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THE EFFECT OF HYPERCAPNIA ON MYOCARDIAL BLOOD FLOW AND METABOLISM

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SUMMARY

1. In closed-chest dogs anaesthetized with trichlorethylene, the inhalation of carbon dioxide sufficient to increase the arterial P_{CO_2} from 40 to about 100 mm Hg, increased myocardial blood flow (measured using a ^{133}Xe clearance technique) and right atrial pressure. There were no consistent changes in mean arterial blood pressure, heart rate or cardiac output.

2. The effect of hypercapnia on myocardial blood flow was not influenced by the previous administration of atropine and propranolol or of bretylium. It can be concluded, therefore, that the elevated arterial P_{CO_2} has a direct vasodilator effect on the myocardial microcirculation.

3. During hypercapnia the coronary sinus P_{O_2} was increased and the coronary arteriovenous oxygen content difference, and calculated myocardial oxygen consumption, reduced. It is suggested that this latter effect may be the result of myocardial depression produced by the decrease in arterial blood pH.

4. There was no evidence of myocardial glucose uptake either before or during hypercapnia. The myocardial extraction of lactate and pyruvate at rest varied between 0 and 55 %. During acute hypercapnia the extraction of lactate usually fell.

5. When the arterial P_{CO_2} was maintained at 100 mm Hg for a period of 1 hr the effects on myocardial blood flow and on oxygen consumption were not sustained.

6. Stepwise increments and decrements in arterial P_{CO_2} of 10–20 mm Hg

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produced corresponding increases and decreases in myocardial blood flow and demonstrated that changes in arterial P_{CO_2} of 20–30 mm Hg can markedly affect blood flow in the myocardium.

INTRODUCTION

The majority of recent experimental studies have demonstrated that myocardial blood flow is increased during hypercapnia (Feinberg, Gerola & Katz, 1960; Kittle, Aoki & Brown, 1965; Eberlein, 1966; Lochner, Hirche & Koike, 1967). A detailed examination of the relationship has not, however, been made between myocardial blood flow, arterial and coronary sinus blood gases and acid–base balance, cardiac output and myocardial oxygen consumption. In addition, there has been only one study of the effect of prolonged hypercapnia on the myocardial circulation (Kittle *et al.* 1965) and no attempts have been made to evaluate the possible role of released autonomic transmitters. The object of the present study was to determine the relationship between hypercapnia, myocardial blood flow and oxygen consumption, in dogs without thoracotomy, in order to provide the background for a more detailed study of flow and metabolism in the myocardium during experimental haemorrhagic and cardiogenic shock. A preliminary account of some of our results have been presented to the Physiological Society (Ledingham, McBride, Parratt & Vance, 1969).

METHODS

Anaesthesia was induced in twenty-seven mongrel adult dogs with a 2·5 % solution of thiopentone sodium administered intravenously (usually 20 mg/kg). After endotracheal intubation, intermittent positive pressure ventilation was established and maintained using a Palmer respiratory pump, the stroke volume of which was adjusted to maintain arterial carbon dioxide tension between 35 and 45 mm Hg; the ventilation rate was kept constant. Reflex movement was prevented by the intramuscular administration of intermittent (100 mg) doses of suxamethonium. Anaesthesia was maintained with trichlorethylene (0·5–1·0 %) vaporized from a Tritec vaporizer (Cyprane Ltd.) in a mixture of oxygen and nitrogen, the proportions of which were adjusted so that the arterial oxygen tension was between 85 and 105 mm Hg. This was facilitated by monitoring the inspired oxygen concentration with a paramagnetic oxygen analyser (Servomex OA. 101 Mk. II, Servomex Controls, Crowborough, Sussex). The animal's temperature was recorded from the rectum and mid-oesophagus using direct recording thermocouples (Ellab, Copenhagen).

Myocardial blood flow was measured using a technique similar to that described by Ross, Ueda, Lichtlen & Rees (1964). A Sones No. 7 or 8 catheter was introduced into the right common carotid artery in the neck and under fluoroscopic control manipulated until the tip lay a distance of 5–10 mm into a major branch (usually the circumflex) of the left coronary artery. Injections of a solution of ^{133}Xe (obtained in 10 ml. ampoules of 1 mc/ml. from the Radiochemical Centre, Amersham, Bucks) were made into the catheter and flushed into the coronary artery with 3 ml. heparinized saline. Usually 0·4–1·0 ml. of the radioactive solution was sufficient to give an

optimum clearance curve. The clearance of the isotope from the myocardium (which is a function of capillary blood flow) was measured with an Ekco GP scintillation counter (incorporating a 2 in. sodium iodide crystal) placed over the precordium, an Ekco rate-meter operating with a 3 sec time constant and an ink-writing recorder (Servoscribe, Kelvin Electronics). The paper speed was 120 mm/min. Background counts remained at an acceptably low level in all satisfactory preparations even after many measurements of myocardial flow.

Two methods are available for analysis of the clearance curve of Xe from the myocardium:

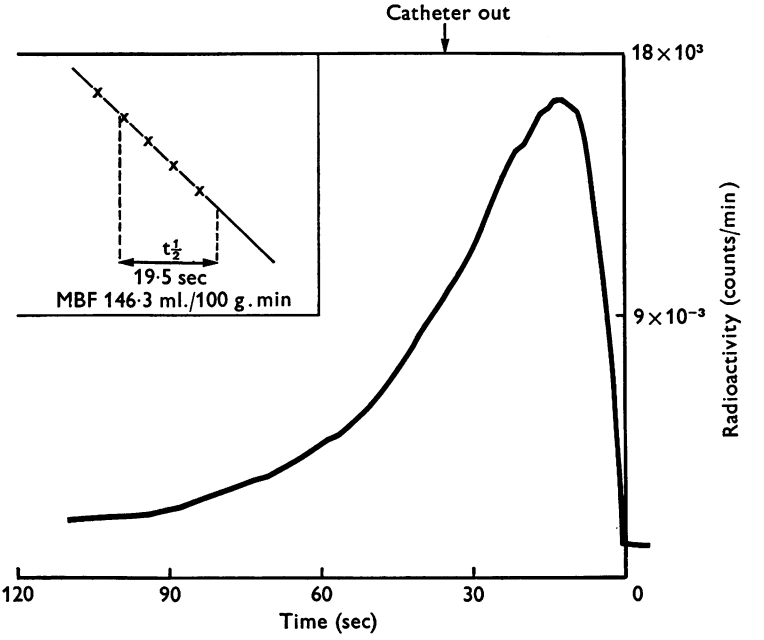

Fig. 1. The precordial clearance of radioactivity (counts/min) after the intra-coronary injection of a bolus of ^{133}Xe. The intra-coronary catheter was withdrawn into the aorta at the arrow; this had no effect on the myocardial clearance curve. The inset shows the semi-logarithmic plot of the exponential portion of the clearance curve, enabling the half-time ($t_{\frac{1}{2}}$), and hence myocardial blood flow, to be calculated.

(1) The semi-logarithmic replot and derivation of half-time ($t_{\frac{1}{2}}$). The major part of the clearance curve is exponential and a straight line plot of counts/sec at 5 sec intervals can be readily drawn on semi-log paper (see Fig. 1). The half-time so obtained can be substituted in the formula:

Myocardial blood flow = $k\lambda 100/\rho$ ml./100 g tissue.min where ρ is the density of the myocardium (1·05 mg/ml. according to Herd, Hollenberg, Thorburn, Kopald & Barger (1962)); λ the partition coefficient of ^{133}Xe between the myocardium and the blood (0·72 according to Conn (1961) and Ross *et al.* (1964)); and k (the clearance rate constant) = $\log_e 2/t_{\frac{1}{2}}$.

(2) The peak height over area method. Analyses by both methods over a wide range of myocardial blood flows have shown a high correlation coefficient (Rees &

Redding, 1967). The bulk of measurements of flow in the present study were made by the semi-logarithmic re-plot method. Full details of the theory of inert gas clearance techniques for the measurement of tissue blood flow are given in the papers by Conn (1962), Herd *et al.* (1962), Ross *et al.* (1964) and Zierler (1965).

In order to measure myocardial oxygen availability and consumption a catheter was positioned under fluoroscopic control in the coronary sinus by way of the right external jugular vein. Simultaneous anaerobic blood samples (usually 2 ml.) were obtained at intervals from the coronary sinus and also from the right atrium and descending aorta through catheters inserted via the right femoral vein and artery respectively. Arterial, coronary sinus and right atrial blood oxygen and carbon dioxide tensions and pH were measured using appropriate systems (Radiometer, Copenhagen). The pH electrode was calibrated using standard buffers of known pH. The oxygen and carbon dioxide electrodes were calibrated with gas mixtures, the oxygen and carbon dioxide concentration of which had been accurately measured using the Lloyd–Haldane apparatus. The oxygen electrode (type E 5044) was covered with a membrane of 20 μ polypropylene and, to allow for the difference in measurement of oxygen tension in gas and blood (McDowall, Ledingham & Tindal, 1968), a blood-gas factor was derived for each experiment using blood tonometered with a known tension of oxygen in a rotating syringe (Torres, 1963). This factor was applied to each of the measurements of oxygen tension before the calculation of oxygen content. The oxygen tension (P_{O_2}), carbon dioxide tension (P_{CO_2}) and pH were corrected for any temperature difference between the electrode system and the mid-oesophageal temperature of the animal using the dog cursor on the Radiometer blood gas calculator (984–300). The latter also permitted calculation of the blood oxygen saturation from pH and P_{O_2} taking into account base excess and the animal's temperature. The oxygen content of blood was calculated in the following manner. Blood oxygen content (ml./100 ml.) = Hb(g) (measured by the cyanmethaemoglobin technique) $\times$ 1·34 $\times$ % saturation/100 + P_{O_2} (mm Hg) $\times$ 0·0031 (Bunsen coefficient). Fig. 2 indicates that there is a satisfactory correlation between this indirect method of measurement of oxygen content and the direct method of Van Slyke. The Van Slyke values were means of duplicate estimations of oxygen content of which the coefficient of variation was 0·27 %. Derived calculations were:

(*a*) Myocardial oxygen consumption (ml./100 g.min) = myocardial blood flow (ml./100 g.min) $\times$ the arterial oxygen content (ml./100 ml.) minus the coronary sinus oxygen content (ml./100 ml.).

(*b*) Lactate and pyruvate consumption were measured as for (*a*) with lactate and pyruvate substituted for oxygen.

(*c*) Whole body oxygen consumption (ml./min) = cardiac output (l./min) $\times$ the arterial oxygen content (ml./100 ml.) minus the right atrial oxygen content (ml./100 ml.) $\times$ 100.

Lactate and pyruvate concentrations were measured in arterial and coronary sinus blood using standard spectrophotometric methods (Boehringer & Soehne). Blood glucose concentrations were estimated using the standard method of Folin & Wu (1920).

Descending aortic blood pressure and right atrial pressure were measured using capacitance transducers (Elema Schönander EMT 35 and 33 respectively) and these, together with the electrocardiogram (lead II) were recorded on an Elema Schönander ink-writing recorder (Mingograph 81). Mean pressures were obtained by integration and the heart rate measured from the e.c.g. Cardiac output was measured by dye dilution (indocyanine green) with a Waters densitometer (XP-302, Waters Company, Rochester, Minnesota).

Hypercapnia was induced by rapidly adding CO_2 to the inspired gas mixture, the

actual concentration (varying between 10 and 15 %) being monitored on an infra-red carbon dioxide analyser (URAS 4, Hartmann & Braun). The inspired carbon dioxide concentration was adjusted to give an arterial carbon dioxide tension of 80–120 mm Hg. Throughout the period of hypercapnia, which was sustained for either 16 min (brief) or 60 min (prolonged), the inspired oxygen concentration was adjusted so that the arterial oxygen tension remained between 85 and 105 mm Hg.

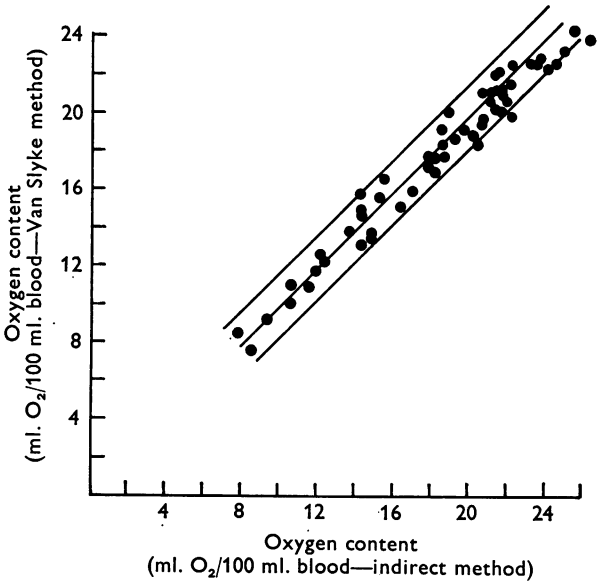

Fig. 2. A comparison of the indirect method of measurement of oxygen content and the Van Slyke method in dog blood (nineteen dogs of mixed breed). The regression line and 95 % confidence limits are indicated; a satisfactory correlation between the two methods was demonstrated. $y = -0{\cdot}37 + 1{\cdot}06x$. $r = 0{\cdot}983$.

Two additional series of experiments were carried out in order to assess the possible role of the autonomic nervous system in the circulatory responses to hypercapnia. In the first series of six dogs atropine (0·04 mg/kg) and propranolol (0·2 mg/kg) were given intravenously in order to antagonize the effect of acetylcholine and of released catecholamines on muscarinic and β-adrenotropic receptors respectively. In the second series of three animals, bretylium (10 mg/kg) was given intravenously in order to prevent the possible release of sympathetic neurotransmitters. Hypercapnia was induced before and after each of these procedures.

In a further series of five dogs the effects of gradually increasing P_{a,CO_2} on myocardial blood flow was studied. Commencing at a P_{a,CO_2} of about 20 mm Hg carbon dioxide was added to the inspired gas mixture to produce a step-wise increase in P_{a,CO_2}. Thus myocardial blood flow was measured at several P_{a,CO_2} levels between 20 and 109 mm Hg. The carbon dioxide content of the inspired gases was then reduced in a similar manner until the P_{a,CO_2} had returned to the initial value.

RESULTS

The effect of brief hypercapnia on acid-base balance, haemodynamics and myocardial blood flow

In the initial series of eighteen animals carbon dioxide was rapidly added to the inspired gas mixture in amounts sufficient to increase the P_{a,CO_2} from 40 to around 100 mm Hg and this was sustained for a period of 8–15 min. This produced an expected decrease in arterial pH from 7·346 ± 0·010 to 7·074 ± 0·063 units. Myocardial blood flow was markedly increased in sixteen of the eighteen animals (mean increase +49 %) and

TABLE 1. Changes in myocardial blood flow, heart rate, mean systemic arterial blood pressure and mean right atrial pressure before and during brief hypercapnia (Mean ± S.E. of mean; sixteen animals)

	Before CO_2	During CO_2
Myocardial blood flow (ml./100 g.min)	112 ± 5	167 ± 6*
Heart rate (beats/min)	154 ± 6	157 ± 10
Mean arterial blood pressure (mm Hg)	119 ± 4	121 ± 5
Mean right atrial pressure (mm Hg)	+0·1 ± 0·5	+2·4 ± 0·8*

* Significantly different from control at a level of $P < 0·001$.

unchanged in the remaining two. Although several measurements of flow were made in the individual dogs during the 15 min period, only the highest value of flow was used in the subsequent calculations. This increase in myocardial blood flow occurred without any significant change in mean arterial pressure or heart rate (Table 1). The unaltered mean heart rate conceals the fact that in five of the sixteen animals (31 %) heart rate, as compared with prehypercapnic values, was increased or decreased by more than 15 beats/min. In only two of these five animals was mean arterial pressure altered by more than 10 mm Hg. Calculated myocardial vascular resistance (mean arterial blood pressure over myocardial blood flow) was markedly decreased (mean decrease −32 %), and mean right atrial pressure was significantly elevated (mean increase +2·3 mm Hg). Although it was not possible to determine accurately the time course of the effect of hypercapnia on myocardial blood flow in these experiments (since myocardial clearance curves could only be recorded, at most, every 3 or 4 min) the evidence suggests that the increase in myocardial blood flow occurs almost immediately the P_{a,CO_2} is elevated. This is illustrated in Fig. 3 where myocardial blood flow was markedly elevated only 2 min after carbon dioxide had been added to the inspired gas mixture. Myocardial blood flow reached its highest value in a mean time of 6·6 min.

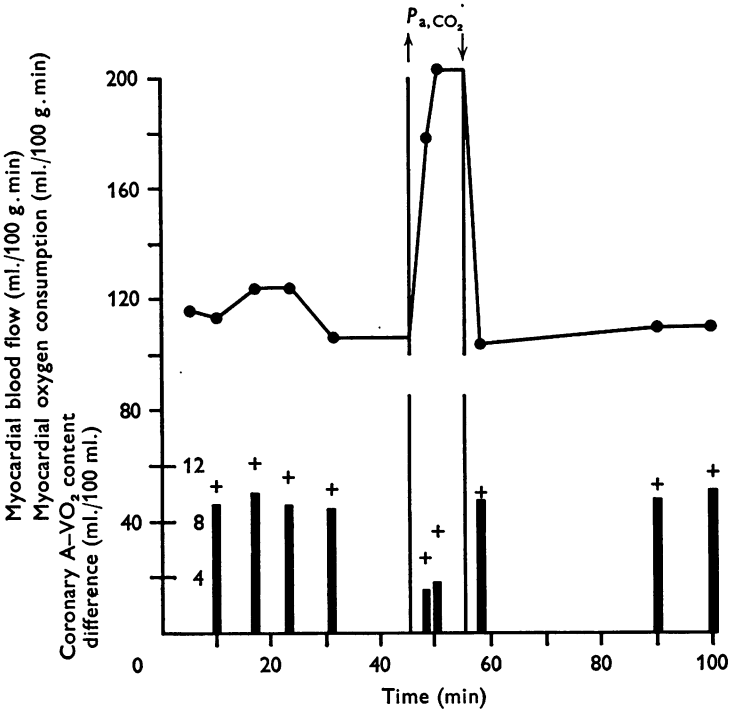

Fig. 3. The effect of hypercapnia on myocardial blood flow (ml./100 g.min; ●—●), myocardial oxygen consumption (ml./100 g.min; + +) and the coronary $A-V$ O_2 content difference (ml./100 ml.; vertical filled blocks) in an anaesthetized dog.

The effect of brief hypercapnia on coronary sinus and mixed venous oxygen tensions

During the period of hypercapnia the oxygen tension of the coronary sinus blood was increased from 30 ± 1 to 57 ± 3 mm Hg (mean $\pm$ S.E. of mean; $P < 0{\cdot}001$). The coronary $A-V$ O_2 content difference (i.e. arterial minus coronary sinus oxygen contents) fell significantly ($P < 0{\cdot}001$) from $10{\cdot}7 \pm 0{\cdot}6$ to $5{\cdot}8 \pm 0{\cdot}7$ ml./100 ml. (i.e. by 46 %) and calculated myocardial oxygen consumption was reduced from $11{\cdot}8 \pm 0{\cdot}7$ to $9{\cdot}7 \pm 1{\cdot}0$ ml./100 g.min ($P < 0{\cdot}01$), i.e. a decrease of 18 %. Although the mixed venous (right atrial) oxygen tension also increased significantly (47 ± 1 to 63 ± 7 mm Hg; $P < 0{\cdot}01$) this was mainly accounted for by a shift to the right of the oxygen dissociation curve due to the decrease in pH associated with hypercapnia. There was thus no significant change in systemic $A-V$ O_2 content difference (i.e. arterial minus right atrial oxygen contents) being $3{\cdot}8 \pm 0{\cdot}2$ ml./100 ml. before and $3{\cdot}6 \pm 0{\cdot}6$ ml./100 ml. during hypercapnia.

In six animals cardiac output was measured within the 16 min period of hypercapnia; a rise in cardiac output was noted in three and a fall in three when compared with the mean cardiac output of 2·68 l. ± 0·33 l./min before hypercapnia.

The effect of brief hypercapnia on the myocardial uptake of glucose, pyruvate and lactate

The diminished myocardial oxygen consumption during hypercapnia prompted us to examine its effect on the myocardial consumption of glucose, pyruvate and lactate. In none of the dogs of the present series was there evidence of glucose consumption either in the control, resting state or during hypercapnia. The arterial and coronary sinus glucose concentrations before hypercapnia were 122 ± 13 mg/100 ml. and 120 ± 13 mg/100 ml. respectively and 154 ± 11 mg/100 ml. and 155 ± 10 mg/100 ml. respectively during hypercapnia. Although there was no significant difference between the arterial and coronary sinus glucose concentrations either before or during hypercapnia there was a significant increase in the absolute concentration of glucose in arterial and coronary sinus blood during carbon dioxide administration. Withdrawal of carbon dioxide was associated with a prompt return to prehypercapnic levels of both arterial and coronary sinus glucose concentrations.

The arterial and coronary sinus lactate levels before hypercapnia were 17·0 ± 2·16 mg/100 g.min and 11·9 ± 1·73 mg/100 g.min respectively. The corresponding pyruvate levels were 1·22 ± 0·13 mg/100 g.min and 0·83 ± 0·08 mg/100 g.min. During hypercapnia the arterial and coronary sinus lactate levels were 13·9 ± 1·7 mg/100 g.min and 11·8 ± 1·6 mg/100 g.min. The corresponding pyruvate levels were 1·01 ± 0·11 mg/100 g.min and 0·73 ± 0·08 mg/100 g.min. As Fig. 4 demonstrates, the myocardial extraction $(A-V/A)$ % of lactate and pyruvate in the resting state varied from 0 to 50 % and from 0 to 55 % respectively. Two animals appeared to be producing pyruvate. During hypercapnia the extraction of lactate fell in ten of the fourteen animals studied; pyruvate extraction fell and rose with equal frequency. Consumption of lactate and pyruvate was not calculated during brief hypercapnia since interpretation of such values in the non-steady state is fraught with difficulties (see Bing, 1965). In four animals in which comparison between pre- and post-hypercapnic lactate and pyruvate consumptions was possible, consumption of lactate fell in three and rose in one while consumption of pyruvate fell in two, rose in one and remained unchanged in the fourth.

The effect of prolonged hypercapnia on myocardial blood flow, oxygen consumption and metabolism

The effects of prolonged hypercapnia were studied in a further nine dogs. The arterial carbon dioxide tension was elevated to about 100 mm Hg and maintained at this level for a period of 60 min. The effects on myocardial blood flow and myocardial oxygen consumption (meaned over 10 min periods), mean arterial blood pressure and heart rate are summarized in Fig. 5. The initial effects on blood flow and oxygen consumption were not

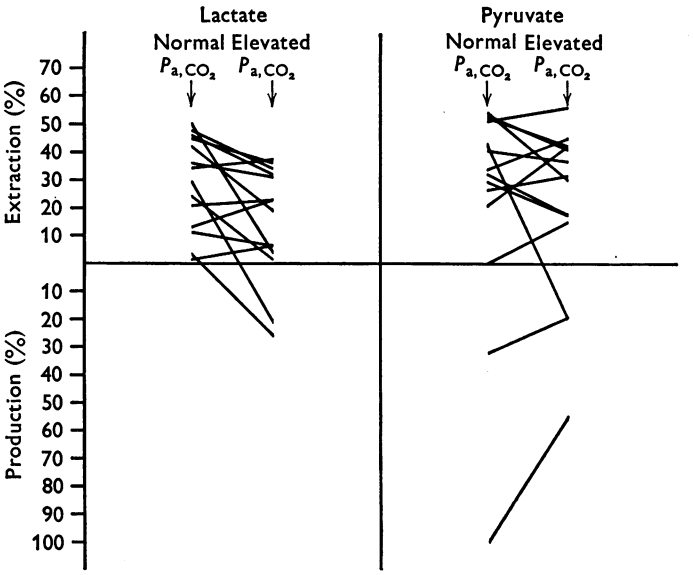

Fig. 4. Changes in the % extraction and/or production of myocardial lactate (on the left) and pyruvate (on the right) during a brief (16 min) period of hypercapnia in fourteen anaesthetized dogs.

sustained over the 60 min period of hypercapnia; both tended to return towards prehypercapnic levels. There were no significant changes in heart rate or in mean arterial blood pressure. On withdrawing the carbon dioxide, myocardial oxygen consumption returned almost immediately to the control levels but myocardial blood flow usually fell below the prehypercapnic level and remained so for a variable period of time.

In eight of the animals the relationship between simultaneously measured cardiac output and myocardial blood flow was studied. In four of the dogs cardiac output rose, at least at some stage during the hypercapnic period; in the other four dogs cardiac output fell. The net change in cardiac output with prolonged hypercapnia was a decrease of 2%. Total body oxygen

consumption fell in all but one of the animals during prolonged hypercapnia (mean decrease −23%). Withdrawal of carbon dioxide was associated with a fall in cardiac output in those animals which had shown a rise in cardiac output during hypercapnia and no change or a rise in cardiac output in those animals which had shown a fall with elevated carbon dioxide. Total body oxygen consumption returned to slightly above prehypercapnic levels upon withdrawal of the carbon dioxide.

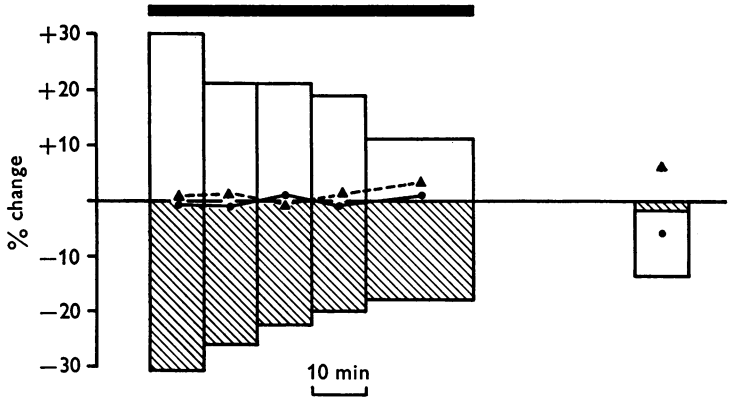

Fig. 5. The effect of prolonged hypercapnia (at the horizontal bar) on myocardial blood flow (open blocks), myocardial oxygen consumption (stippled blocks), heart rate (▲ - - - ▲) and mean systemic arterial blood pressure (●—●), all expressed as % of control, prehypercapnic levels. The changes in myocardial blood flow and oxygen consumption were not sustained throughout the period of elevated P_{a,CO_2}.

In five of the animals arterial and coronary sinus lactate, pyruvate and glucose estimations were made. As in the brief exposure procedures, there was no significant difference between the glucose concentrations of arterial and coronary sinus blood. However, the increase in absolute glucose concentrations previously noted in the first 16 min of hypercapnia became more marked at the end of 60 min (116 ± 8 and 116 ± 9 mg/100 ml. for prehypercapnic arterial and coronary sinus blood respectively; 212 ± 37 and 207 ± 31 respectively at the end of 60 min of hypercapnia). The arterial and coronary sinus lactate levels before hypercapnia were 20·5 ± 4·3 and 15·2 ± 4·4 mg/100 ml. respectively and 23·7 ± 2·6 and 15·9 ± 2·3 mg/100 ml. respectively at the end of 60 min of hypercapnia. The corresponding values for pyruvate were: prehypercapnia 1·45 ± 0·20 and 0·87 ± 0·19 and, at the end of 60 min hypercapnia, 1·09 ± 0·24 and 0·79 ± 0·09 mg/100 ml.

The changes in lactate extraction during prolonged hypercapnia are illustrated in Fig. 6. The previously noted tendency for lactate extraction to fall during brief exposures to carbon dioxide was reversed during

prolonged hypercapnia. Less striking but similar trends were noted with pyruvate extraction.

Before hypercapnia, lactate consumption was $5{\cdot}7 \pm 1{\cdot}1$ mg/100 g.min and pyruvate consumption $0{\cdot}58 \pm 0{\cdot}13$ mg/100 g.min. At the end of prolonged hypercapnia, lactate consumption was $7{\cdot}7 \pm 2{\cdot}1$ mg/100 g.min and pyruvate consumption $0{\cdot}43 \pm 0{\cdot}11$ mg/100 g.min.

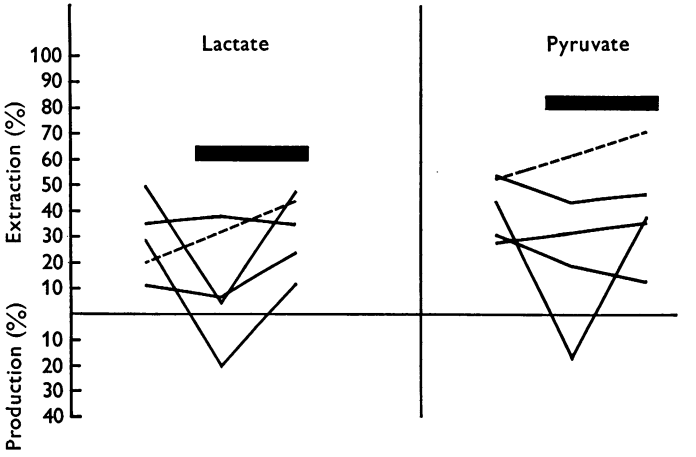

Fig. 6. Changes in the % extraction and/or production of myocardial lactate (on the left) and pyruvate (on the right) during prolonged (60 min) hypercapnia (at the horizontal bars) in five anaesthetized dogs.

The effect of step-wise increments and decrements of P_{a,CO_2} on myocardial blood flow

There was a tendency for myocardial blood flow to increase between P_{a,CO_2} levels of 40 and 60–80 mm Hg (Fig. 7*A*). These results are, however, complicated by the fact that during prolonged hypercapnia myocardial blood flow tended to return towards control levels (see Fig. 6). The relationship between P_{a,CO_2} and myocardial blood flow was more closely demonstrated during the period of withdrawal of CO_2 (Fig. 7*B*). With each step-wise decrement in P_{a,CO_2} there was a similar decrease in myocardial blood flow. This series of experiments demonstrates, in addition, that changes in P_{a,CO_2} of 20–30 mm Hg can markedly affect blood flow in the myocardium.

The effect of atropine and propranolol on the myocardial responses to hypercapnia

In the dose used (0·04 mg/kg), atropine increased heart rate (mean increase 44 beats/min; range 8–88 beats/min) and myocardial blood flow (mean increase 17 ml./100 g.min; range 0–57 ml./100 g.min). The haemodynamic effects of this dose of atropine, together with propranolol (0·2

mg/kg) are summarized in Fig. 8. As previous studies have indicated, propranolol, which in this dose is sufficient both to antagonize the effects of infused catecholamines and of stellate ganglion stimulation (Gaal, Kattus, Kolin & Ross, 1966; Wendling, Eckstein & Abboud, 1967) decreased myocardial blood flow and increased myocardial vascular resistance (Parratt & Grayson, 1966). The responses to hypercapnia were similar

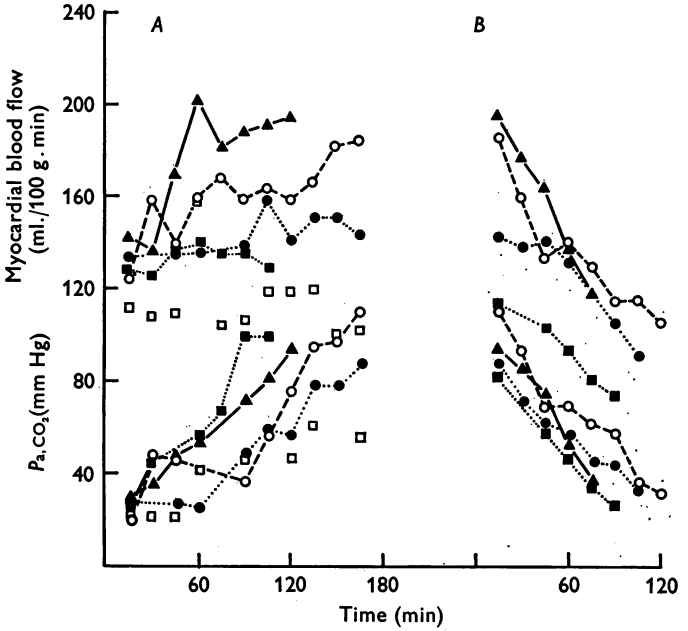

Fig. 7. The effect of stepwise increments (at *A*) and stepwise decrements (at *B*) in arterial CO_2 tension (mm Hg; below) on myocardial blood flow (ml./100 g.min; above) in five anaesthetized dogs. Each point represents from one to three observations of both CO_2 tension and myocardial blood flow in each animal.

to those obtained before administration of the drugs, i.e. there was a marked increase in myocardial blood flow and a further fall in myocardial oxygen consumption with little change in mean arterial pressure or in heart rate. The results from one experiment are illustrated in Fig. 9.

The effect of bretylium on the myocardial responses to hypercapnia

Bretylium (10 mg/kg) was administered intravenously to three animals. There were initial increases in heart rate, mean arterial blood pressure and in myocardial blood flow, effects attributed to released catecholamines (Parratt, 1967). After a period of about 1 hr (i.e. when these effects had disappeared and when release of adrenergic transmitters would be prevented) myocardial blood flow had decreased by 13 %, mean arterial blood

pressure was virtually unchanged and calculated myocardial vascular resistance had increased by 28 % (Table 2). In these animals, where the possible release of sympathetic neurotransmitters had been prevented, hypercapnia still increased mean blood flow. Arterial and coronary sinus glucose concentrations, which rose after administration of bretylium, were further increased during hypercapnia.

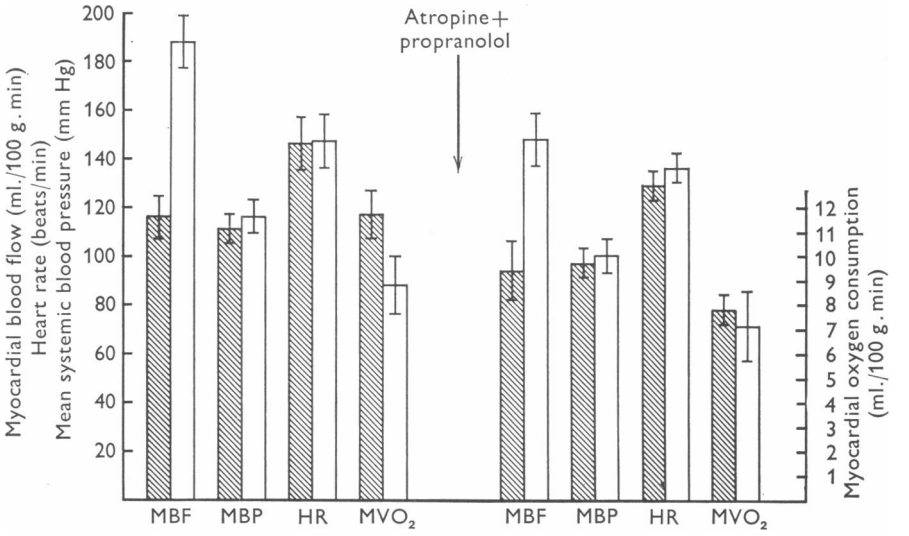

Fig. 8. The effect of a combination of atropine (0·04 mg/kg I.V.) and propranolol (0·2 mg/kg I.V.) on the cardiovascular responses of dogs to acute hypercapnia. MBF = myocardial blood flow (ml./100 g.min); MBP = mean systemic arterial blood pressure (mm Hg); HR = heart rate (beats/min); MVO_2 = myocardial oxygen consumption (ml./100 g.min). Stippled blocks before hypercapnia; open blocks during hypercapnia. Values are means ± S.E. of mean.

DISCUSSION

The inert gas clearance of measuring myocardial blood flow is well established and has been extensively utilized in this laboratory (McBride & Ledingham, 1968). The method involves the principle of indicator dilution, although the indicator (in this case ^{133}Xe) does not remain in the vascular compartment but diffuses throughout the tissue space. The removal of the indicator by a progressive re-equilibration with fresh capillary blood gives the essential measurements, viz. that of clearance of the isotope from the myocardium.

The position of the coronary artery catheter within the lumen of the coronary artery raises the possibility of obstruction to flow. Two pieces of experimental evidence demonstrate that this criticism is untenable. First, removal of the catheter during the fast phase of the clearance curve did not

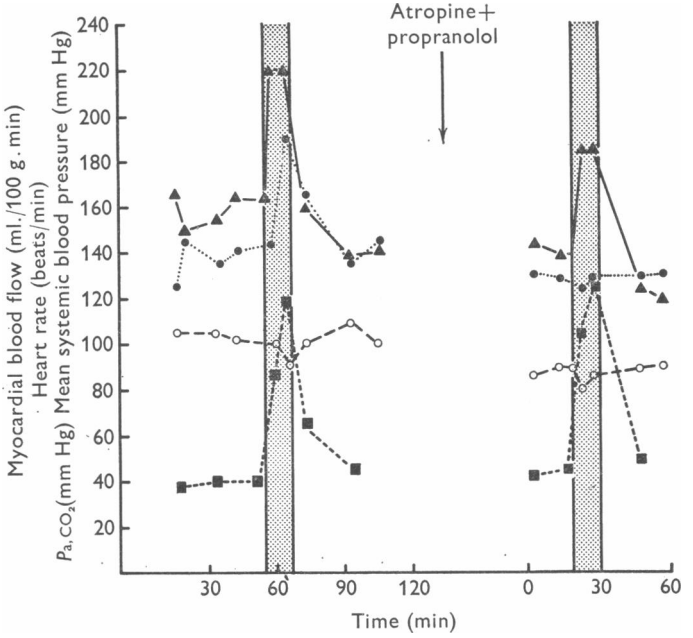

Fig. 9. The effect of elevating the arterial P_{CO_2} (■ - - -■; mm Hg), during the shaded blocks, on myocardial blood flow (ml./100 g.min; ▲—▲), heart rate (beats/min; ●·····●) and mean systemic arterial blood pressure (mm Hg; ○ – – ○) in an anaesthetized dog before (on the left) and after (on the right) the intravenous injection of atropine (0·04 mg/kg) and propranolol (0·2 mg/kg). Hypercapnia still increased myocardial blood flow but the increase in heart rate that occurred in this particular dog during hypercapnia was abolished by the previous administration of atropine and propranolol.

TABLE 2. Myocardial and haemodynamic effects of bretylium tosylate (10 mg/kg I.V.)

	Control	After bretylium 10–20 min	After bretylium 60 min
Mean blood pressure (mm Hg)	104 (97–115)	120 (100–145)	110 (95–120)
Heart rate (beats/min)	173 (160–200)	217 (192–240)	176 (168–184)
Myocardial blood flow (ml./100 g.min)	81 (76–89)	99 (89–106)	67 (54–76)
Myocardial A–V O_2 content* difference (ml./150 ml.)	9·67; 4·91	15·64; 5·87	9·51; 4·91
Myocardial O_2 consumption* (ml./100 g.min)	8·61; 3·73	16·58; 5·99	6·96; 3·73

* Two experiments only.

influence the rate of clearance over a wide range of flows. Secondly, insertion and removal of the catheter did not influence local flow in an area of myocardium supplied by the catheterized artery, as measured by a heat clearance technique (I. McA. Ledingham & J. R. Parratt, unpublished observations). There is also the possibility of regurgitation of a variable amount of ^{133}Xe into the root of the aorta. Clearly regurgitation is much more likely to occur if the tip of the catheter is at the orifice of the coronary artery. In the present study, the catheter tip was 5–10 cm within the coronary vessel and regurgitation of radio-opaque medium injected through the catheter was minimal. Although some workers have devised elaborate surgical procedures to ensure absence of all regurgitation (Ratliff, Hackel & Mikat, 1969), its presence in small amounts does not significantly influence the validity of the method. It was not therefore considered necessary to add these modifications to the present experimental model.

This study has demonstrated that raising the P_{a,CO_2} to around 100 mm Hg markedly increases myocardial blood flow. This was unrelated to changes in perfusion pressure, heart rate and cardiac output and was accompanied by a fall in myocardial oxygen consumption. It would be reasonable to conclude that the most likely explanation for this flow increase was a direct action of the raised carbon dioxide tension (and/or the resultant decrease in pH) on the myocardial vascular smooth muscle. Thus carbon dioxide is dilator to the myocardial circulation as it is to the cerebral circulation (Harper, Glass & Glover, 1961), the splanchnic circulation (McGinn, Mendel & Perry, 1967) and the skin (McArdle, Roddie, Sheperd & Whelan, 1957).

We have not examined in detail the responses of the myocardial circulation to arterial carbon dioxide tensions between normal (40 mm Hg) and 90 mm Hg but from our preliminary observations (see Fig. 7) there was no doubt that increments and decrements of P_{a,CO_2} produced corresponding alterations in myocardial blood flow. Certainly between P_{a,CO_2} levels of 50 and 70 mm Hg consistent elevations in myocardial blood flow could be demonstrated and it was perhaps relevant that the coronary sinus P_{CO_2} (which probably fairly accurately reflected the carbon dioxide tension of the capillary blood) was not infrequently at this level. Since the ^{133}Xe clearance technique used in this study measured capillary blood flow the possibility arises that the nutritional myocardial blood flow might in fact be regulated by carbon dioxide production by the myocardial cells or by the resultant decrease in capillary blood pH. Although from our experiments it appeared that, on prolonged exposure to raised carbon dioxide, the myocardial vessels became partially refractory to its vasodilator effect, this need not argue against the possibility that the carbon dioxide tension

of the capillary blood may regulate capillary blood flow. A change in myocardial carbon dioxide production has been advanced recently as an explanation for the mode of action of the coronary vasodilator drug hexobendine (Kraupp, Grossman, Stühlinger & Raberger, 1968).

The vasodilator effect of carbon dioxide on the myocardial vessels does not appear to be mediated either through changes in cardiac work (and hence oxygen consumption) or through the release of autonomic transmitters. The effect was seen after blockade of β-adrenotropic receptors, partial blockade of muscarinic receptors and neurone blockade of the sympathetic nervous system.

There remains the problem of whether the dilator effect of carbon dioxide is due to a direct effect on vascular smooth muscle or whether it results from a change in blood pH. Scheuer (1968) attempted to examine this question by infusing sodium bicarbonate. In his experiments myocardial blood flow in dogs was measured using ^{131}I aminopyrine. Sodium bicarbonate, sufficient to increase the arterial blood pH from 7·36 to 7·59 units increased the P_{a,CO_2} from 38 to 91 mm Hg and this resulted in a marked increase in myocardial blood flow (from 60 to 168 ml./100 g. min). In order to produce these effects, however, relatively large volumes of bicarbonate were required and there were marked increases in the tension time index, heart rate and in myocardial oxygen consumption, which suggests that the effects of myocardial blood flow may have been secondary to increased cardiac work. Kittle *et al.* (1965) demonstrated in the anaesthetized dog that myocardial blood flow increased in response to the administration of 30% carbon dioxide, even when arterial pH was held at a relatively constant level by the intravenous infusion of 0·9 N trishydroxymethylaminomethane (Tris).

In a separate and preliminary group of studies we infused lactic acid and hydrochloric acid intravenously in dogs and showed that, initially at least, myocardial blood flow did increase markedly with a fall in pH (in the absence of a change in P_{a,CO_2}), although others have failed to demonstrate this effect with hydrochloric acid (Kittle *et al.* 1965; Goodyer, Eckhardt, Ostberg & Goodkind, 1961). It is still, therefore, open to question whether carbon dioxide is the primary coronary vasodilator or whether its effect is mediated through pH changes.

Some studies have shown that elevation of P_{a,CO_2} to 90 mm Hg is associated with a hyperdynamic circulation and elevated levels of cardiac output (Prys-Roberts & Kelman, 1966). These alterations were considered to be secondary to central nervous system stimulation resulting in a generalized sympathetic discharge. In our studies, apart from the first few minutes of hypercapnia, no consistent change in systemic circulatory parameters were observed, presumably because at a P_{a,CO_2} level of 110 mm Hg (the

mean arterial value present throughout the period of prolonged hypercapnia) myocardial depression balanced the effects of augmented filling of the right atrium caused by the raised venous pressure. Thus in isolated hearts, contractility was significantly impaired when pH was lowered to 7·1 units or less (Opie, 1965) whilst, in the intact heart, carbon dioxide in concentrations similar to those used here reduced the force of myocardial contraction (Boniface & Brown, 1953; Monroe, French & Whittenberger, 1960; Manley, Nash & Woodbury, 1964; Ng, Levy & Zieske, 1967).

A consistent finding in these experiments was the decrease in myocardial oxygen consumption during hypercapnia. We must regard this as an effect separate from the vasodilator action on coronary vessels since, by itself, a decrease in oxygen demand would lead to a decrease in myocardial blood flow. Apparently, the only other reported procedures which increase myocardial blood flow yet decrease myocardial oxygen consumption are vagal stimulation and the artificial induction of very fast heart rates (Laurent, Bolene-Williams, Williams & Katz, 1956). This decrease in myocardial oxygen consumption may simply be a reflexion of the general decrease in total body oxygen consumption that occurs during prolonged hypercapnia, but another explanation is that it may result from a decrease in myocardial contractility that follows a reduction in arterial blood pH. In such circumstances one would also expect a decrease in myocardial blood flow but since carbon dioxide (like other coronary vasodilator substances) presumably abolishes the autoregulatory mechanisms that relate blood flow to myocardial oxygen demand, the myocardium is considerably over-perfused.

The fasted myocardium derives its energy mainly from lipid metabolism, although carbohydrate sources are also utilized (Hackel, 1960). In this study there was no evidence of glucose uptake by the myocardium which, in the control phase, might simply indicate an elevated threshold for glucose. When, however, hyperglycaemia (arterial blood levels exceeding 200 mg/100 ml.) had occurred in response to hypercapnia the continued absence of glucose extraction suggests interference in the handling of this metabolite by the myocardium. The small rise in lactate consumption and small fall in pyruvate consumption noted at the end of prolonged hypercapnia probably reflected corresponding minor changes in the arterial concentrations of these substrates.

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