Dextran 110 in 0.9% saline. This resulted in an increasing haemodilution throughout the experiment. Mean haemoglobin concentration for the eleven dogs during the five consecutive phases were 22.4, 21.7, 19.5, 18.5 and 18.1 (g/100 ml).

The blood gas and pH changes occurring throughout the five phases are shown in table 1. Although the arterial oxygen tension remained stable throughout the procedure, there were considerable reductions in coronary sinus oxygen tension during hypocapnia, suggesting an increase in myocardial oxygen extraction and this is confirmed in a later table. A similar but less striking pattern is seen in mixed venous oxygen tension. The coronary sinus and mixed venous PCO_2 and pH changes paralleled those of the arterial blood.

The important haemodynamic data including myocardial blood flow changes are seen in table 2. There were significant reductions in myocardial blood flow during both hypocapnic phases. Although a slight fall in arterial blood pressure occurred and was sustained throughout the total period of hyperventilation (in phases 2, 3 and 4), this did not become statistically significant. Blood pressure returned to control level on resumption of normoventilation. Although cardiac output fell gradually throughout the period of the investigation, there were no significant alterations between succeeding phases.

Arterial oxygen content and myocardial oxygen availability extraction and consumption changes throughout the experiment are seen in table 3. The steady fall in haemoglobin concentration previously noted resulted in a reduction in arterial oxygen content over the total period of the investigation. This trend is also apparent in the myocardial oxygen availability figures but these are of course influenced by the blood flow changes. There was a highly significant increase in myocardial oxygen extraction during hypocapnia and, although oxygen consumption showed a slight downward trend there were no significant changes between succeeding phases. In most of the experiments the second phase (i.e. the phase of increased ventilation) was maintained for only some 20-25 minutes; however, in two of the animals it was maintained for a longer period with similar results in both cases. Figure 7 shows results from one of these animals. Throughout the period of hyperventilation the myocardial blood flow remained at a reduced level but rose promptly again when the arterial carbon dioxide tension was returned to normal by adding carbon dioxide gas.

The absolute concentrations of glucose, lactate, pyruvate and non-esterified fatty acid in arterial and coronary sinus blood are shown in table 4. The onset of hyperventilation and hypocapnia was accompanied by a significant increase in lactate concentration in arterial and coronary sinus blood. There were no significant changes in systemic levels of pyruvate, NEFA or glucose associated with $PaCO_2$ changes. At no time did the myocardium appear to utilise important quantities of glucose but there was consistant extraction of lactate, pyruvate and NEFA from the arterial blood by the myocardium and the mean per cent extraction of these substrates is shown in table 5.

	Control		Hyperventilation		Hyperventilation + CO_2		CO_2 Off		Normoventilation
Arterial PCO_2 (mmHg)	± 40.7 0.7	p<0.001	± 24.9 0.4	p<0.001	± 41.8 0.6	p<0.001	± 25.1 0.6	p<0.001	± 40.7 1.0
Arterial pH (units)	±7.334 −0.012	p<0.001	±7.438 −0.006	p<0.001	±7.306 −0.012	p<0.001	±7.435 −0.008	p<0.001	±7.330 −0.005
Arterial PO_2 (mmHg)	100.8 ± 1.7		105.8 ± 1.9		97.4 ± 2.0		101.0 ± 1.9		102.4 ± 1.7
Coronary Sinus PO_2 (mmHg)	± 32.9 0.7	p<0.001	± 25.2 0.9	p<0.001	± 33.8 0.9	p<0.001	± 22.8 0.9	p<0.001	± 30.9 0.9
Mixed Venous PO_2 (mmHg)	± 55.2 1.5	p<0.025	± 48.4 1.7		± 50.1 1.0	p<0.001	± 41.6 0.9	p<0.025	± 45.2 1.3
Coronary Sinus PCO_2 (mmHg)	± 55.6 0.8	p<0.001	± 39.6 0.8	p<0.001	± 57.4 1.2	p<0.001	± 38.0 0.9	p<0.001	± 54.1 1.5
Coronary Sinus pH (units)	±7.278 −0.007	p<0.001	±7.380 −0.005	p<0.001	±7.254 −0.014	p<0.001	±7.377 −0.010	p<0.001	±7.275 −0.008
Mixed Venous PCO_2 (mmHg)	± 47.6 0.7	p<0.001	± 33.4 0.5	p<0.001	± 49.6 0.7	p<0.001	± 34.5 1.2	p<0.001	± 46.7 0.7
Mixed Venous pH (units)	±7.296 −0.007	p<0.001	±7.402 −0.006	p<0.001	±7.268 −0.012	p<0.001	±7.408 −0.009	p<0.001	±7.302 −0.002

TABLE 1. PCO_2, PO_2 and pH changes in arterial, coronary sinus and mixed venous blood during five phases of the hypocapnia investigation (mean ± SEM, 11 dogs.)

	Control		Hyperventilation		Hyperventilation + CO_2		CO_2 Off		Normoventilation
Myocardial Blood Flow (ml/100g/min)	106.5 ± 5.4	$p<0.005$	86.8 ± 4.2	$p<0.005$	107.1 ± 4.5	$p<0.001$	76.7 ± 3.2	$p<0.05$	90.0 ± 6.5
Mean Arterial Blood Pressure (mmHg)	144.2 ± 5.7		133.5 ± 5.3		137.5 ± 7.4		137.1 ± 5.3		144.4 ± 4.5
Heart Rate (beats/min)	168.9 ± 9.1		187.2 ± 9.2		175.0 ± 8.5		176.6 ± 10.1		169.4 ± 9.1
Cardiac Output (l/min)	3.65 ± 0.50		3.32 ± 0.48		2.88 ± 0.23		2.66 ± 0.29		2.77 ± 0.34

TABLE 2. Changes in myocardial blood flow, mean arterial blood pressure, heart rate and cardiac output produced by hypocapnia induced by two methods (Mean ± SEM, 11 dogs).

	Control		Hyperventilation		Hyperventilation + CO_2		CO_2 Off		Normoventilation
Arterial O_2 Content (ml/100ml)	29.4 ± 0.9		28.5 ± 1.5		25.5 ± 0.7		23.6 ± 1.0		23.7 ± 1.0
Myocardial O_2 Availability (ml/100g/min)	31.0 ± 1.4	$p<0.001$	24.2 ± 1.1	$p<0.05$	27.0 ± 1.0	$p<0.001$	18.0 ± 1.1	N.S.	20.2 ± 1.5
Myocardial O_2 Extraction (%)	48.0 ± 2.0	$p<0.005$	58.0 ± 2.0	$p<0.001$	45.0 ± 2.0	$p<0.001$	63.0 ± 3.0	$p<0.005$	49.0 ± 2.0
Myocardial O_2 Consumption (ml/100g/min)	15.0 ± 1.0		14.1 ± 1.0		12.4 ± 0.5		11.3 ± 0.7		10.7 ± 1.1

TABLE 3. Effects of hypocapnia induced by two methods on arterial O_2 content and myocardial O_2 availability, extraction and consumption. (Mean ± SEM, 11 dogs.)

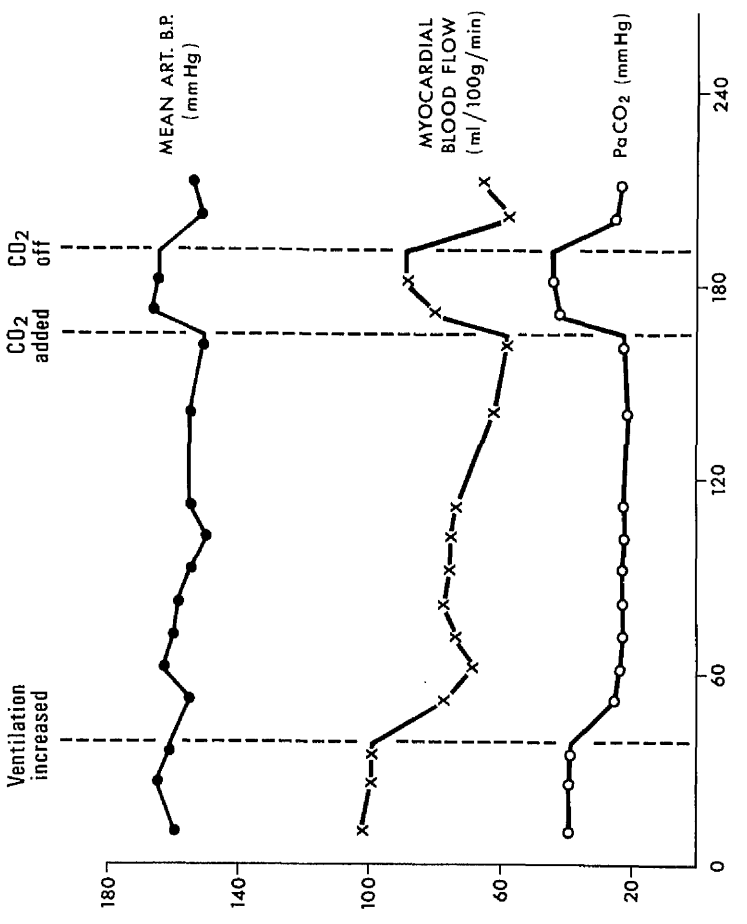

Fig. 7. The effect of a prolonged period of hypocapnia (60 min) on myocardial blood flow in a single dog is shown. Blood flow remained at a reduced level while the $PaCO_2$ was low but returned to normal whenever the $PaCO_2$ was restored to 40mm Hg.

Myocardial consumption of lactate, pyruvate and NEFA is shown in Table 6. Hypocapnia was not associated with significant changes in consumption of these substrates.

		Control		Hyperventilation	Hyperventilation + CO_2	CO_2 Off	Normoventilation
LACTATE (mg/100ml)	Art.	20.2 ± 1.7	$p < 0.025$	27.2 ± 2.8	26.0 ± 4.7	20.9 ± 3.5	17.5 ± 1.7
	C.S.	12.4 ± 1.0	$p < 0.01$	19.4 ± 2.3	18.0 ± 5.6	16.9 ± 3.0	15.8 ± 1.5
PYRUVATE (mg/100ml)	Art.	1.1 ± 0.1		1.5 ± 0.2	1.1 ± 0.1	0.9 ± 0.1	0.9 ± 0.2
	C.S.	0.6 ± 0.1		0.8 ± 0.1	0.6 ± 0.1	0.8 ± 0.2	0.7 ± 0.2
NEFA (mEq/l)	Art.	0.89 ± 0.10		1.12 ± 0.11	0.99 ± 0.13	1.10 ± 0.17	1.15 ± 0.14
	C.S.	0.70 ± 0.11		0.84 ± 0.12	0.82 ± 0.15	0.90 ± 0.10	0.88 ± 0.11
GLUCOSE (mg/100ml)	Art.	79.0 ± 13.0		89.0 ± 5.0	87.0 ± 6.0	98.0 ± 7.0	94.0 ± 6.0
	C.S.	87.0 ± 5.0		88.0 ± 6.0	88.0 ± 6.0	92.0 ± 5.0	88.0 ± 7.0

TABLE 4. Absolute concentrations of lactate, pyruvate, non-esterified fatty acid (NEFA) and glucose in arterial (Art.) and coronary sinus (C.S.) blood. (Mean ± S.E.M., 11 dogs).

	Control	Hyperventilation	Hyperventilation + CO_2	CO_2 Off	Normoventilation
LACTATE % extraction	36	28	38	19	12
PYRUVATE % extraction	43	38	33	25	29
NEFA % extraction	23	28	18	15	13

TABLE 5. Effects of hypocapnia on the mean % extraction by the myocardium from arterial blood of lactate, pyruvate and non-esterified fatty acid (NEFA). (11 dogs).

	Control	Hyperventilation	Hyperventilation + CO_2	CO_2 Off	Normoventilation
LACTATE (mg/100g/min)	7.9 ± 1.2	6.7 ± 2.0	7.8 ± 1.9	5.9 ± 1.8	5.6 ± 1.9
PYRUVATE (mg/100g/min)	0.5 ± 0.1	0.6 ± 0.1	0.4 ± 0.2	0.3 ± 0.1	0.3 ± 0.1
NEFA (mEq/100g/min)	0.024 ± 0.006	0.024 ± 0.007	0.020 ± 0.007	0.022 ± 0.011	0.022 ± 0.009

TABLE 6. The consumption of lactate, pyruvate and non-esterified fatty acid (NEFA) by the myocardium (Mean ± S.E.M., 11 dogs).

DISCUSSION

Previous studies of the effects of hypocapnia on myocardial blood flow have shown considerable disagreement. In 1960, Feinberg, Gerola and Katz reported no change between control and hypocapnic flows but when an increased load was applied to the heart in the form of a clamp on the aorta, flow during hypocapnia was apparently greater than during normocapnia. Rowe, Castillo and Crumpton (1962) reported a slight but non-significant increase in flow during hypocapnia in anaesthetised dogs, while McArthur (1965) and Scheuer (1968) demonstrated a reduction in flow with hyperventilation. However, Scheuer's animals, which were very vigorously hyperventilated, showed a mean fall of 49% in arterial blood pressure which could have accounted for a large part of the observed flow changes.

The results of the group of experiments on the effects of hypocapnia described here show that hyperventilation of a moderate degree (i.e. sufficient to reduce the arterial carbon dioxide tension from 40 mmHg to about 25 mmHg) is accompanied by a mean reduction of 18% in myocardial blood flow. It has also been demonstrated that this flow reduction was not dependent on haemodynamic changes associated with increased minute ventilation since a mean flow reduction of 26% occurred when hypocapnia was produced by withdrawing carbon dioxide gas from the inspired gases of the hyperventilated animal. Oxygen consumption of the myocardium was unaffected.

The reduction in mixed venous oxygen tension during hypocapnia indicates an increase in total body oxygen extraction and

taken in cojunction with the unchanged cardiac output, this suggests an increase in total body oxygen consumption. This is in keeping with the results of several investigations both in animals and humans, for example, Cain (1970) and Karetzsky and Cain (1970).

The observation that myocardial blood flow did not return to control level during the final phase of the experiment is probably explained on the grounds that a certain amount of myocardial depression was occurring due to a prolonged period of anaesthesia. This suggestion is supported by the downward trend in consumption of oxygen, lactate and pyruvate by the myocardium.

The arterial pH increase with hyperventilation is slightly less than that which would be expected with the degree of arterial carbon dioxide tension changes observed. This is probably accounted for by the slight increase which occurred in systemic lactate level at this time. This small but significant rise in arterial blood lactate concentration is in keeping with the work of Papadopolous and Keats (1959) who showed an increase in lactate levels with hyperventilation. They suggested that the increased levels of fixed acid occurring during hyperventilation were produced as a response to respiratory alkalosis and not as a result of tissue hypoxia.

The systemic haemodynamic effects of the degree hyperventilation utilised were unremarkable. Hyperventilation caused a slight but non-significant fall in mean arterial pressure and a slight but also non-significant rise in heart rate. Most workers

have reported a fall in blood pressure with hyperventilation but the majority of studies have attained lower carbon dioxide levels than those reached here, for example in Scheuer's study quoted above, the mean $PaCO_2$ during hyperventilation was 13.7 mmHg, and Little and Smith (1964) who also showed falls in blood pressure, attained end expiratory $PaCO_2$ levels of 14 - 15 mmHg. Richardson, Wasserman and Patterson (1961) suggest that the magnitude of circulatory effects of hyperventilation is related to the extent of reduction in carbon dioxide levels and also to the rapidity with which these reduced levels are attained. Although cardiac output fell gradually throughout the study, there were no significant changes between succeeding phases of the study, again emphasising the lack of systemic haemodynamic upset with a moderate level of hyperventilation and hypocapnia in the healthy animal.

In a study of passive hyperventilation in conscious humans where $PaCO_2$ was reduced to a mean level of 23.8 mmHg (i.e. comparable to that of this study), Cullen, Eger and Gregory (1969) also failed to demonstrate changes in cardiac output or heart rate and similarly, Marshall, Cohen, Klingenmaier, Neigh and Pender (1971) showed that cardiac index was not significantly different during hypocapnia and normocapnia in anaesthetised humans. These findings are presumably related to the findings of Leigh, J.M., Blackburn, J.P., Conway, C.M., Lindop, M.J. and Reitan, J.A. (personal communication) who observed that in dogs, myocardial contractility was unaffected by hypocapnia (although it was increased during hypercapnia). Related to these observations by other workers, this study shows that with hypocapnia

of a moderate degree, myocardial oxygen consumption was unaffected although oxygen availability was reduced pari passu with the blood flow. The maintenance of oxygen consumption is explained by the large increases which occurred in oxygen extraction when blood flow was reduced.

The energy requirements of the myocardium are met largely by the metabolism of glucose, lactate, pyruvate and fatty acids although other substrates such as ketone bodies and amino acids are utilised. Olsen and Piatnek (1959) point out that in the fasting state, the metabolism of carbohydrate lessens while fatty acids are used in preference. This observation may account for the lack of uptake of glucose by the heart in the circumstances of these studies, since the animals had fasted for some 18 - 20 hours prior to the commencement of the experiments.

CHAPTER 4.

THE EFFECTS OF HALOTHANE-INDUCED HYPOTENSION ON MYOCARDIAL BLOOD FLOW AND OXYGEN CONSUMPTION.

In order that the effects of halothane-induced hypotension could be studied, anaesthesia was induced and maintained with pentobarbitone 30mg/kg given intravenously. Since pentobarbitone is a long-acting barbiturate, it was unnecessary to give trichloroethylene to maintain anaesthesia. Twelve dogs were included in the study (weight range 23 - 28kg.) After control measurements had been made, halothane was added to the inspired gas mixture from a Fluotec Mk. 2 vaporiser in 0.5%, 1.0% and 1.5% concentrations. The order of administration of the three dose levels of halothane was randomised and measurements were made after 15 and 30 minutes administration of each dose. At least 30 minutes were allowed to elapse between the administration of different doses.

Table 7 illustrates the haemodynamic changes occurring with the three doses of halothane. Heart rate, mean arterial blood pressure, cardiac output and myocardial blood flow all showed reductions which became increasingly more marked as the dose of halothane increased. With 1% and 1.5% halothane however, myocardial blood flow decreased to a degree which was proportionately greater than the fall in blood pressure. This was due to an increase in myocardial vascular resistance. Systemic vascular resistance was not significantly affected. These data are summarised in graphic form in figures 8 and 9.

	0.5% halothane			1.0% halothane			1.5% halothane		
	Control	15 min.	30 min.	Control	15 min.	30 min.	Control	15 min.	30 min.
Heart rate (beats/min)	175 ± 6	173 ± 6	171 ± 6	163 ± 6	170 ± 8	155 ± 7	171 ± 8	154 ± 6*	140 ± 7**
Mean B.P. (mmHg)	135 ± 6	125 ± 6*	118 ± 5*	132 ± 7	113 ± 6*	99 ± 7**	133 ± 6	90 ± 5**	65 ± 5**
Cardiac output (l /min)	2.78 ± 0.36	2.34* ± 0.25	2.20* ± 0.27	2.69 ± 0.25	2.38* ± 0.23	2.17* ± 0.18	2.49 ± 0.24	1.89** ± 0.25	1.43** ± 0.12
Myocardial blood flow (ml/100g/min)	98 ± 5	89 ± 5*	87 ± 4*	100 ± 6	83 ± 6**	65 ± 5**	97 ± 6	61 ± 4**	40 ± 3**
Myocardial vascular resistance (units)	136 ± 5	142 ± 7	138 ± 9	134 ± 6	139 ± 7	154 ± 8*	140 ± 7	149 ± 9	161 ± 12*
Systemic vascular resistance (units)	54 ± 5	59 ± 5	60 ± 6	56 ± 8	53 ± 7	49 ± 5	58 ± 5	56 ± 7	51 ± 7

TABLE 7. Myocardial blood flow, vascular resistance and systemic haemodynamic changes with increasing dosage of halothane. (12 dogs : Mean ± S.E.M.) Degree of significance from control values are denoted by asterisks * = $P<0.05$, ** = $P<0.01$.

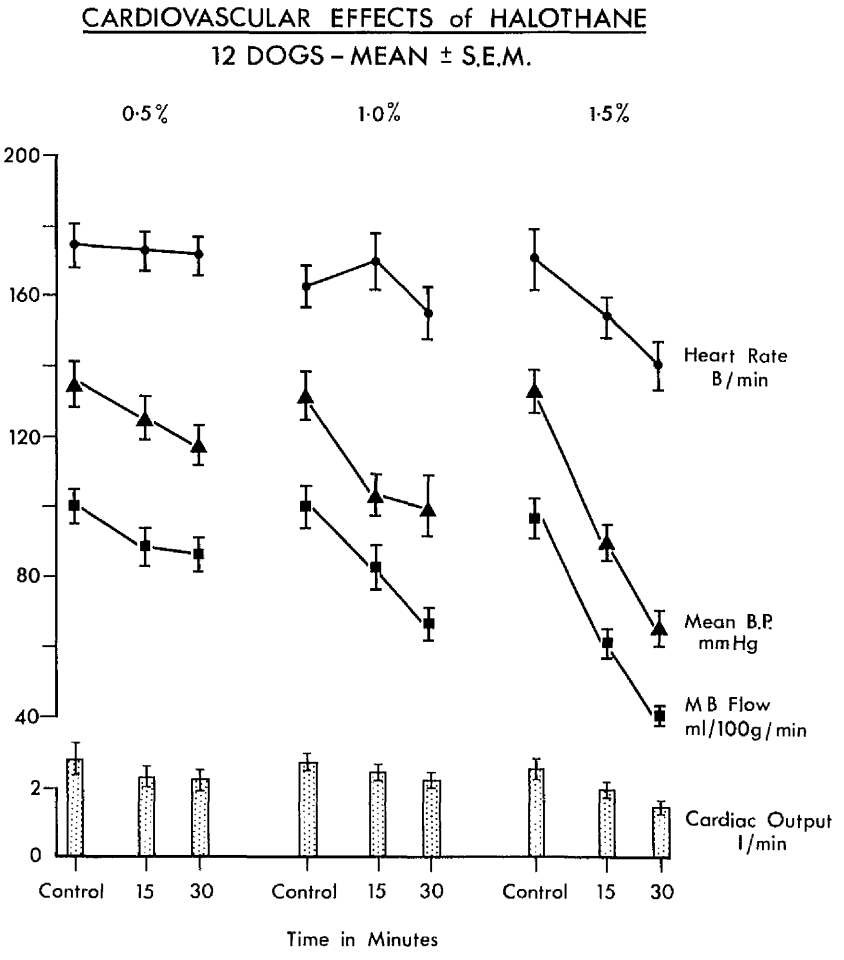

Fig. 8. The effects of 0.5%, 1.0% and 1.5% halothane on heart rate, mean arterial pressure (mean B.P.), myocardial blood flow (M.B. flow) and cardiac output.

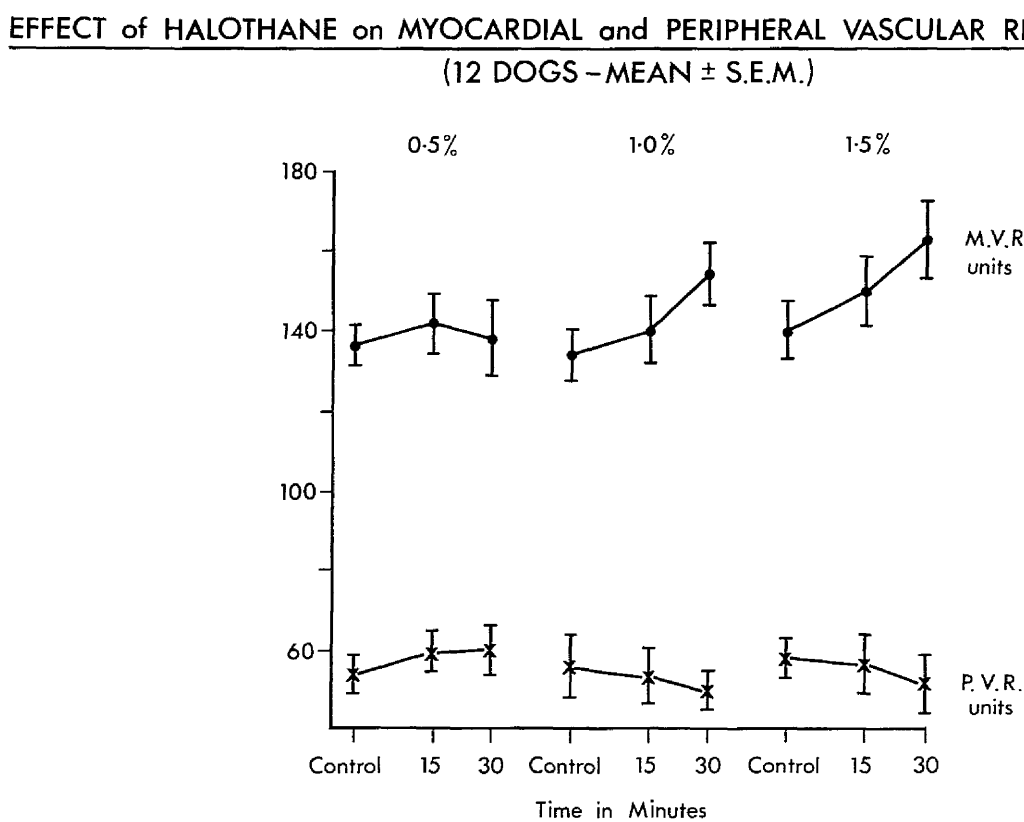

Fig. 9. The effects of 0.5%, 1.0% and 1.5% halothane on myocardial vascular resistance (M.V.R.) and systemic vascular resistance (P.V.R.)

The data for myocardial and total body oxygen availability, extraction and consumption are detailed in Table 8, the myocardial data being summarised in graphical form in figure 10. Myocardial and total body oxygen availability are dependent on myocardial blood flow and cardiac output respectively (since arterial oxygen content was unaltered) and therefore they were reduced by halothane in a manner corresponding to the reduction in blood flow and cardiac output. The myocardial and total consumption of oxygen were reduced to an increasingly marked degree as halothane dosage increased, however, the oxygen consumption in both cases fell to a proportionately smaller degree than the availability so that there was a small increase in oxygen extraction with the 1.5% halothane dose. Although this change in extraction was non-significant the coronary sinus oxygen tension fell significantly after 30 minutes of 1.5% halothane, the figures being as follows:-

Control 29.5 $\pm$ 1.9 mmHg falling to 26.3 $\pm$ 1.5 mmHg ($P < 0.05$).

DISCUSSION

The use of hypotensive anaesthesia may prove beneficial to patients for two reasons. Firstly, because it leads to a reduction in operative blood loss (Rollason and Hough, 1960; Enderby, 1961; Linacre, 1961) there is a diminished requirement for blood transfusion and therefore a reduced risk of the dangers which accrue from blood transfusions such as mismatched transfusion, transference of blood borne infection (notably homologous serum jaundice), electrolyte upsets and upsets in the blood clotting mechanism. Secondly, when bleeding during surgery is diminished, the duration of surgery is

	0.5% halothane			1.0% halothane			1.5% halothane		
	Control	15 min	30 min	Control	15 min	30 min	Control	15 min	30 min
Myocardial O_2 availability (ml/100g/min)	24 ± 1.4	21.5* ± 1.4	21.0* ± 1.1	24.2 ± 1.8	20.4* ± 1.9	16.2** ± 1.5	23.6 ± 1.6	14.7** ± 1.1	9.9** ± 1.0
Myocardial O_2 extraction (%)	49 ± 4	48 ± 5	49 ± 4	51.1 ± 4.2	51.7 ± 4.7	52.8 ± 4.3	51.1 ± 4.1	52.8 ± 4.2	55.7 ± 4.6
Myocardial O_2 consumption (ml/100g/min)	11.9 ± 1.6	10.7 ± 1.5	10.6 ± 1.2	12.7 ± 1.5	10.8* ± 1.6	8.9* ± 1.2	12.4 ± 1.6	7.9** ± 1.0	5.7** ± 0.9
Total body O_2 availability (ml/min)	670 ± 82	570* ± 63	537* ± 84	644 ± 61	574* ± 57	525* ± 45	610 ± 63	461* ± 61	328** ± 31.
Total body O_2 extraction (%)	16.9 ± 2.3	19.1 ± 2.4	19.2 ± 2.1	18.5 ± 2.2	19.9 ± 2.3	20.7 ± 2.5	18.6 ± 2.1	21.6* ± 2.4	24.1* ± 2.5
Total body O_2 consumption (ml/min)	107 ± 17	102 ± 14	96 ± 12	114 ± 14	112 ± 16	109 ± 15	106 ± 10	91 ± 11	76* ± 11

TABLE 8 Myocardial and total body oxygen availability, extraction and consumption with increasing dosage of halothane. (12 dogs. Mean ± S.E.M.)
Degree of significance from control values are denoted by asterisks * = $P < 0.05$, ** = $P < 0.01$.

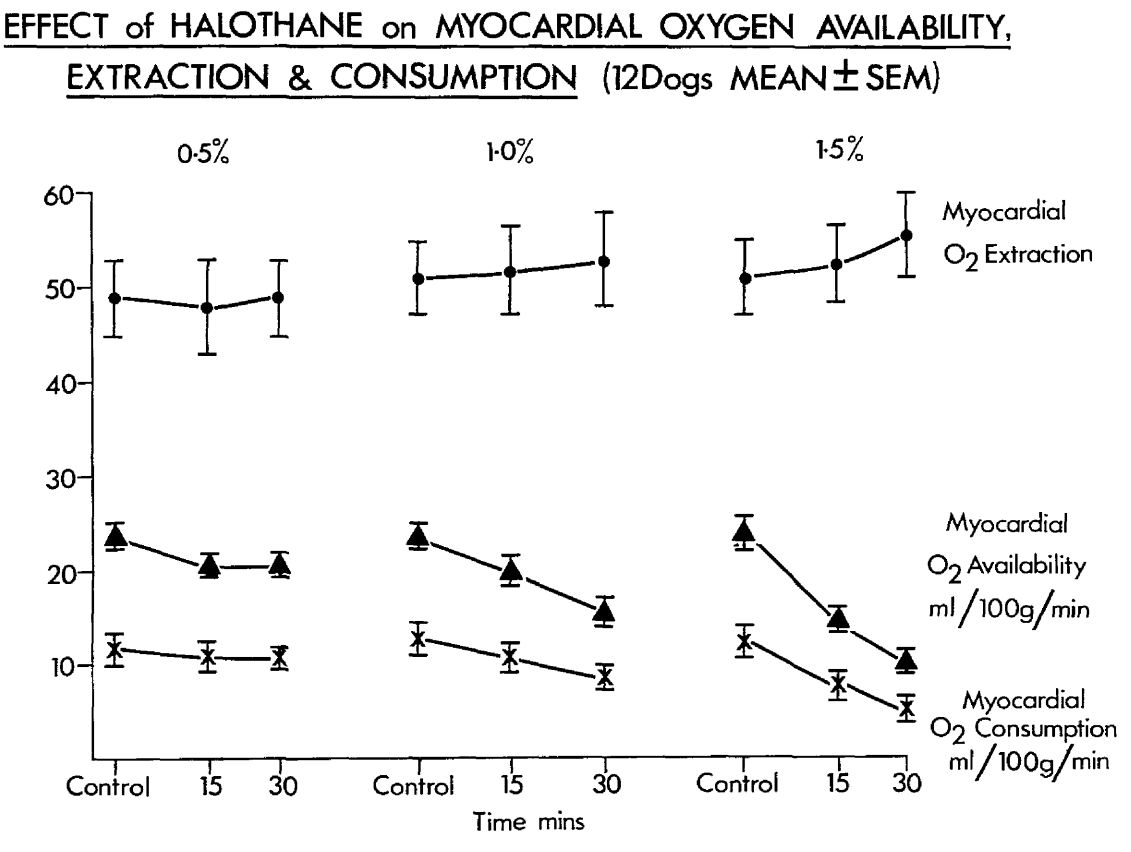

Fig. 10. The changes in myocardial oxygen extraction, availability and consumption with 0.5%, 1.0% and 1.5% halothane.

reduced and there are benefits from this, such as less exposure of tissues and therefore less fluid evaporation, less heat loss and reduced exposure to air-borne infection. Also, when bleeding is less severe, there is a reduced use of ligatures and diathermy coagulation and hence less dead tissue in the wound which again helps to reduce the likelihood of infection.

A large variety of methods of achieving hypotension during anaesthesia and surgery have been employed and one of the more popular of these has been the use of artificial ventilation with varying concentrations of halothane in the inspired gases (Neill and Nixon, 1965; Robinson, 1967; Prys-Roberts, Lloyd, Fisher, Kerr and Patterson, 1974). It is well appreciated that halothane causes a reduction in myocardial contractility with concomitant depression of blood pressure, heart rate and cardiac output in both animals (Severinghaus and Cullen, 1958; Gil-Rodriguez, Hill and Lundberg, 1971; Rusy, Moran and Fox, 1971; Prys-Roberts, Gersch, Baker and Reuben, 1972; Hughes, 1973) and man (Johnstone, 1956; Payne, 1963).

Although there is considerable information on the systemic haemodynamic effects of halothane, there is little information available on its effects on myocardial blood flow. Merin (1969), and Weaver, Bailey and Preston (1970) suggested that, in dogs, halothane caused a reduction in coronary blood flow without changes in vascular resistance (i.e. that flow fell pari passu with the blood pressure). In an isolated heart preparation with artificially perfused coronary arterial system, Wolf, Claudi, Rist, Wardak,

Niederer and Graedel (1972) showed a reduction in coronary flow with halothane accompanied by an increase in coronary vascular resistance.

The study described here shows that halothane causes a dose dependent reduction in systemic arterial blood pressure, cardiac output and heart rate accompanied by a dose dependent reduction in myocardial blood flow. The reduction in blood flow was proportionately greater than the reduction in arterial blood pressure due to an increase in myocardial vascular resistance with the 1% and 1.5% doses.

It has been widely believed that halothane causes a widespread peripheral vasodilatation with reduction in systemic vascular resistance (Raventos, 1956; Johnstone, 1956; Johnstone, 1961). More recently however, it has been argued that halothane does not cause widespread vasodilatation but has different effects in different vascular beds so that the overall effect on total vascular resistance is not marked (Prys-Roberts et al., 1974). The results presented here support this latter view since the myocardial vasculature showed vasoconstriction with the higher doses of halothane, while the systemic vascular resistance was not significantly affected.

The reduction in myocardial oxygen consumption with halothane probably resulted from a considerable reduction in the work of the heart which could have arisen from the reductions in heart rate, blood pressure, cardiac output and presumably also in myocardial contractility. The reduction in myocardial blood flow caused a

marked reduction in oxygen availability to the heart and the increased myocardial vascular resistance played a part in reducing the oxygen availability even further so that the oxygen availability was reduced to a proportionately greater degree than the oxygen consumption with the 1.5% dose of halothane. There was thus a small reduction in coronary sinus PO_2 (i.e. an increase in oxygen extraction) with this dose.

CHAPTER 5.

THE COMBINED EFFECTS OF HALOTHANE HYPOTENSION AND HYPOCAPNIA ON MYOCARDIAL BLOOD FLOW.

As indicated in the foregoing two chapters, hypocapnia or hypotension are frequently induced in anaesthetised patients and not infrequently both conditions are induced simultaneously (Neill and Nixon, 1965; Prys-Roberts et al., 1974). Since the results reported in Chapters 3 and 4 indicate that hypocapnia and hypotension are both associated with reduced myocardial blood flow, it seemed obvious that the results of combining the two should be examined experimentally in an attempt to determine if their myocardial blood flow effects are additive.

Eleven animals were included in the study (weight range 17-31 kg). Anaesthesia was induced as in Chapter 4 (i.e. with pentobarbitone 30mg/kg given intravenously). Ventilation was adjusted to produce a $PaCO_2$ of about 25 mmHg and then CO_2 gas was added to the inspired gas mixture to return the $PaCO_2$ to about 40 mmHg. $PaCO_2$ was thus within the normal range for control measurements. The experiments were once again carried out in five phases as follows :-

1. Control phase - basal anaesthesia with pentobarbitone only - $PaCO_2$ normal.

2. Hypotension - halothane 1 - 1.5% added. Measurements were made after blood pressure had been stable for at least 10-15 min. $PaCO_2$ still about 40 mmHg.

3. Hypotension + hypocapnia - halothane maintained at previous level and CO_2 gas withdrawn from inspired gases ($PaCO_2$ about 25 mmHg).

4. Hypotension only - CO_2 gas re-added ($PaCO_2$ about 40 mmHg).

5. Halothane off - return towards control situation. Measurements were taken when blood pressure had returned to not less than 80% of the control level.

The blood gas and pH changes in arterial, coronary sinus and 'mixed venous' blood are shown in Table 9. Arterial PO_2 remained unchanged throughout but arterial PCO_2 showed the expected changes when CO_2 gas was removed from and later added to the ventilating gas mixture. These changes were accompanied by corresponding changes in arterial pH. Coronary sinus and mixed venous blood exhibited parallel PCO_2 and pH changes to those of the arterial blood. The other feature of this table was that coronary sinus and mixed venous O_2 tensions fell when hypotension was induced, this despite a constant PaO_2, thus suggesting an increase in O_2 extraction by the heart and in toto.

Table 10 shows the haemodynamic and vascular resistance changes occurring throughout the experiment. Mean blood pressure, heart rate, cardiac output and myocardial blood flow decreased to a highly significant degree when halothane was introduced and myocardial vascular resistance rose markedly at this time. Systemic vascular resistance was not significantly altered.

With the addition of hypocapnia to hypotension, myocardial blood flow fell even further whereas the other variables in Table 10 were not significantly affected. The reduction in blood flow with hypocapnia was reversed when $PaCO_2$ was restored to normal.

During the final phase of the investigation when arterial blood pressure had returned to some 86% of mean control level, myocardial blood flow and cardiac output had returned only to 64% and 63% of their mean control values. There was at this time a highly significant increase in systemic vascular resistance.

The highly significant reductions in blood flow and cardiac output when hypotension was induced are reflected in reductions in myocardial and total oxygen availability (Table 11). This table also shows that there were reductions in myocardial and total oxygen consumption at this time but that the reductions in consumption were proportionately smaller than the reductions in availability so that myocardial and total oxygen extraction increased. The changes in blood flow which accompanied hypocapnia caused corresponding changes in myocardial oxygen availability and during the phase of recovery, myocardial O_2 availability increased

	Control		Hypotension (normal $PaCO_2$)		Hypotension + Hypocapnia		Hypotension (normal $PaCO_2$)	Halothane off (normal $PaCO_2$)
$PaCO_2$ (mmHg)	107 ± 1.5		108 ± 1.1		107 ± 1.0		107 ± 1.4	104 ± 1.3
$PaCO_2$ (mmHg)	42 ± 0.6		42 ± 0.8	P<0.001	26 ± 1.0	P<0.001	41 ± 1.1	42 ± 0.8
Coronary sinus PO_2 (mmHg)	37 ± 0.9	P<0.05	32 ± 1.4		29 ± 1.4		32 ± 1.4	32 ± 1.5
Coronary sinus PCO_2 (mmHg)	57 ± 0.8		57 ± 0.8	P<0.001	38 ± 1.3	P<0.001	52 ± 1.2	54 ± 1.1
Right atrial PO_2 (mmHg)	58 ± 1.1	P<0.01	52 ± 1.4	P<0.01	45 ± 1.7		48 ± 1.8	50 ± 1.5
Right atrial PCO_2 (mmHg)	51 ± 0.67		50 ± 0.9	P<0.001	36 ± 1.4	P<0.001	47 ± 1.2	49 ± 1.0

TABLE 9. Arterial, coronary sinus and right atrial blood gas changes with halothane induced hypotension and hypocapnia (mean ± SEM - 11 dogs).

	Control		Hypotension (normal $PaCO_2$)		Hypotension + Hypocapnia		Hypotension (normal $PaCO_2$)		Halothane off (normal $PaCO_2$)
Mean arterial pressure (mmHg)	158 ± 4.1	P<0.001	88 ± 2.7		81 ± 3.7	P<0.05	94 ± 4.4	P<0.001	137 ± 4.5
Heart rate (beats/min)	178 ± 3.04	P<0.001	146 ± 4.3		144 ± 4.8		144 ± 5.3		156 ± 5.0
Cardiac output (l/min)	3.55 ± 0.13	P<0.001	2.22 ± 0.13		2.02 ± 0.1		2.09 ± 0.1		2.24 ± 0.09
Right atrial pressure (mmHg)	0.29 ± 0.2		0.82 ± 0.15		0.73 ± 0.2		1.14 ± 0.33	P<0.01	0.21 ± 0.17
Myocardial blood flow (ml/100g/min)	142 ± 5.1	P<0.001	67 ± 4.3	P<0.05	54 ± 2.7	P<0.05	65 ± 3.3	P<0.001	91 ± 4.4
Myocardial vascular resistance (units)	113 ± 4.5	P<0.001	139 ± 9.2		152 ± 7.14		148 ± 6.5		156 ± 7.8
Systemic vascular resistance (units)	46 ± 2.6		41 ± 2.2		41 ± 2.1		46 ± 2.66	P<0.001	62 ± 2.4

TABLE 10. Haemodynamic data during five phases of halothane hypotension and hypocapnia study. (Mean ± S.E.M., 11 dogs).

	Control		Hypotension (normal $PaCO_2$)		Hypotension + Hypocapnia		Hypotension (normal $PaCO_2$)		Halothane off (normal $PaCO_2$)
Myocardial O_2 availability (ml/100g/min)	32.5 ± 1.1	P<0.001	15.2 ± 0.94	P<0.05	12.5 ± 0.7	P<0.05	15.0 ± 0.8	P<0.001	21.1 ± 1.1
Myocardial O_2 extraction (%)	40.8 ± 1.6	P<0.001	48.7 ± 2.5		46.2 ± 3.2		45.7 ± 2.9		48.3 ± 3.3
Myocardial O_2 consumption (ml/100g/min)	13.1 ± 0.64	P<0.001	7.2 ± 0.48		5.9 ± 0.58		6.9 ± 0.62	P<0.01	9.9 ± 0.75
Total O_2 availability (ml/min)	803 ± 38	P<0.001	513 ± 34		469 ± 28		484 ± 30		520 ± 26
Total O_2 extraction (%)	15 ± 0.9	P<0.05	18 ± 1.0		20 ± 2.2		21 ± 1.9		18 ± 1.5
Total O_2 consumption (ml/min)	121 ± 9.8	P<0.05	91 ± 7.7		94 ± 12.1		99 ± 9.5		94 ± 7.3

TABLE 11. Changes in myocardial and total body oxygen availability, extraction and consumption caused by halothane induced hypotension and hypocapnia. (Mean ± S.E.M., 11 dogs).

significantly from hypotensive levels. However the increase in availability was relatively smaller than the increase in consumption so that myocardial O_2 extraction at this time was significantly higher than the control level ($P < 0.01$).

DISCUSSION

The results presented in this chapter confirm those of Chapter 4 where halothane hypotension is described. Therefore halothane caused a reduction in blood pressure, heart rate, cardiac output and myocardial blood flow. There was a simultaneous increase in vascular resistance within the myocardium. When hypocapnia was superadded to hypotension a further significant fall in blood flow occurred so that the combination of hypotension and hypocapnia produced a very marked fall in myocardial oxygen availability to 38% of control level.

The other noteworthy finding in this study was that during the phase of recovery from hypotension (i.e. the final phase), when blood pressure and myocardial oxygen consumption had returned to 86% and 76% of their respective mean control values, the myocardial blood flow, myocardial oxygen availability and cardiac output had returned to only 64%, 62% and 63% of their respective mean control levels. These latter three variables therefore, lagged far behind the blood pressure in their rate of recovery after hypotension. The significant increase in total vascular resistance when halothane was withdrawn indicates that the recovery of blood pressure was due, in considerable part, to vasoconstriction and not to returning

cardiac output and myocardial function. It appears therefore that blood pressure observations do not give a reliable guide to returning cardiac function after halothane hypotension.

CHAPTER 6.

MYOCARDIAL BLOOD FLOW RESPONSES TO HYPERCAPNIA.

Raised arterial carbon dioxide tension has been shown to be associated with increased myocardial blood flow (Feinberg, Gerola and Katz, 1960; Kittle, Aoki and Brown, 1965; Eberlein, 1966; Lochner, Hirche and Koike, 1967). These studies, however, did not examine the relationship between flow responses and blood carbon dioxide tension and acid-base status. The study described here attempts to do so as well as examining the possible role of the sympathetic nervous system in the blood flow responses.

Anaesthesia for this series of experiments was administered as described in Chapter 2 (i.e. induction with thiopentone and maintenance with trichloroethylene). Hypercapnia was produced by the addition of CO_2 gas to the inspired gas mixture. Four sets of experiments were carried out :-

1. Briefly sustained hypercapnia - $PaCO_2$ elevated for about 15 - 20 minutes.

2. Prolonged hypercapnia - $PaCO_2$ elevated for 60 minutes.

3. Stepwise increments and decrements in $PaCO_2$.

4. Attempts to determine the mechanism of the flow response to hypercapnia.

The inspired oxygen concentration was adjusted when necessary so that the $PaCO_2$ remained around 100 mmHg at all times; a total of 30 dogs were studied (weight range 17-35 kg.)

BRIEFLY SUSTAINED HYPERCAPNIA

Sixteen dogs were subjected to hypercapnia by the rapid addition of CO_2 gas to the inspired gas mixture in volumes which raised the $PaCO_2$ from about 40 mmHg to 90 - 100 mmHg. This elevation was sustained for up to 20 minutes. The important blood gas and pH data associated with this change are shown in Table 12.

	PaO_2 (mmHg)	$PaCO_2$ (mmHg)	Arterial pH (units)	C. Sinus PO_2 (mmHg)	Rt. Atrial PO_2 (mmHg)
Control	96 ± 4	40 ± 1	7.346 ± 0.010	30 ± 1	47 ± 1
		P < 0.001	P < 0.001	P < 0.001	P < 0.01
Raised $PaCO_2$	102 ± 5	96 ± 6	7.074 ± 0.063	57 ± 3	63 ± 7

TABLE 12. Blood gas and arterial pH changes associated with briefly sustained hypercapnia. (Mean ± S.E.M., 16 dogs).

The rapid elevation of $PaCO_2$ from 40 to 90 - 100 mmHg resulted in a corresponding decrease in arterial pH. The coronary sinus and mixed venous blood showed parallel changes in PCO_2 and pH. The coronary sinus and right atrial blood both underwent increases in PO_2 during hypercapnia. The large increase in coronary sinus PO_2 indicated a reduction in myocardial oxygen extraction and this was reflected in a reduction in arterial-coronary sinus oxygen content difference (10.7 ± 0.6 to 5.8 ± 0.7 ml/100ml - $P < 0.001$).

The myocardial blood flow and haemodynamic changes with brief hypercapnia are shown in Table 13. Blood flow showed a mean increase of 42% and right atrial pressure also increased markedly while arterial blood pressure and heart rate remained unchanged.

	Myocardial blood flow (ml/100g/min)	Mean arterial B.P. (mmHg)	Heart rate (b/min)	Rt.atrial pressure (mmHg)
Control	112 ± 5	154 ± 6	119 ± 4	+ 0.1 ± 0.5
	P<0.001			P<0.001
Raised $PaCO_2$	167 ± 6	157 ± 10	121 ± 5	+ 2.4 ± 0.8

TABLE 13. Myocardial blood flow and haemodynamic changes with briefly sustained hypercapnia.

The large decrease in coronary arterio-venous oxygen content difference already mentioned taken in conjunction with the increased blood flow through the myocardium during hypercapnia show a decrease in myocardial oxygen consumption, the figures being 11.8 ± 0.7 to 9.7 ± 1.0 ml/100g/min ($P < 0.01$) - an 18% reduction. Although the right atrial PO_2 was elevated during hypercapnia, the arterial-mixed venous oxygen content difference was not significantly altered (3.8 ± 0.2 ml/100ml before and 3.6 ml/100ml during hypercapnia).

Cardiac output measurements were obtained in only six of the animals in this study. These did not show a consistent pattern of change, three being increased and three decreased during hypercapnia.

Figure 11 shows the typical rapid and marked increase in myocardial blood flow and reduction in myocardial oxygen consumption during hypercapnia in a single dog.

In Table 14 the arterial and coronary sinus concentrations of glucose, lactate and pyruvate before and during brief hypercapnia in 14 animals are seen.

		Glucose (mg/100ml)	Lactate (mg/100ml)	Pyruvate (mg/100ml)
Control	Art.	122 ± 13	17 ± 2.2	1.22 ± 0.13
	C.S.	120 ± 13	11.9 ± 1.7	0.83 ± 0.08
Hypercapnia	Art.	154 ± 11	14 ± 1.7	1.01 ± 0.11
	C.S.	155 ± 10	11.8 ± 1.6	0.73 ± 0.08

TABLE 14. Arterial (Art.) and coronary sinus (C.S.) concentrations of glucose, lactate and pyruvate before and during hypercapnia. (Mean ± SEM - 14 dogs).

As in the study of hypocapnia (Chapter 3), the heart did not appear to be utilising glucose since there was no difference between arterial and coronary sinus concentrations either before or during hypercapnia. However the elevation of $PaCO_2$ did result in a

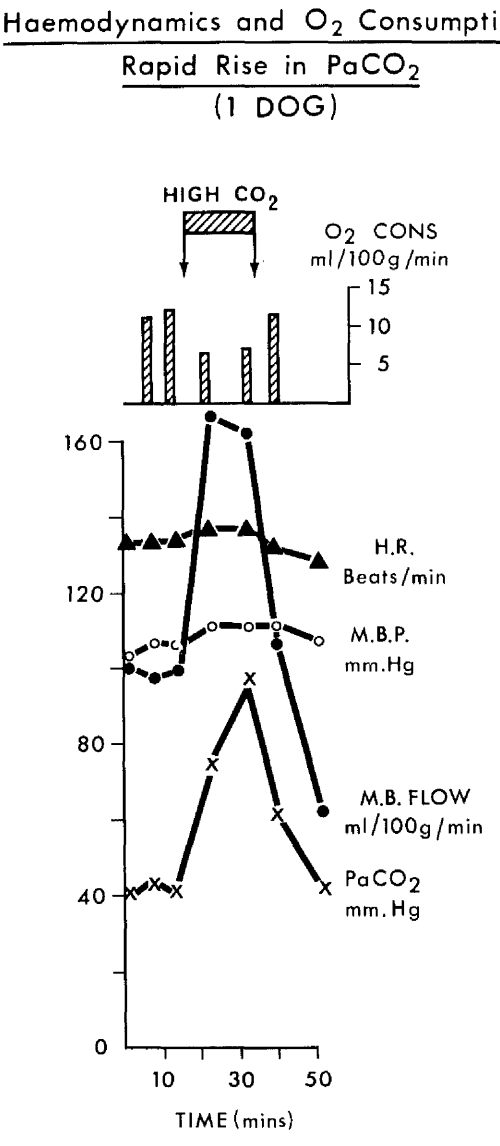

Fig. 11. The marked and rapid rise in myocardial blood flow (M.B.Flow) and reduction in myocardial oxygen consumption (O_2 cons.) with hypercapnia is shown from a single dog. There was sometimes a tendency for flow to undershoot below control level on return to normal $PaCO_2$ and this is demonstrated here.

substantial increase in the blood levels of glucose.

Figure 12 illustrates the myocardial extraction of lactate and pyruvate in the 14 animals from which this data was available. In the control state, extraction varied from 0 - 50% for lactate and 0 - 55% for pyruvate. During hypercapnia the extraction of lactate fell in 10 of the 14 animals while pyruvate extraction increased or decreased with equal frequency.

PROLONGED HYPERCAPNIA

The effects of a more prolonged period of hypercapnia were examined in a different group of nine dogs. The effects of elevation of $PaCO_2$ to about 100 mmHg for 60 minutes are illustrated in figure 13 as percentage changes. A 30% increase in myocardial blood flow occurred initially along with a similar decrease in myocardial oxygen consumption but both of these tended to return towards the pre-hypercapnic level as the experiment proceeded. Heart rate and blood pressure were remarkably unaffected. Measurements made in the immediate post-hypercapnic period showed that myocardial blood flow had fallen to about 15% below pre-hypercapnic level. This undershoot was sometimes seen after brief hypercapnia also (see figure 11). It was rapidly self correcting.

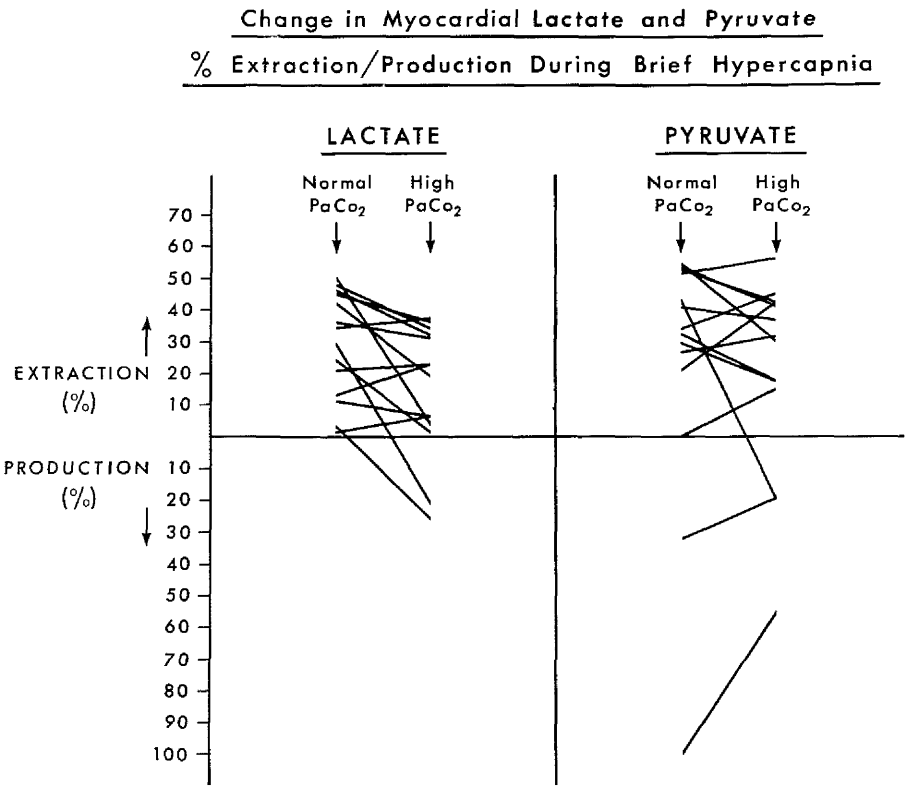

Fig. 12. The changes in myocardial extraction of lactate and pyruvate produced by hypercapnia. Changes from 14 dogs are shown.

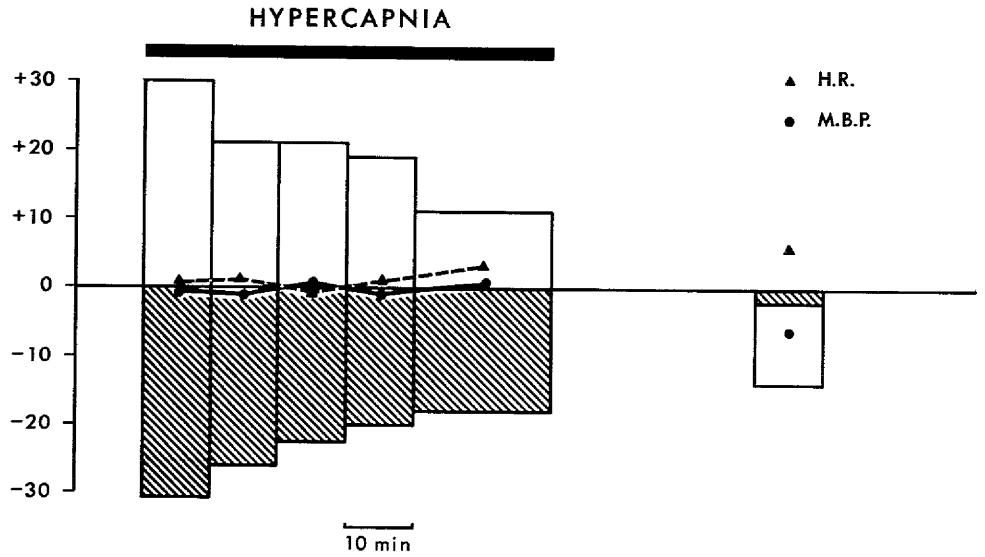

Fig. 13. The % changes in 9 dogs in myocardial blood flow (open columns), myocardial oxygen consumption (hatched columns), heart rate (H.R.) and mean arterial pressure (M.B.P.) during hypercapnia sustained for 60 minutes. The post-hypercapnic changes are seen in the extreme right hand columns.

THE EFFECTS OF STEPWISE INCREMENTS AND DECREMENTS IN $PaCO_2$

In a different group of five dogs the effects of gradually increasing $PaCO_2$ on myocardial blood flow was examined. Commencing at a $PaCO_2$ of about 20 mmHg, carbon dioxide was added to the inspired gas mixture to produce a stepwise increase in $PaCO_2$ so that myocardial blood flow could be measured at several $PaCO_2$ levels between 20 and 90 mmHg. The carbon dioxide content of the inspired gases was then reduced in a similar manner.

The effects of these manoeuvres on myocardial blood flow are seen in figure 14. There was a tendency for myocardial blood flow to increase between $PaCO_2$ levels of 40 and 60 - 80 mmHg. This is however complicated by the fact that when hypercapnia is prolonged, there is a tendency for flow to return to control levels (see figure 13). The relationship between $PaCO_2$ and myocardial blood flow is more clearly seen when $PaCO_2$ was being reduced. With each decrement in $PaCO_2$ there was a corresponding decrease in blood flow. These experiments show that fairly small changes in $PaCO_2$ of the order of 20 mmHg can have a considerable effect on blood flow in the myocardium.

ATTEMPTS TO DETERMINE THE MECHANISM OF THE MYOCARDIAL BLOOD FLOW RESPONSE TO HYPERCAPNIA.

The possibility that the increase in myocardial blood flow might be mediated through a response of the autonomic nervous system or through the influence of increased circulating catechol amines was considered. To examine these possibilities, certain

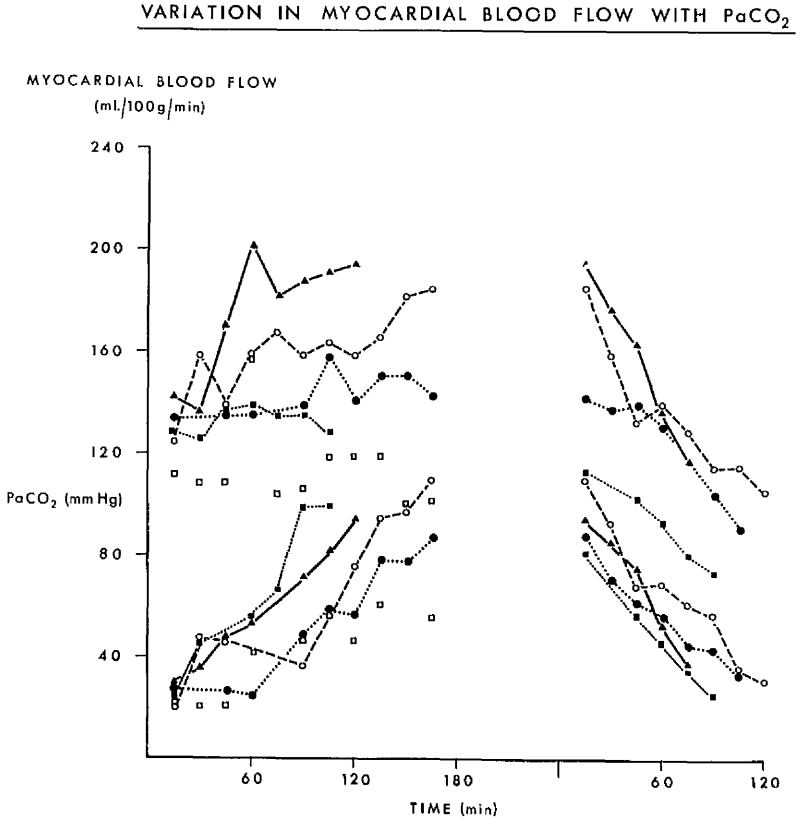

Fig. 14. illustrates the effects on myocardial blood flow of stepwise increments and decrements in $PaCO_2$. It is obvious that small changes in $PaCO_2$ of the order of 20 mmHg can produce changes in blood flow. These data are taken from five individual dogs.

drugs were administered as follows.

In seven dogs, the brief hypercapnia stimulus was applied as described earlier in this chapter. After this, atropine, a parasympatholytic agent, was administered in the dosage 0.04 mg/kg. This was followed a few minutes later by the β adrenergic blocking agent propranolol (0.2 mg/kg). Atropine caused a mean increase in heart rate of 44 beats/min and a mean increase in myocardial blood flow of 17 ml/100g/min. The haemodynamic effects of the two drugs is seen in figure 15. Previous studies (Parratt and Grayson, 1966) have shown that propranolol in the dose given in this study (i.e. 0.2 mg/kg) causes a decrease in myocardial blood flow. This was in agreement with the findings in this experiment. When the haemodynamic status of the animals had stabilised after the administration of atropine and propranolol, the brief hypercapnic stimulus was repeated. The effects of hypercapnia before and after atropine and propranolol are seen in a single dog in figure 16 and in the group of seven dogs in figure 17. Atropine and propranolol did not affect the responses to hypercapnia.

It was also considered that the myocardial blood flow response to increased $PaCO_2$ might in fact be due to the decrease in pH which accompanies hypercapnia. In an attempt to investigate this possibility, a group of animals were subjected to infusions of lactic acid or hydrochloric acid.

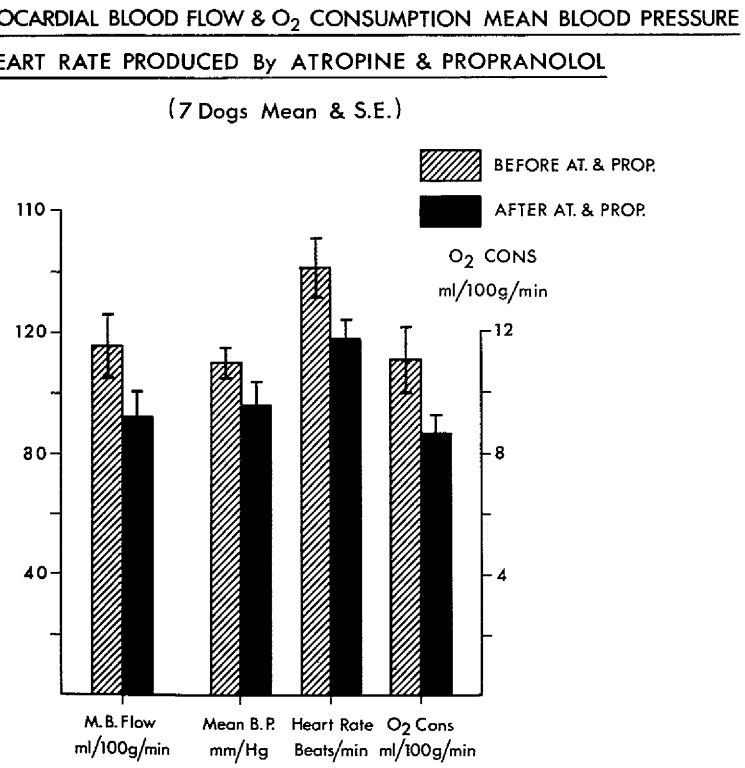

Fig. 15. Changes in myocardial blood flow and oxygen consumption, mean arterial pressure and heart rate produced by the administration of 0.04 mg/kg of atropine and 0.2 mg/kg of propranolol. All four variables were significantly reduced by the mixture of drugs. (Mean ± SEM - 7 dogs).

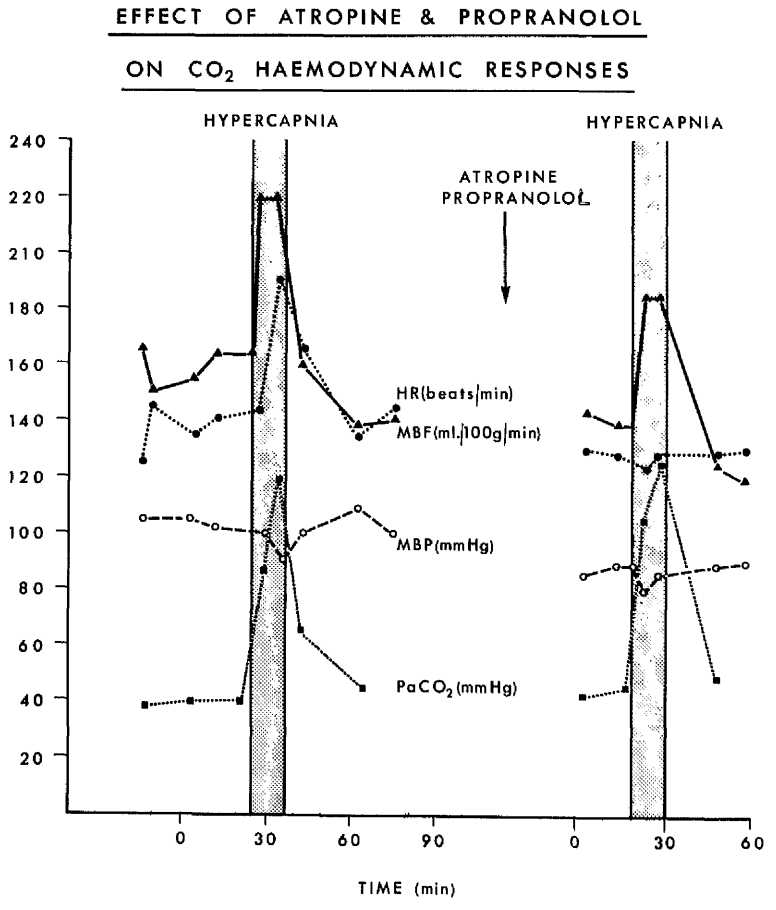

Fig.16. The effects in a single dog of hypercapnia (shaded columns) on myocardial blood flow (M.B.F.), mean arterial pressure (M.B.P.) and heart rate (H.R.) before and after atropine and propranolol. The drugs did not affect the responses to increased $PaCO_2$.

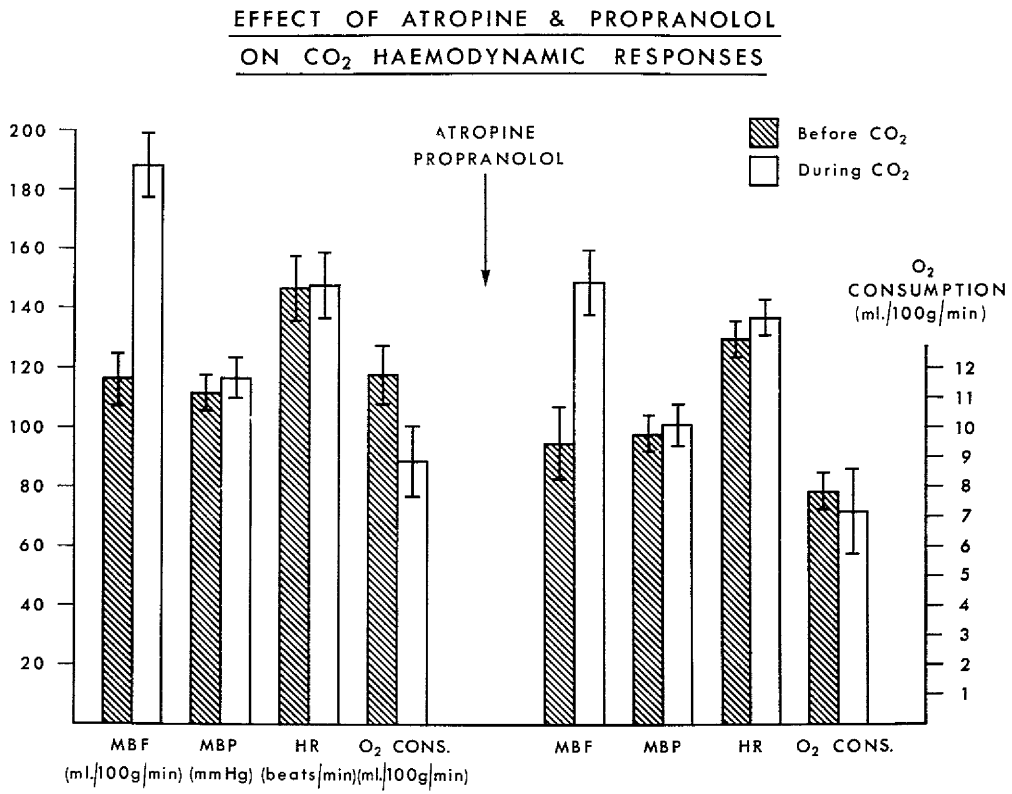

Fig. 17. The changes produced by hypercapnia in myocardial blood flow (M.B.F.), myocardial oxygen consumption (O_2 cons.), mean arterial pressure (M.B.P.) and heart rate (H.R.) before and after the administration of atropine and propranolol. Atropine and propranolol did not alter the responses to hypercapnia. (Mean ± SEM - 7 dogs).

Figures 18 and 19 show respectively the effects of infusions of lactic and hydrochloric acids each in a single dog. The infusion of each acid was accompanied by a sharp fall in pH to about 7.200. This produced a rapid rise in myocardial blood flow in both dogs (with a fall in oxygen consumption in the lactic acid dog). There was a slight rise in $PaCO_2$ with each acid infusion but this was not sufficient to cause the flow increase which was seen. Figure 20 shows a comparison between the myocardial blood flow responses to lactic acid infusion and hypercapnia. The responses were similar.

Because of the natural bufferring capacity of the blood, a fairly large volume of acid solution had to be infused rapidly to produce the desired reduction in blood pH. To determine if the volume of infusate played any part in increasing blood flow, the effects of a 140 ml infusion of lactic acid were compared with those of 140 ml infusion of normal saline. The results of this comparison are seen in figure 21. Although lactic acidosis produced a brisk flow increase no change in flow occurred with normal saline. To confirm the reactivity of the animal, hypercapnia was produced at the end of the experiment with the usual rapid and marked flow increase.

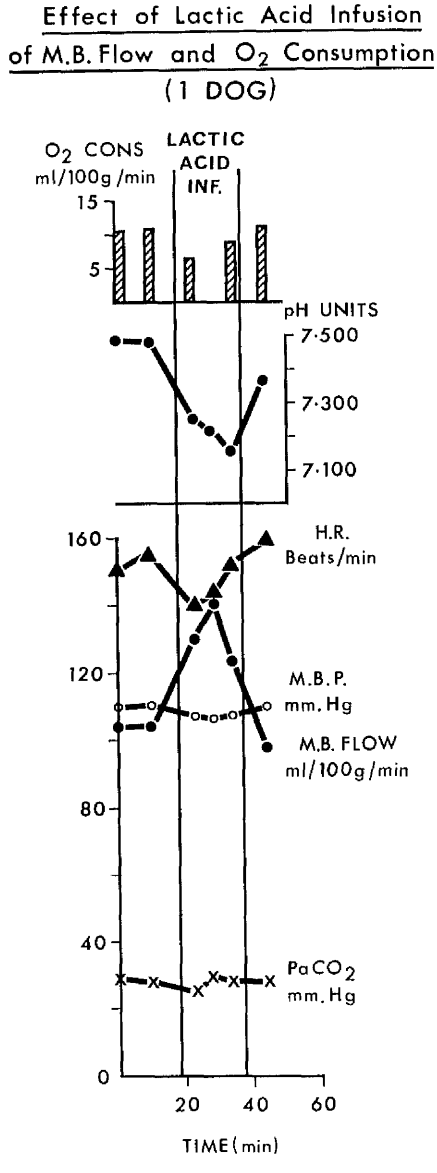

Fig. 18. The effect of lactic acid infusion on myocardial blood flow and oxygen consumption, heart rate, mean arterial pressure, $PaCO_2$ and arterial pH. A sharp increase in myocardial blood flow occurred together with a reduction in oxygen consumption.

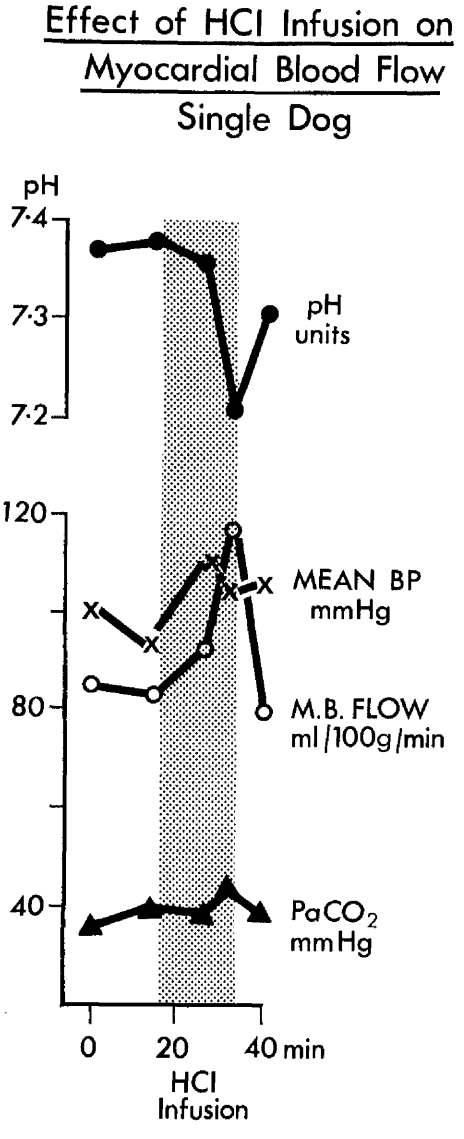

Fig. 19. The effect of hydrochloric acid infusion (shaded area) on myocardial blood flow, mean arterial pressure, $PaCO_2$ and arterial pH in a single dog. Acid infusion was accompanied by a sharp increase in myocardial blood flow.

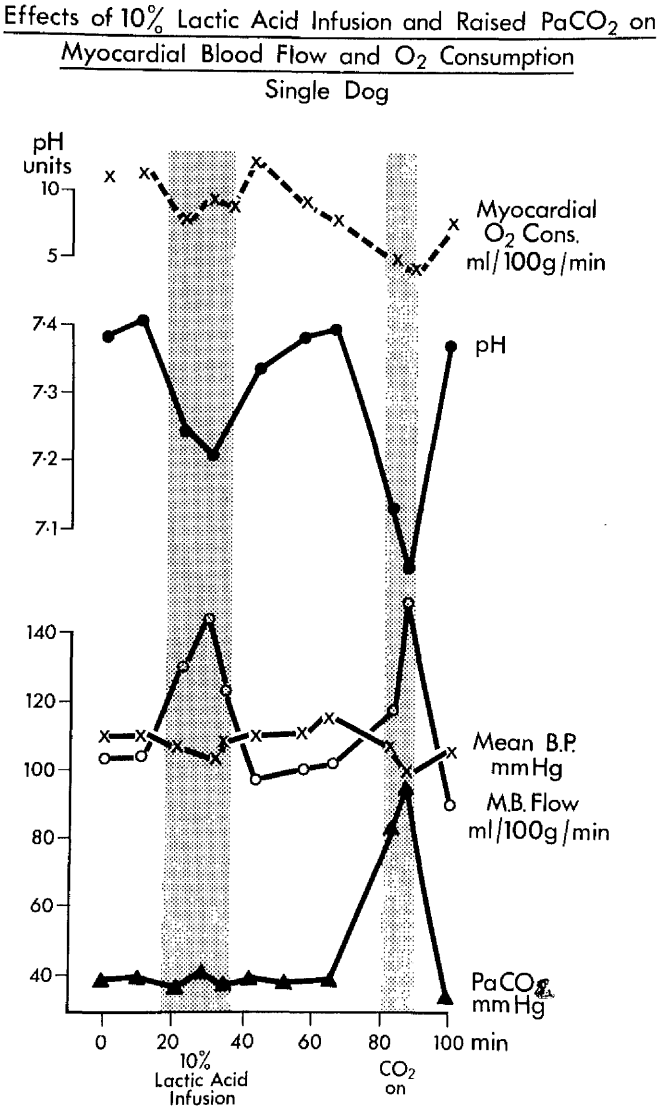

Fig. 20. A comparison in a single dog between the effects of 10% lactic acid infusion and hypercapnia. The effects on myocardial blood flow were similar, however hypercapnia caused a greater reduction in oxygen consumption of the myocardium. This may have been due to the fact that there was a greater reduction in pH with hypercapnia.

Effects of Infusions of Lactic Acid and NaCl and of Raised $PaCO_2$ on Myocardial Blood Flow

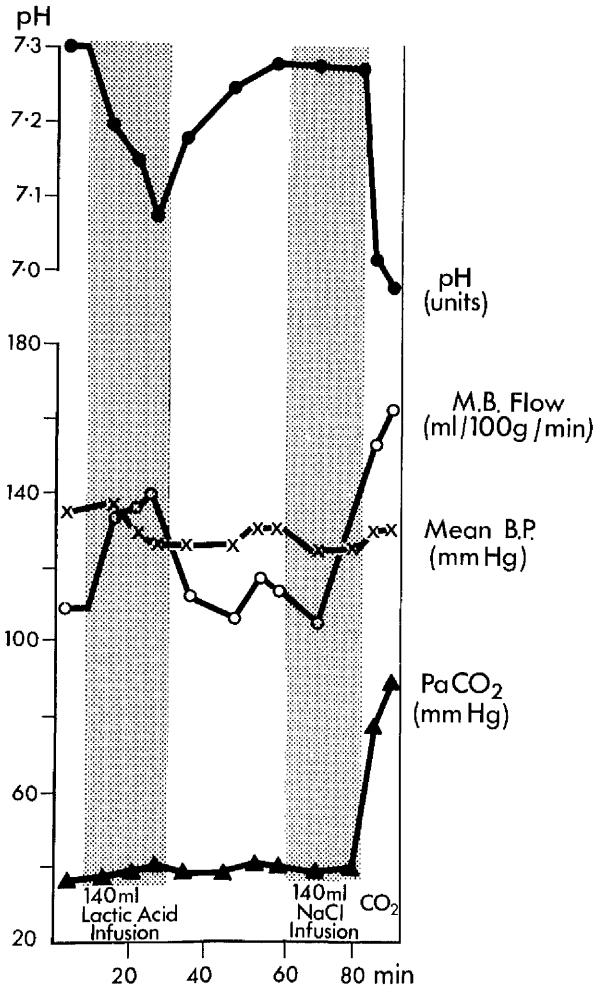

Fig. 21. A comparison in a single dog of the effect of infusion of 140ml 10% lactic acid and 140ml sodium chloride solution. The sodium chloride solution was without effect whereas lactic acid caused an increase in myocardial blood flow. The reactivity of the animal was confirmed by giving CO_2 at the end of the experiment whereupon a brisk increase in flow occurred.

DISCUSSION

These studies have shown that raising the $PaCO_2$ to about 90 - 100 mmHg causes a considerable increase in myocardial blood flow. This increase was not related to changes in blood pressure (and hence in perfusion pressure), heart rate or cardiac output nor was it secondary to an increase in myocardial oxygen consumption since oxygen consumption in fact decreased. The fact that the blood flow responses to hypercapnia were unaffected by partial blockade of the parasympathetic system by atropine and blockade of β adrenoreceptors by propranolol make it unlikely that the autonomic nervous system or circulating catechol amines were responsible for the observed responses. It would appear likely therefore, that the effect of raised $PaCO_2$ on myocardial blood flow is a direct effect of CO_2 on the myocardial vasculature. Thus, in common with the cerebral circulation (Harper, Glass and Glover, 1961), the splanchnic circulation (McGinn, Mendel and Perry, 1967) and the skin (McCardle, Roddie, Sheperd and Whelan, 1957), the myocardial vasculature responds to raised carbon dioxide tension by vasodilatation. This response in the myocardium occurs whether the elevation of $PaCO_2$ be large (i.e. up to 100 mmHg) or relatively small (i.e. up to 60 mmHg). After prolonged exposure to raised $PaCO_2$ the myocardial vasculature appeared to become less responsive and blood flow tended to return to normocapnic levels as did oxygen consumption.

The combination of raised blood flow and reduced oxygen consumption appears to be an unusual one and apparently the only

other procedures which produce these findings are vagal stimulation and the artificial induction of very rapid heart rates (Laurent, Bolene-Williams, Williams and Katz, 1956).

Studies by Prys-Roberts and Kelman (1966) showed that elevation of $PaCO_2$ to 90 mmHg produced what they referred to as a hyperdynamic circulation with raised cardiac output. This was thought to be a result of increased sympathetic nervous discharge. In this study no consistent systemic circulatory changes occurred, possibly because the raised $PaCO_2$ caused a degree of myocardial depression which counterbalanced any possible stimulatory effects. This idea is supported by the findings of the reduced myocardial oxygen consumption which one would expect if contractility were depressed.

It appears therefore, that the predominant effects of raised $PaCO_2$ on the heart are twofold, one which causes a marked dilatation in the coronary vascular bed and another which causes myocardial depression which is associated with reduced oxygen consumption.

The fact that virtually identical changes were observed with the infusion of acid solutions strengthens the possibility that the pH changes associated with raised $PaCO_2$ may be the important factor mediating the flow increases. It should be pointed out that certain other workers have failed to demonstrate flow changes with infusions of hydrochloric acid (Kittle et al., 1965; Goodyer, Eckhardt, Ostberg and Goodkind, 1961). Scheuer

(1968) attempted to determine whether the flow responses were due to a CO_2 effect or a pH effect by infusing sodium bicarbonate solution. Sufficient solution was infused to increase the arterial blood pH from 7.360 to 7.590 units with a resulting increase in $PaCO_2$ from 38 to 91 mmHg. This resulted in a substantial flow increase (from 60 to 168 ml/100g/min). However large volumes of infusate were used to produce these changes, sufficient in fact to increase heart rate, tension-time index and myocardial oxygen consumption, so it may be that the flow increase was at least in part if not wholly due to increased myocardial work.

In 1965, Kittle et al. showed that myocardial blood flow increased with elevated $PaCO_2$ even when the arterial blood pH was kept constant by the simultaneous infusion of 0.9 N trishydroxymethylaminomethane (Tris). It may well be therefore that both raised $PaCO_2$ and decreased arterial pH have similar but independent effects on the myocardium. The data from this study are insufficient to allow a conclusion on this matter to be arrived at.

CHAPTER 7.

MYOCARDIAL BLOOD FLOW RESPONSES TO HYPOXIA.

It has long been recognised that hypoxia will produce increases in myocardial blood flow (Hilton and Eicholtz, 1924-25; Eckenhoff et al., 1947; Berne, Blackmon and Gardner, 1957; Feinberg, Gerola and Katz, 1958; Auckland, Kiil, Kjekshus and Semb, 1967). Previous studies however have not attempted to relate blood flow changes to blood oxygen levels and in particular to arterial oxygen tension. This was the primary object of the study described here.

A total of 27 animals were studied (weight range 19 - 33 kg). Anaesthesia was administered as described in Chapter 2 (i.e. induction with thiopentone and maintenance with trichloroethylene).

In the first group of 5 dogs, hypoxia was produced by gradually lowering the inspired oxygen concentration (FIO_2) by small decrements. Blood flow and other measurements could thus be made at progressively lower levels of PaO_2. Figure 22 shows the changes that occurred in myocardial blood flow, blood pressure and heart rate during this procedure. No marked response in blood flow occurred until the PaO_2 had fallen to less than 40 mmHg when a significant increase occurred ($P < 0.01$ at mean PaO_2 of 35 mmHg and $P < 0.001$ at mean PaO_2 of 25 mmHg). Blood pressure tended to increase gradually throughout the experiment but this did not

attain significant levels. Heart rate tended to fall when PaO_2 fell to less than 50 mmHg but this was not a significant change. It appears therefore that there is a critical level of PaO_2 around 35 mmHg above which myocardial blood flow does not alter. It is regretted that oxygen consumption data was not available for these five experiments.

Having demonstrated that a critical level of PaO_2 existed, 27 experiments were carried out in the remaining 22 dogs in such a way that the FIO_2 was reduced to a mean level of 10.6% in a single step (rapidly induced hypoxia). This produced a mean PaO_2 of 29 mmHg. The arterial and coronary sinus oxygen tension, saturation and content changes associated with this reduction in FIO_2 are shown along with pCO_2 and pH changes in table 15. As was to be expected, pO_2, saturation and content all fell significantly but pCO_2 and pH were unaltered.

During the period of hypoxia, several sets of measurements were made and the data quoted are those which coincided with the maximum myocardial blood flow change and, as indicated above, the arterial and coronary sinus pCO_2 were unchanged at that time. When however, the hypoxic stimulus was maintained for up to 15 min. beyond this time, as it was in 21 experiments, $PaCO_2$ rose significantly to 48 ± 1.5 mmHg ($P < 0.001$). This relatively short period of hypoxia did not produce changes in base excess (i.e. the non-respiratory component of acid base balance).

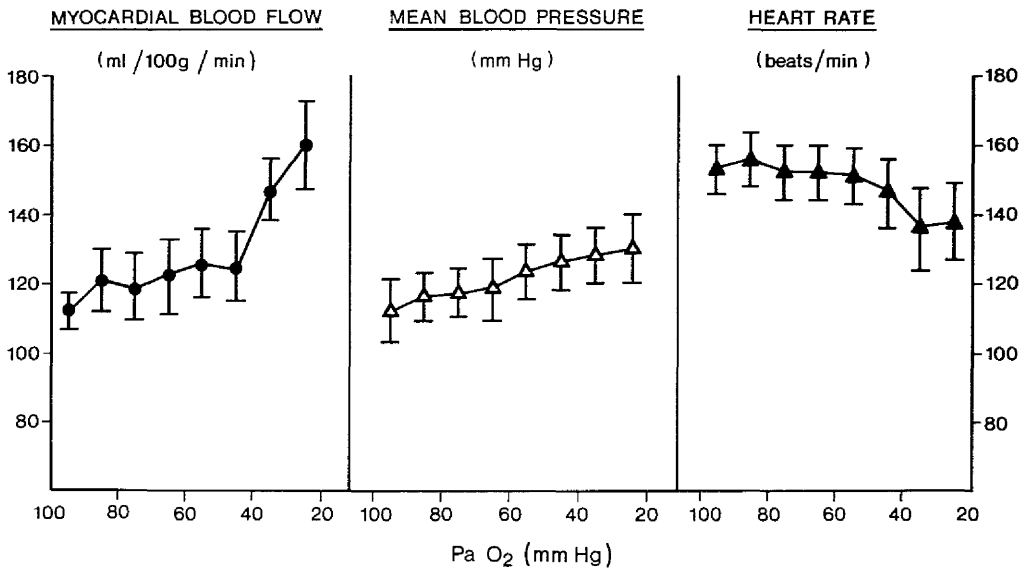

Fig. 22. The effects of gradually induced hypoxia on myocardial blood flow, mean arterial blood pressure and heart rate. (Mean ± SEM - 5 dogs). Blood flow increased only when PaO_2 had fallen to less than 40 mmHg.

	Arterial			Coronary sinus		
	Control		Hypoxia	Control		Hypoxia
PO_2 (mmHg)	97 ± 2	P<0.001	29 ± 1	34 ± 1	P<0.001	18 ± 1
O_2 Saturation (%)	97 ± 0.3	P<0.001	48 ± 2	55 ± 3	P<0.001	22 ± 2
O_2 Content (ml/100ml)	20.8 ± 0.5	P<0.001	11.0 ± 5	10.9 ± 0.5	P<0.001	4.6 ± 0.3
PCO_2 (mmHg)	40 ± 1		41 ± 1	51 ± 1		50 ± 2
pH (units)	7.330 ± 0.008		7.328 ± 0.014	7.306 ± 0.015		7.312 ± 0.021

TABLE 15. The effects of rapidly induced hypoxia on arterial and coronary sinus O_2 tension, saturation and content, PCO_2 and pH (Mean ± SEM 22 dogs - 27 experiments).

Table 16 shows the haemodynamic and myocardial blood flow changes which occurred with the induction of hypoxia and in the immediate post-hypoxic period when the FIO_2 was returned to control levels. Hypoxia caused a 37% increase in myocardial blood flow, a 10% increase in arterial blood pressure and a large increase in right atrial pressure. Heart rate and myocardial vascular resistance showed reductions of 13% and 22% respectively. All of these returned to near control levels when the FIO_2 was restored to pre-hypoxic levels.

The changes in myocardial oxygen availability, consumption and extraction with hypoxia are seen in Table 17. Oxygen availability decreased during hypoxia despite the large blood flow increase, however mean oxygen consumption was unchanged because of a rise in oxygen extraction.

Although the heart rate showed a mean reduction of 13%, there were in fact two distinct patterns of heart rate response to the hypoxic challenge. In 16 experiments the heart rate decreased and in the remaining 11 experiments there was an increase in heart rate. Table 18 shows the changes which occurred in mean arterial pressure and myocardial blood flow and oxygen consumption in relation to these two different heart rate responses. Blood flow increased to a larger extent when heart rate increased than when it decreased (45% as opposed to 32%) and similarly with arterial pressure (18% as compared with 9%). In the case of myocardial oxygen consumption, there was a 26% increase when heart rate rose as compared with a slight decrease when heart rate fell.

	Control		Hypoxia		Post Hypoxia
PaO_2 (mmHg)	97 ± 2	P<0.001	29 ± 1	P<0.001	96 ± 5
Mean Blood Pressure (mmHg)	119 ± 3	P<0.05	131 ± 5	P<0.05	113 ± 3
Heart Rate (beats/min)	158 ± 6	P<0.02	138 ± 9	P<0.02	158 ± 7
Right Atrial Pressure (mmHg)	+0.6 ± 0.1	P<0.01	+2.7 ± 0.1	P<0.01	-0.4 ± 0.4
Myocardial Blood Flow (ml/100g/min)	118 ± 5	P<0.001	162 ± 6	P<0.001	108 ± 6
Myocardial Vascular Resistance (units)	1.08 ± 0.05	P<0.01	0.84 ± 0.06	P<0.01	1.10 ± 0.39

TABLE 16. Haemodynamic and myocardial blood flow changes with rapidly induced hypoxia and with subsequent restoration of normal PaO_2. (Mean ± SEM. 22 dogs - 27 experiments).

	Control		Hypoxia.
Myocardial O_2 availability (ml/100mg/min)	23.4 ± 1.0	P<0.005	17.2 ± 0.9
Myocardial O_2 consumption (ml/100g/min)	10.2 ± 0.6		10.6 ± 0.9
Myocardial O_2 extraction (%)	43 ± 4	P<0.01	55 ± 5

TABLE 17. Changes in myocardial oxygen availability, consumption and extraction resulting from hypoxia. (Mean ± SEM 22 dogs - 27 experiments).

	Heart rate decreased (16 experiments)			Heart rate increased (11 experiments)		
	Control		Hypoxia	Control		Hypoxia
Heart rate (beats/min)	160 ± 10	P<0.01	116 ± 6	150 ± 10	P<0.05	177 ± 12
Myocardial blood flow (ml/100g/min)	122 ± 6	P<0.001	161 ± 7	113 ± 10	P<0.001	164 ± 9
Mean arterial blood pressure (mmHg)	121 ± 4		131 ± 7	116 ± 4	P<0.01	137 ± 5
Myocardial oxygen consumption (ml/100g/min)	9.5 ±0.6		8.9 ±1.0	9.6 ±1.9		12.1 ± 1.2

TABLE 18. Relationship of heart rate changes to changes in myocardial blood flow, mean arterial pressure and myocardial oxygen consumption in response to rapidly induced hypoxia. (Mean ± SEM 22 dogs - 27 experiments).

The blood flow responses in two dogs which showed different heart rate changes are illustrated in figure 23.

An attempt was made to relate blood flow changes to certain oxygen data and figure 24 shows the relationship between blood flow and arterial oxygen tension, coronary sinus oxygen tension and coronary sinus oxygen content. Blood flow appeared to be most closely related to coronary sinus oxygen tension. The critical level of arterial PO_2 for flow increase (i.e. about 35 mmHg) corresponded to a coronary sinus PO_2 of 18 mmHg which in turn corresponded to an oxygen content in the coronary sinus of 5.0 ml/100ml. After the critical level of PO_2 had been reached, further small decrements in PaO_2 were accompanied by further increments in blood flow (see figures 22 and 23). This suggests therefore, that the flow response at the critical PaO_2 level may not be maximal and this is confirmed in figure 25 where the flow changes produced by hypoxia are compared with those produced by hypercapnia. Even at a PaO_2 of 20 mmHg, the flow increase was exceeded by that produced by an elevated $PaCO_2$ of 84 mmHg.

Arterial and coronary sinus concentrations of lactate, pyruvate and glucose were measured in 12 animals from the rapidly induced hypoxia series. These data are shown in Table 19.

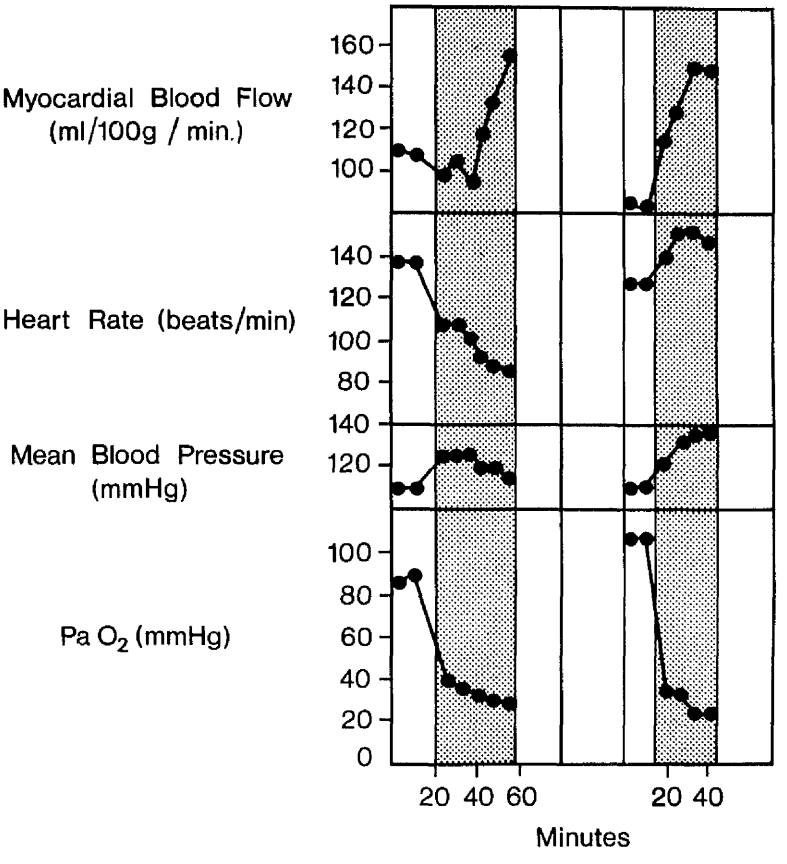

Fig. 23. This illustrates the two different heart rate responses to hypoxia (shaded areas) in two dogs. The data on the right hand side where the heart rate increased indicated that blood flow and blood pressure showed a larger increase than that on the left hand side where heart rate decreased.

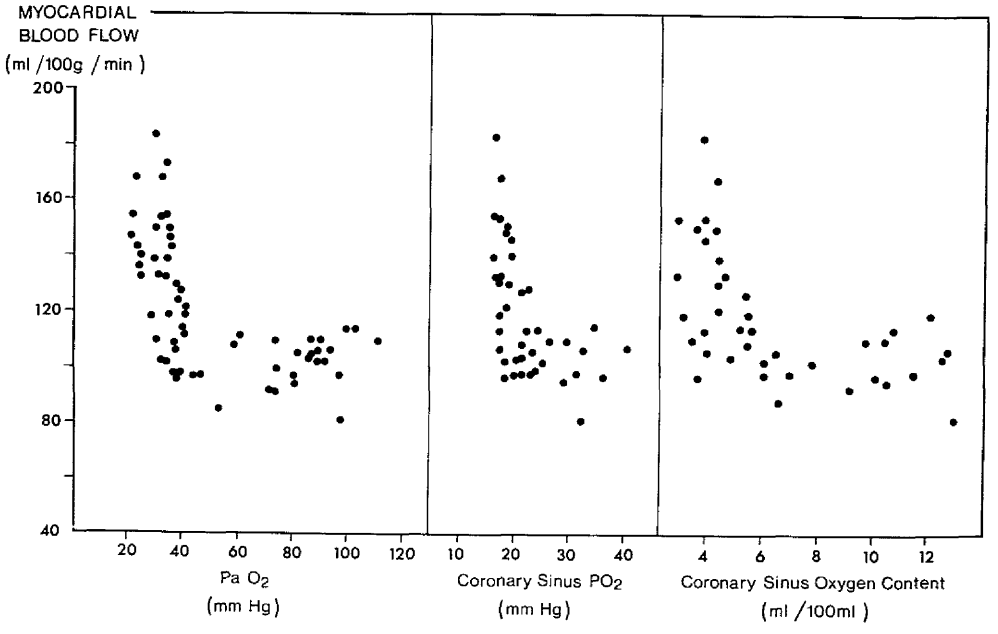

Fig. 24. The relationship between myocardial blood flow and PaO_2, coronary sinus PO_2 and coronary sinus O_2 content. The closest relationship is with coronary sinus PO_2. These data are taken from all 27 animals in the hypoxia investigation.

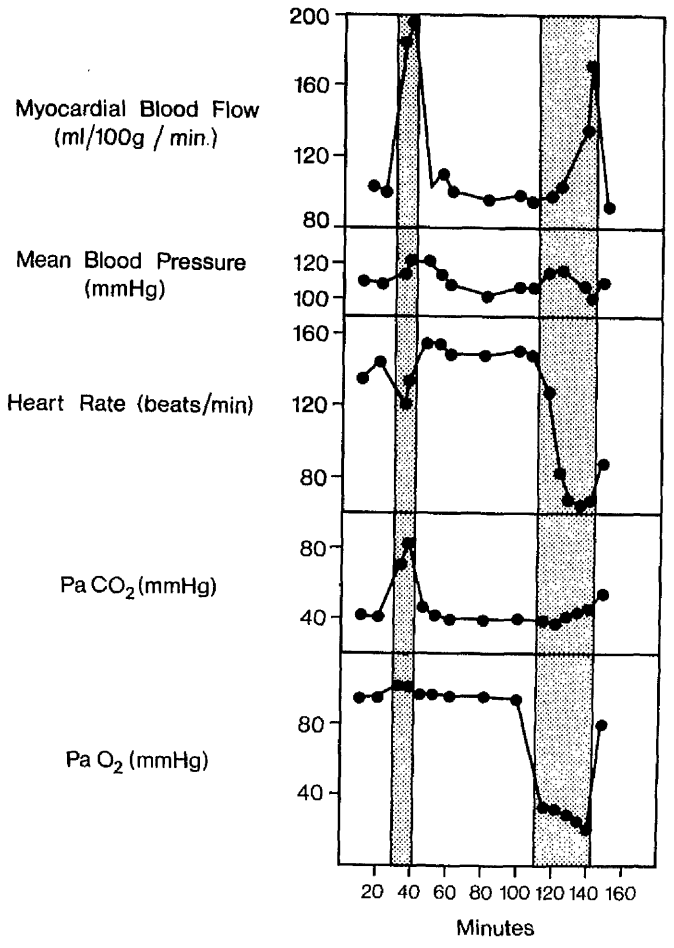

Fig.25. A comparison in a single dog between the effects of hypoxia and raised $PaCO_2$. When the PaO_2 was reduced to 20 mmHg this did not produce maximal coronary vasodilatation since the flow response was exceeded by that of an elevated $PaCO_2$ of 84 mmHg.

	Control		Hypoxia	
	Arterial	C. Sinus	Arterial	C. Sinus
Lactate (mg/100ml)	19.8 ± 3.0	15.1 ± 2.2	29.9 ± 5.4	26.5 ± 4.8
Pyruvate (mg/100ml)	1.3 ± 0.1	0.9 ± 0.1	1.4 ± 0.1	1.2 ± 0.1
Glucose (mg/100ml)	115 ± 6	113 ± 6	130 ± 6	128 ± 7

TABLE 19. The effects of rapidly induced hypoxia on arterial and coronary sinus (C.Sinus) concentrations of lactate, pyruvate and glucose. (Mean ± SEM. 12 dogs).

In the control period the myocardium appeared to extract lactate and pyruvate but probably not glucose. During hypoxia a mild systemic lactic acidosis developed but there appeared to be no change in extraction of the three substrates. (The data used to compile Table 19 did not necessarily coincide with the maximum blood flow change).

Electrocardiographic changes occurred frequently during hypoxia. Eleven animals showed ventricular extrasystoles (3 of which were multifocal), four developed nodal rhythm, two developed complete heart block and ST segment and T wave changes occurred in eight. In all cases the return to normal oxygenation promptly restored the electrocardiographic pattern to normal.

After the rapidly induced hypoxic stimulus, seven animals were given atropine and propranolol in the same dose as that used in Chapter 6 (i.e. 0.04 mg/kg of atropine and 0.2 mg/kg of propranolol). The changes produced by atropine and propranolol were detailed in Chapter 6 and similar changes occurred once again. After the administration of the two drugs, the rapidly induced hypoxic stimulus was repeated. The haemodynamic changes produced by hypoxia before and after atropine and propranolol in the seven dogs are shown in figure 26 and in a single dog of the group in figure 27. The responses to hypoxia were uninfluenced by the administration of the drugs.

In a small group of the 22 animals in the main series hypoxia was rapidly induced and maintained for some 60 minutes. Myocardial blood flow remained elevated during the period of hypoxia but despite this, myocardial oxygen consumption fell progressively after the first 10-15 minutes and this was accompanied by an increasingly severe systemic metabolic acidosis. The results from one of these animals is shown in figure 28.

DISCUSSION

The myocardium, because of its constant work load, has a continuous high level of energy requirement. Since the energy production of anaerobic metabolism is small in comparison to that of aerobic metabolism, the myocardium must have a constant supply of oxygen. It will rapidly fail if this supply is not maintained as a result of either hypoxaemia or coronary occlusion (Bing, 1965;

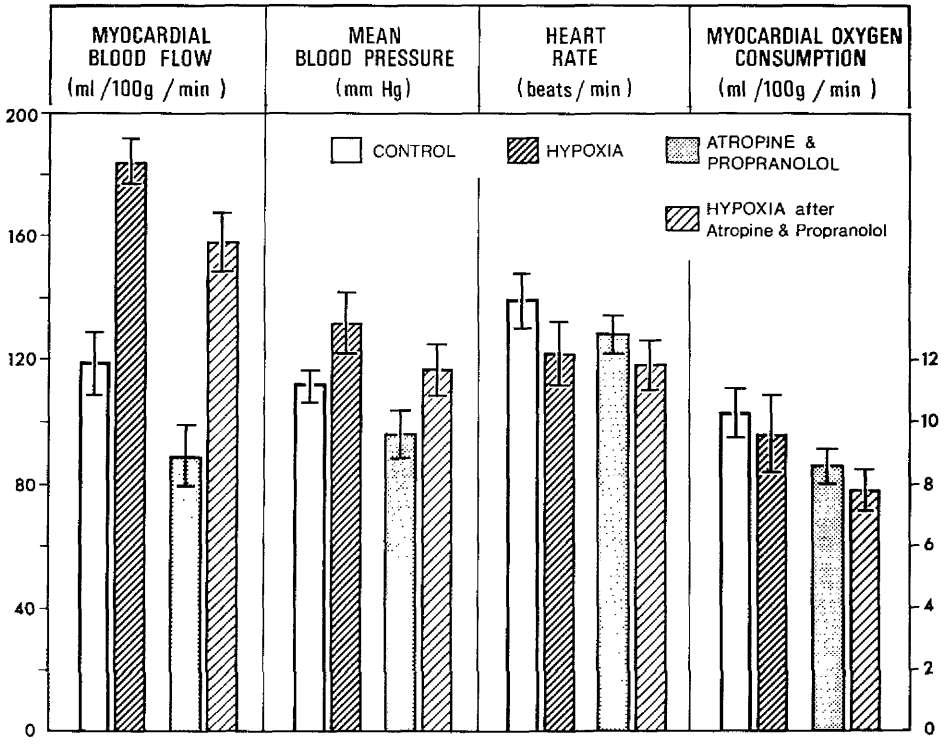

Fig. 26. The responses of myocardial blood flow, myocardial oxygen consumption, mean arterial pressure and heart rate to hypoxia before and after atropine and propranolol. The drugs did not modify the responses to hypoxia. (Mean ± SEM 7 dogs).

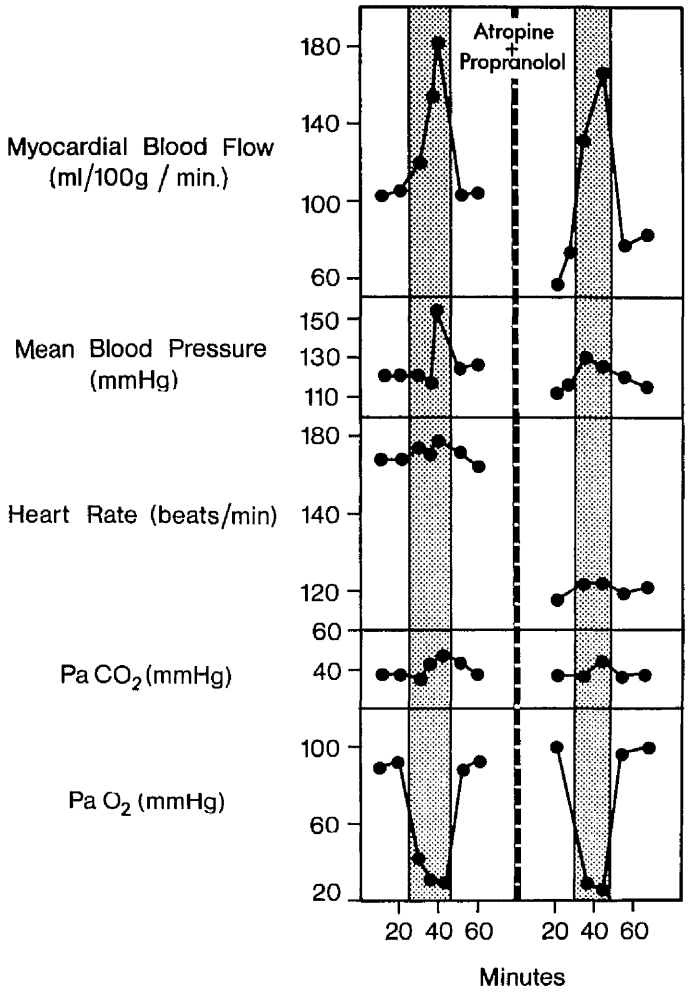

Fig. 27. The responses to hypoxia (shaded areas) in a single dog before (left hand side) and after (right hand side) atropine and propranolol. The responses were uninfluenced by the drugs.

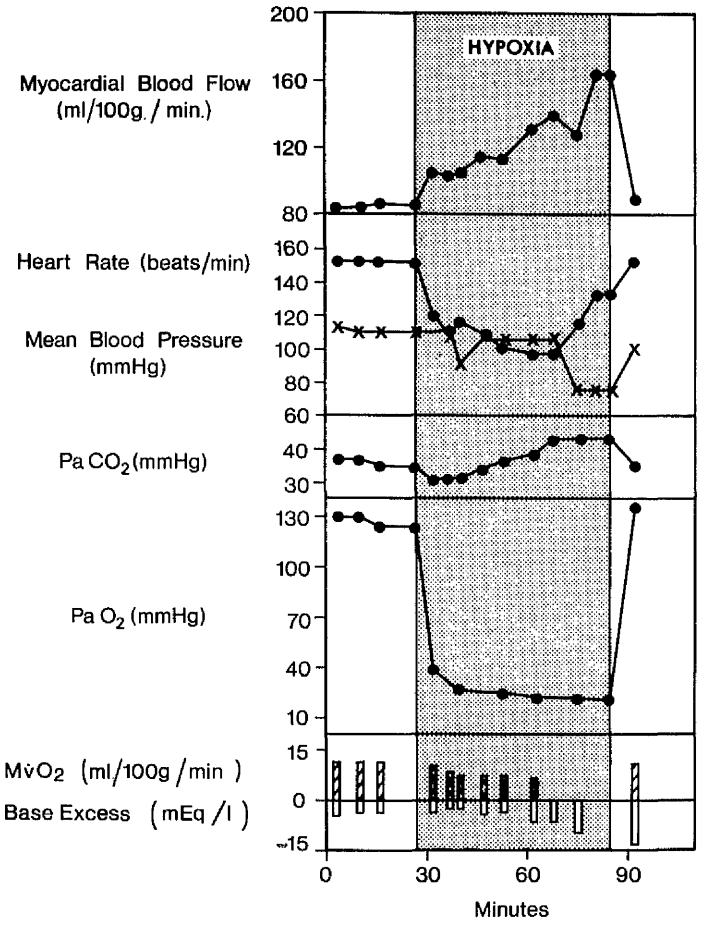

Fig. 28. The effects of hypoxia sustained for 60 minutes on myocardial blood flow, heart rate, mean arterial pressure, $PaCO_2$, myocardial oxygen consumption (MvO_2) and base excess.

Tennant and Wiggers, 1935). In this study, the myocardium responded to hypoxia in a twofold manner, one by increasing its blood flow and the other by increasing the proportion of oxygen extracted from the blood. It was thus enabled to obtain enough oxygen to maintain its function.

The demonstration of a critical level of arterial oxygen tension at which myocardial blood flow shows an increase is not a universal finding in other studies. The critical level suggested here is about 30-35 mmHg PaO_2. Berne et al. (1957) suggested, from work on open chest dogs with artificially perfused coronary arterial systems, that there was a critical level of hypoxia at which flow increases occurred and that this appeared to be when the coronary sinus blood oxygen content fell to less than 5.5 vols.%. This study is in fairly close agreement with Berne's suggestions since figure 24 shows that the critical level of coronary sinus oxygen content was about 5 ml/100ml (i.e. 5 vols.%). Figure 24 shows also that the scatter of coronary sinus oxygen tension values was somewhat less than that of the arterial oxygen tension values, suggesting that there is a good relationship between myocardial blood flow and coronary sinus oxygen tension which is presumably related in turn to myocardial tissue oxygen tension. It is of interest that the critical level of PaO_2 (i.e. about 32-33 mmHg) coincided with the control level of coronary sinus oxygen tension (see Table 15) again suggesting that myocardial tissue oxygen tension may be an important factor in the control of myocardial blood flow.

Hypoxia in this study was associated with an increase in $PaCO_2$, a factor which has been shown to increase myocardial blood flow (see Chapter 6). However, the maximum flow increase occurred before the $PaCO_2$ had risen and therefore the $PaCO_2$ increase cannot be considered as a causative factor in the blood flow response to hypoxia.

The heart rate responses to hypoxia have been described by Daly and Scott (1963) and Kontos, Mauck, Richardson and Patterson (1965). These workers concluded that the response of heart rate to hypoxia depends on whether the animal is artificially ventilated or breathes spontaneously. Spontaneously breathing animals respond to hypoxia by hyperventilation which contributes to the tachycardia which is a frequent response to hypoxia. This is apparently initiated by a reflex from the stretching of the hyperventilated lung (Daly and Scott, 1963). Although Krasney (1967) has reported tachycardia as a response to hypoxia in the artificially ventilated animal, the usual response is a bradycardia which results from carotid chemoreceptor stimulation by hypoxic blood (Kontos et al., 1965). In this study, about one third of the animals responded to hypoxia with a tachycardia. This was probably due to stimulation of the sympathetic nervous system and release of adrenaline from the adrenal medulla by the hypoxic stimulus. The majority of the animals however, responded with a slowing of heart rate which was on occasion quite marked (see figures 23 and 25). This was probably due to stimulation of carotid and aortic body chemoreceptors by hypoxic blood and possibly also to a direct myocardial depressant effect of hypoxia (Kahler, Goldblatt and Braunwald, 1962).

The lack of effect of atropine and propranolol on the responses to hypoxia indicate that these responses are not mediated through the autonomic nervous system nor through the release of catechol amines into the blood stream from the adrenal medulla. This finding is contrary to that of Folle and Aviado (1965) who concluded, from experiments in open chest dogs with coronary sinus outflow measurement, that the β adrenoreceptor blocking drug sotalol abolished the increase in coronary sinus outflow which resulted from inhalation of 5% oxygen in nitrogen.

The results of the study reported here would suggest that the myocardial vascular response to hypoxia is due to a direct effect of lowered arterial or tissue oxygen tension (or to the release of some metabolite associated therewith) on vascular smooth muscle.

The observation of a consistant increase in arterial carbon dioxide tension with hypoxia indicates an increase in pulmonary dead space. Hypoxia is known to cause pulmonary vasoconstriction (Duke, 1951; Bergofsky, Haas and Porcelli, 1968) and this will almost certainly be associated with disturbances of pulmonary ventilation/perfusion relationships which may give rise to areas within the lungs where perfusion is inadequate in relation to the volume of gas ventilating (i.e. increased intrapulmonary dead space). Almost invariably, this is accompanied by increased intrapulmonary shunt effect (i.e. when the volume of blood perfusing an area of lung is excessive relative to the volume of gas ventilating it). Increased shunt effect may have played a part in causing the slight fall in PaO_2 which often occurred during hypoxia after the FIO_2 was stable (see

figures 23, 25 and 28).

The metabolic disturbances associated with a brief period of hypoxia were not severe and amounted only to a slight degree of systemic lactic acidosis which presumably indicates that there was true tissue hypoxia in some areas of the body. This was not the case in the heart since the myocardium continued to extract lactate rather than produce it. Although this would appear to suggest that most of the animals could obtain enough oxygen for myocardial function, the electrocardiographic changes seen would suggest that a few were on the verge of failure particularly those which developed complete heart block since Harris (1951) has shown that the commonest terminal electrocardiographic abnormality during hypoxia is the development of pacemaker or atrioventricular conduction failure. These animals recovered uneventfully after re-oxygenation.

In contrast, the effect of maintaining a lowered PaO_2 for 60 minutes produced an increasingly severe degree of base deficit. Towards the end of this period of hypoxia arterial blood pressure fell and the initial heart rate reduction was reversed (see figure 28). It is assumed that these changes indicate that the myocardium was by this time on the point of failure. Nevertheless, haemodynamics and myocardial oxygen consumption returned to control levels within a very short time of returning to a normal PaO_2 thus indicating the capacity for recovery of the healthy heart.

CHAPTER 8.

THE EFFECTS OF HAEMORRHAGIC HYPOTENSION ON MYOCARDIAL BLOOD FLOW AND OXYGEN CONSUMPTION.

Anaesthesia for this study was administered as described in Chapter 2. After control measurements had been made, the animals were rendered hypotensive by the withdrawal of blood through a wide bore cannula inserted into the right femoral artery. Bleeding took place over a period of 10 - 20 minutes.

Two groups of animals were studied:-

1. Moderate haemorrhage - arterial blood pressure reduced to about 75 mmHg.

2. Severe haemorrhage - arterial blood pressure reduced to about 45 mmHg.

The FIO_2 was adjusted to maintain a relatively constant PaO_2 at all times.

MODERATE HAEMORRHAGE

Nine dogs were included in this group. The average quantity of blood withdrawn was 43 ml/kg (range 25 - 63 ml/kg). This resulted in a decrease in mean packed cell volume from 43% to 38% and a decrease in mean haemoglobin concentration from 15.0 to 13.0 g/100 ml.

The haemodynamic effects of this blood loss are seen in Table 20.

	Mean arterial B.P. (mmHg)	Heart rate (beats/min)	Myocardial blood flow (ml/100g/min)	Cardiac output (l/min)	Myoc. vasc. resistance (units)
Control	122 ± 6	165 ± 12	111 ± 7	4.16 ± 0.56	112 ± 6
	P<0.001		P<0.001	P<0.001	
Haemorrhage	73 ± 2	194 ± 21	61 ± 5	1.36 ± 0.12	125 ± 12

TABLE 20. The haemodynamic changes associated with moderate blood loss. (Mean ± SEM. 9 dogs).

Heart rate tended to increase but this did not reach a significant level in this series of animals. Myocardial blood flow and cardiac output were markedly reduced. Myocardial vascular resistance tended to increase.

Table 21 shows the arterial blood gas, pH and base excess changes along with the coronary sinus PO_2 changes resulting from moderate haemorrhage.

	Art.PO_2 (mmHg)	Art.PCO_2 (mmHg)	Art.pH (units)	Art.base excess (meq/l)	C.Sinus PO_2 (mmHg)
Control	99 ± 3	41 ± 2	7.386 ± 0.026	-1 ± 2	31 ± 2
		P<0.05	P<0.05	P<0.01	
Haemorrhage	95 ± 3	48 ± 3	7.262 ± 0.048	-9 ± 2	27 ± 4

TABLE 21. Arterial (Art.) blood gas, pH and base excess changes with moderate haemorrhage (Mean ± SEM 9 dogs).

Arterial carbon dioxide tension rose significantly while arterial pH and base excess fell indicating the onset of metabolic acidosis. Although the reduction in coronary sinus oxygen tension was small, there was a considerable increase in myocardial oxygen extraction as can be seen in Table 22.

	Myocardial oxygen consumption (ml/100g/min)	Myocardial oxygen availability (ml/100g/min)	Myocardial oxygen extraction (%)
Control	9.49 $\pm$ 1.3	22.17 $\pm$ 1.7	46 $\pm$ 2
	$P \leq 0.01$	$P < 0.001$	$P < 0.01$
Haemorrhage	6.19 $\pm$ 0.9	10.11 $\pm$ 0.6	68 $\pm$ 4

TABLE 22. Changes in myocardial oxygen availability, extraction and consumption with moderate haemorrhage. (Mean $\pm$ SEM - 9 dogs.)

The mean myocardial oxygen availability fell by some 54% and although mean oxygen extraction increased by 48% this was not enough to maintain oxygen consumption which decreased by 34%.

SEVERE HAEMORRHAGE

This group included eleven dogs from which the average amount of blood withdrawn was 51 ml/kg (range 41 - 66 ml/kg). The mean packed cell volume in these animals fell from 46% to 36% and the mean haemoglobin concentration from 17.1 to 13.6 g/100ml.

The blood pressure reduction achieved by this amount of bleeding is seen in Table 23. The accompanying myocardial blood

flow and cardiac output reductions were highly significant as was the reduction in myocardial vascular risistance.

	Mean arterial B.P. (mmHg)	Heart rate (beats/ min)	Myocardial blood flow (ml/100g/min)	Cardiac Output (l/min)	Myoc.vasc. resistance (units)
Control	141 ± 4	186 ± 14	116 ± 7	3.13 ± 0.40	125 ± 7
	P<0.001		P<0.001	P<0.01	P<0.01
Haemorrhage	47 ± 3	193 ± 13	52 ± 6	1.26 ± 0.48	96 ± 7

TABLE 23. Haemodynamic changes associated with severe haemorrhage. (Mean ± SEM - 11 dogs).

The corresponding changes in arterial blood gases and pH are shown in Table 24.

	Art.PO_2 (mmHg)	Art.PCO_2 (mmHg)	Art.pH (units)	Art.base excess (meq/l)
Control	103 ± 2	41 ± 1	7.369 ± 0.037	-2 ± 1
		P<0.01	P<0.001	P<0.001
Haemorrhage	97 ± 5	57 ± 5	7.117 ± 0.051	-15 ± 2

TABLE 24. Arterial blood gas, pH and base excess changes with severe haemorrhage. (Mean ± SEM - 11 dogs).

Arterial carbon dioxide tension increased markedly and there was a highly significant reduction in arterial pH and base excess.

	Myocardial O_2 consumption (ml/100g/min)	Myocardial O_2 availability (ml/100g/min)	Myocardial O_2 extraction (%)
Control	11.6 ± 1.2	21.55 ± 1.8	52 ± 5
	P<0.001	P<0.001	P<0.01
Haemorrhage	5.1 ± 0.6	7.62 ± 1.0	65 ± 4

TABLE 25. Changes in myocardial oxygen consumption, availability and extraction with severe haemorrhage. (Mean ± SEM - 11 dogs).

Myocardial oxygen availability was very markedly reduced as was oxygen consumption (Table 25). Myocardial oxygen extraction increased significantly.

With severe haemorrhage there was evidence of myocardial ischaemia. ST segment depression occurred in all animals while in some, extrasystoles occurred and in some, nodal rhythms occurred.

DISCUSSION

Severe blood loss is rapidly fatal if energetic measures to arrest the bleeding and replace the lost blood volume are not taken. Evidence exists to suggest that the heart itself is the main structure responsible for the fatal outcome (Guyton and Crowell, 1961; Crowell and Guyton, 1961&1962). The heart fails probably as a result of hypoxia which results from the reduction in blood flow through the myocardial tissue together with the reduction in arterial oxygen content consequent on the fall in haemoglobin concentration.

The other very important factor accompanying haemorrhage is metabolic acidosis which has been shown to depress myocardial contractility (Thrower, Darby and Aldinger, 1961; Opie, 1965; Ng, Levy and Zieske, 1967).

The development of metabolic acidosis during haemorrhagic hypotension contrasted with the acid-base status during hypotension induced with halothane. In the halothane experiments (Chapter 4) acidosis was not seen. It is of course, well recognised that there are major differences between haemorrhagic hypotension and drug induced hypotension but the development of acidosis in haemorrhage is one of the best acknowledged of these differences and probably results from inadequate tissue perfusion and hypoxia. Another important difference which has been suggested in recent years is the possible existance of a 'myocardial depressant factor' which is released during haemorrhage (Lefer, 1970; Fisher, Heimbach, McArdle, Maddern, Hutcheson and Ledingham, 1973; McArdle and Fisher, 1973). It has been suggested that this factor, which is thought to be a small peptide or glucopeptide molecule, acts in some way as a metabolic inhibitor when haemorrhagic shock has been prolonged and contributes to the lack of responsiveness to resuscitation in irreversible shock (Heimbach, Fisher, Hutton, McArdle and Ledingham, 1973).

It has been suggested previously that during haemorrhagic hypotension, the myocardial vasculature exhibits the phenomenon of 'autoregulation' which means that the vascular resistance is adjusted by some inherent mechanism which allows blood flow to be maintained at a relatively stable level in the face of a changing

blood pressure (Berne, 1959; Mosher, Ross, McFate and Shaw, 1964; Grayson and Parratt, 1966). Such a mechanism would help to explain the difference in myocardial vascular resistance in moderate and severe haemorrhage. It would also appear that such a mechanism is abolished by halothane (see Chapter 4). In Chapter 6 it was shown that both respiratory and metabolic acidosis would cause increased myocardial blood flow. It is of interest that both metabolic acidosis and a raised $PaCO_2$ occurred during haemorrhage, and one is led to speculate that these two factors may have played a part in the marked reduction in myocardial vascular resistance during severe haemorrhage and that they may indeed be responsible at least in part for the occurrence of autoregulation of blood flow in the myocardium. It would follow therefore that the absence of autoregulation during halothane induced hypotension may be related to the absence of acidosis.

The increase which occurred in arterial carbon dioxide tension during moderate and severe haemorrhage indicates an increase in pulmonary dead space ventilation which is a well recognised phenomenon during haemorrhage and occurs due to altered ventilation-perfusion relationships within the lung. Undoubtedly this would also have led to a reduction in arterial oxygen tension if the inspired oxygen fraction had not been adjusted to maintain full oxygenation.

CHAPTER 9.

SUMMARY OF RESULTS AND GENERAL DISCUSSION.

The results presented in previous chapters show that :-

1. Hypocapnia of moderate degree ($PaCO_2$ 25 mmHg) causes a reduction in myocardial blood flow with an associated increase in myocardial oxygen extraction so that oxygen consumption was unaltered. Significant metabolic changes were not observed in the myocardium.

2. Hypotension induced with halothane is accompanied by dose dependent reductions in myocardial blood flow and oxygen consumption and also in heart rate and cardiac output. There was an associated increase in myocardial vascular resistance with the higher doses examined.

3. The decremental effects of halothane hypotension and hypocapnia on myocardial blood flow are additive when the two conditions are produced simultaneously. During recovery from halothane hypotension, the blood pressure gives a poor indication of returning myocardial function.

4. Hypercapnia causes a marked increase in myocardial blood flow accompanied by a reduction in oxygen consumption of the myocardium. Blood pressure and heart rate are unaffected.

Similar results were produced by infusions of lactic and hydrochloric acids. The CO_2 responses were unaffected by partial parasympathetic or β adrenergic blockade.

5. Hypoxia was accompanied by an increase in myocardial blood flow when PaO_2 was reduced to less than 35 mmHg. When this was sustained for short periods only, myocardial oxygen consumption was unaffected. Hypoxia caused an increase in blood pressure and either an increase or decrease in heart rate. The responses to hypoxia were unaffected by partial parasympathetic blockade or β adrenergic blockade.

6. Haemorrhagic hypotension is associated with considerable reductions in myocardial blood flow. Severe haemorrhage is accompanied by a marked fall in myocardial vascular resistance and also by respiratory and metabolic acidosis. Myocardial oxygen consumption was reduced and oxygen extraction increased, the latter especially so during moderate hypotension.

These results present a certain challenge to two fairly widely held concepts in myocardial physiology. Firstly, it is often said that oxygen extraction by the myocardium remains fairly constant under varying conditions and that oxygen uptake can therefore only increase substantially as a result of an increase in blood flow. Several of the results quoted here do not bear this out, for example, during hypocapnia mean oxygen extraction increased by 21% over control (Chapter 3), during hypoxia there was a mean extraction increase of

28% (Chapter 7) and during moderate and severe haemorrhagic hypotension there were mean extraction increases of 48% and 25% respectively (Chapter 8). Secondly, myocardial blood flow changes are regarded as being closely related to changes in myocardial oxygen consumption (Braunwald, Sarnoff, Case, Stainsby and Welsh, 1958; Feinberg, Katz and Boyd, 1962). During hypercapnia however, blood flow and oxygen consumption in the myocardium were divergent (Chapter 6) and during hypocapnia, blood flow fell while oxygen consumption was unaltered (Chapter 3). It would appear therefore that if myocardial oxygen consumption is indeed a determinant of blood flow then it is not an overriding one and its effects are subject to considerable modification by prevailing conditions.

The foregoing catalogue of results described changes occurring in the experimental animal in laboratory conditions. This is obviously a far cry from the clinical situation in which these patho-physiological conditions are likely to be encountered, however it is important that such basic experimental information be obtained. When it is borne in mind that methods of measurement of organ blood flow are, as a rule, of a highly invasive character, particularly so with regard to the myocardium, it is obvious that such information cannot be obtained from human sources, at least not with currently available methods of measurement of tissue blood flow. Dogs were selected for the experiments because, in most respects, the cardio-vascular systems of dog and human tend to react in a similar manner to physiological and pharmacological stimuli. It would be surprising therefore, if the results from the experiments described herein do not give a reasonable guide to the types of response which occur in the human.

The reasons for the choice of the ^{133}Xenon method of measurement of blood flow have previously been outlined but attention is once again drawn to the relative lack of trauma involved in the preparation of the animals in comparison to other methods. This is a factor which, it is felt, increases the validity of the results.

The choice of trichloroethylene as the basal anaesthetic for most of the experiments was made because it had been shown, in other series of experiments from the same laboratory, to provide a haemodynamically stable preparation which was nevertheless highly reactive to all kinds of stimuli and this was borne out in the experiments described here. Pentobarbitone was used as the basal anaesthetic for those experiments where halothane was utilised as a part of the experimental protocol (Chapters 4 and 5). This avoided the possible complexities of simultaneous administration of two inhalation agents. It is not possible to estimate the extent to which the administration of basal anaesthesia influenced the results of individual experiments.

Perhaps it is projecting into the realms of science fiction to hope that at some time in the future, a non-invasive method of measurement of tissue blood flow will emerge, however, for the present one can suggest certain extensions of the foregoing experiments which could profitably be undertaken. In the clinical situation few of the conditions investigated and described here occur in isolation, for example hypercapnia and hypoxia frequently occur in combination and haemorrhagic hypotension is often associated with hypercapnia and/or

hypoxia. It would seem reasonable therefore, if such combinations of respiratory and circulatory disturbances were to be investigated, perhaps in a manner similar to that of halothane hypotension and hypocapnia as in Chapter 5.

Further experiments are at present being planned in which the eventual aim will be to measure coronary artery blood flow in the conscious animal by means of a chronically implanted electromagnetic flow probe. It is possible that certain information will derive from these experiments which will throw further light on the conditions discussed here.

Although there are obvious difficulties in translating the results of animal studies to the human clinical situation, the primary object of these studies was to obtain information which, in the absence of human studies, provide a certain amount of guidance to those who encounter in patients, the conditions which were studied. It is felt therefore that tentative suggestions can and should be made regarding the clinical implication of the results which were obtained and such suggestions follow.

It has generally been assumed by those working in anaesthesia that hypocapnia is, as a rule, a harmless departure from the normal physiological state. Clinical experience would seem to bear this out as far as the healthy subject is concerned, however several workers have pointed out possible risks from hypocapnia in patients with non-healthy hearts. For example, Flemma and Young (1964) showed that in dogs and in post-thoracotomy patients, hyperventilation caused

a fall in serum K^+ and that certain patients on digitalis therapy developed cardiac arrhythmias, probably as a result of this fall in serum K^+. The results of the hypocapnia investigation reported here show that blood flow in the myocardium is reduced during hypocapnia although myocardial oxygen consumption is maintained due to an increase in oxygen extracted by the myocardium. In a situation where the blood flow to the heart may already be decreased, such as in haemorrhagic hypotension (see Chapter 8) or in ischaemic heart disease, a further reduction in blood flow due to hypocapnia may render the myocardium unable to obtain sufficient oxygen for adequate function. Further support for a more cautious approach to hypocapnia where there is pre-existing cardiovascular disease is provided by Prys-Roberts, Foex, Greene and Waterhouse (1972). These workers described a patient who, while hypocapnic during anaesthesia developed electrocardiographic evidence of myocardial ischaemia which was abolished when normocapnia was reinstituted.

Two items of possible clinical importance emerged from the studies of halothane hypotension (Chapters 4 and 5). Firstly, there was the interesting finding that during hypotension there was an increase in myocardial vascular resistance (i.e. myocardial vasoconstriction). Normally one would attempt to avoid hypotension in a patient with cardiac disease but this finding would seem to make it important to avoid hypotension in such patients who have been anaesthetised with halothane lest the reduced perfusion pressure together with the coronary vasoconstriction should render the myocardium ischaemic. Such circumstances have been observed in patients (R. S. Neill, personal communication). The second point from the

halothane studies is that during the recovery from halothane hypotension, the return of the arterial blood pressure outstripped the other variables measured, especially myocardial blood flow and cardiac output. Clinically it is often assumed that the returning blood pressure indicates a return of satisfactory cardiac function and myocardial tissue perfusion. Clearly this may not be the case.

The addition of hypocapnia to halothane hypotension caused a profound reduction in myocardial oxygen availability and, once again, this may be of critical importance in the case of the patient with ischaemic or other cardiac disease.

Hypercapnia is generally regarded as undesirable in the anaesthetised patient because of the acidosis which accompanies it and because it is thought to give rise to increased sympathetic activity and raised catechol amine blood levels. This combination of circumstances is thought to give rise to cardiac arrhythmias. In the study of hypercapnia described here, myocardial perfusion was increased during hypercapnia without obvious cardiac upset, indeed the myocardium appeared to be excessively perfused since coronary sinus PO_2 increased and oxygen consumption of the myocardium decreased. Although one would not advocate hypercapnia in the anaesthetised patient, it may be that as far as the heart is concerned, a brief period of hypercapnia may not be as harmful as it is generally thought to be.

As far as hypoxia is concerned, one must on general metabolic grounds, state that it is to be avoided, however it was of interest that the healthy heart did not increase its blood flow till arterial PO_2 was, by clinical standards, very low (i.e. below 35 mmHg). The capacity for recovery from very serious hypoxia-induced cardiac arrhythmias was also striking.

The profound depression of all the measured cardiovascular variables during haemorrhage was in keeping with clinical experience of patients with severe blood loss. It is obvious that such patients are haemodynamically very unstable and from the anaesthetic point of view it would seem to be important to avoid techniques which might further reduce blood pressure and myocardial perfusion, for example hypotensive doses of anaesthetic drugs and/or hypocapnia.

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STATEMENT OF COLLABORATION AND LIST OF PUBLISHED WORK CONTAINED IN THESIS.

It is obvious that experiments of the complexity of those which have been described could not have been carried out by one person and I have been fortunate to have been a member of a group of persons who have been involved in this work. The other members of the group have changed over the six years during which the work has progressed. Those involved in the earliest experiments (i.e. those on hypercapnia) were Drs. I. McA. Ledingham, J. R. Parratt, T. I. McBride and myself. Subsequently, Dr. McBride left the group and the three remaining carried out the experiments on hypoxia and haemorrhage. Drs. Ledingham and Parratt then diversified their interests into other aspects of coronary blood flow and cardiac investigations and I was joined by Drs. D. M. Brown and G. Smith. Drs. Brown, Smith and myself carried out the work on hypocapnia and, along with Dr. Jean McMillan, the work on halothane hypotension. Dr. J. Thorburn joined the group after Dr. McMillan's departure and took part in the investigation concerning the combination of halothane hypotension and hypocapnia. All of the above-mentioned are aware that this work is being compiled into thesis form and all are in agreement with this being done.

The following papers concerning work described herein have been published or are in the hands of the publishers:

The effects of hypocapnia on myocardial blood flow and metabolism.

J. P. VANCE, D. M. BROWN and G. SMITH.

British Journal of Anaesthesia (1973) 45, 455-463.

The effect of halothane on myocardial blood flow and vascular resistance in the intact anaesthetised dog.

G. SMITH, J. P. VANCE, D. M. BROWN and J. C. McMILLAN.

British Journal of Anaesthesia (in press).

The combined effect of halothane-induced hypotension and hypocapnia on canine myocardial blood flow and oxygen consumption.

J. P. VANCE, G. SMITH, J. THORBURN and D. M. BROWN.

British Journal of Anaesthesia (in press).

The effects of hypoxia on myocardial blood flow and oxygen consumption: negative role of beta adrenoreceptors.

J. P. VANCE, J. R. PARRATT and I. McA. LEDINGHAM.

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I. McA. LEDINGHAM, T. I. McBRIDE, J. R. PARRATT and J. P. VANCE.

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APPENDIX

This appendix describes briefly the principles on which the various items of apparatus used in the experiments operate and also the principles underlying certain of the methods of measurement which have not been detailed in the chapter on 'Materials and Methods'.

Palmer pump ventilator.

This is a simple but efficient ventilator for animal work in which the power is provided by an electric motor with a belt drive system to a piston. The flow pattern is thus a sine wave. Controls are provided to adjust the tidal volume and the pump rate is adjusted by altering the pulleys on which the belt runs.

Carbon dioxide analyser. (Hartmann and Braun, URAS 4).

This apparatus incorporates a low pressure suction pump which allowed constant sampling of gases from the catheter mount tubing attached to the endotracheal tube. Carbon dioxide could thus be sampled in inspiratory and expiratory gases. The apparatus operates on the basis that gases have a specific pattern of absorption of light in the infra-red wave lengths. Two beams of infra-red radiation are compared with each other, one of which passes through a measuring cuvette through which is also passed the gas to be analysed. The fact that infra-red radiation increases the temperature of an absorbing gas is utilised to provide a

measurement of the absorbed bands and thereby the concentration of carbon dioxide.

Tritec vaporiser. (Cyprane Ltd., Keighley, Yorks.)

This is a vaporiser which operates by having a series of wicks saturated with trichloroethylene exposed to a gas stream which vaporises the liquid trichloroethylene. The concentration of the vapour in the inhaled mixture is regulated by adjusting the proportion of the inhaled gases which pass over the wicks. The effect of temperature on the quantity of liquid vaporised is minimised by a bi-metallic strip which adjusts the volume of gas entering the vaporising chamber as the temperature alters.

Fluotec vaporiser Mk. II. (Cyprane Ltd., Keighley, Yorks.)

This vaporiser, designed to deliver halothane, operates on the same principle as the Tritec.

Oxygen analyser. (Servomex Controls Ltd., Crowborough, Sussex. Model DCL, 101 Mk. II).

An extremely accurate piece of apparatus ($\pm$ 0.1% oxygen) operating on the principle that oxygen molecules will be deflected in a magnetic field. This deflection is utilised to move a light source which plays on a calibrated scale, the degree of deflection depending on the proportion of oxygen present.

Mingograf 81. (Elema-Schonander, Stockholm, Sweden).

This is an eight channel, ink-jet recorder. The ink jets are driven by galvanometers which have been specifically designed to have a level of inertia low enough to record high frequency biological signals. The ink-jet system has several advantages over other systems, e.g. it provides an instantly visible record, it has a high resonance frequency, there is no friction with the paper and adjacent traces may cross each other without damaging the apparatus.

For measuring intravascular pressures, capacitance transducers also supplied by Elema-Schonander were used. The EMT 35 was used for arterial pressures, its pressure range being -300 to +300 mmHg and the EMT 33 was used for right atrial pressures, its range being -30 to +30 mmHg.

^{133}Xenon.

The characteristics of the isotope are as follows:

Atomic number	54
Mass number	133
Radiation	Beta and gamma
Beta	0.110 MEV
Gamma	Main component 81 KEV (35.5%)
Physical half life	5.27 days

Equipment for counting radioactivity.

The system supplied by Ecko Electronics was utilised. The scintillation detector (M5401) incorporates a thallium activated sodium iodide crystal which is sensitive to gamma radiation. This detector is narrowly collimated and therefore looks at a fairly specific area. It is thus suitable for the type of work described in this thesis. The signals from the detector were passed to a pulse height analyser (M5010) and ratemeter (M5190) which gated and counted the impulses. The output from the ratemeter was fed to a potentiometric pen recorder which gave the radioactive clearance curve, the interpretation of which has previously been described in detail.

Measurement of cardiac output.

Cardiac output was measured by estimating the rate of dilution of 1 ml of indocyanine green (cardio-green) dye which was injected into the right atrial catheter. The diluted dye was withdrawn from the femoral arterial catheter through a Waters cuvette densitometer. The concentration of dye in the blood determines how much light from a light source in the densitometer will pass through the cuvette. The changing concentration of the dye can thus be recorded as a curve and the output of the heart can be determined by measuring the area under the curve. A potentiometric recorder (servoscribe) was used to record the curve.

Estimation of non-esterified fatty acids.

When shaken with copper nitrate solution in chloroform, the non-esterified fatty acids form soluble copper salts. After separation of the phases by centrifugation and removal of the supernatant watery phase, a determination of the copper in the chloroform layer is carried out. Diethyldythiocarbamate is used as a colouring agent for copper, the intensity of the colour being proportional to the amount of non-esterified fatty acid present. The optical density of the solution is compared with that of a standard solution to give the quantity of copper present and thus the quantity of non-esterified fatty acids.

Blood glucose was estimated by the method of Folin and Wu. (Journal of Biological Chemistry, 41, 367-371, 1920).

Blood lactate estimation.

The blood is first deproteinised with 0.6N perchloric acid. After centrifugation, the supernatant solution is mixed with 0.5M glycine buffer (of pH 9.0), 0.027M NAD and lactic dehydrogenase. This mixture is incubated at 25^{o}C after which the optical density is read against a blank solution using a wavelength of 340 nm. The optical density is multiplied by a known factor to give lactate concentration in mg/100ml.

Blood pyruvate estimation.

The blood is first deproteinised using IN perchloric acid. After centrifugation, the supernatant solution is mixed with 0.7M

tripotassium phosphate, and after cooling in an ice bath the solution is filtered. The filtrate is rewarmed to 25°C and 2.5mM NADH is added. The optical density of this solution is then read (E_1). Lactic acid dehydrogenase is now added and the optical density is read again when the reaction is complete (E_2). E_2 is then subtracted from E_1 and the difference multiplied by a known factor to determine the pyruvate concentration in mg/100ml.

Haemoglobin concentration.

The cyanmethaemoglobin method was used. To 0.2 ml of blood 5 ml of a solution containing 1mM potassium dihydrogen phosphate, 0.75mM potassium cyanide and 0.6mM potassium hexacyanoferrate was added. After thorough mixing, the optical density of the solution was read against that of distilled water using a wavelength of 520-560 nm. This was then multiplied by a known factor to give haemoglobin concentration in g/100ml.