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Effect of Elevations of Coronary Artery Partial Pressure of Carbon Dioxide (P_{CO_2}) on Coronary Blood Flow

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This study was designed to examine the effect of increases in the partial pressure of carbon dioxide (P_{CO_2}) in coronary artery blood on coronary blood flow, coronary reactive hyperemia and the coronary response to intracoronary adenosine administration. The left anterior descending coronary artery was cannulated and perfused over a wide range of perfusion pressure (P) and flow (F) with blood equilibrated with 0 to 40% carbon dioxide in 16 open chest dogs. Increases in coronary artery P_{CO_2} from 20 ± 2 to 93 ± 8 to 211 ± 22 mm Hg (mean ± SEM) increased the coronary flow from 28 ± 3 to 68 ± 16 to 87 ± 22 ml/min, respectively, at a perfusion pressure of 60 mm Hg and from 49 ± 6 to 139 ± 30 to 206 ± 48 ml/min, respectively, at a perfusion pressure of 100 mm Hg.

Coronary reactive hyperemia following a 30 second coronary perfusion line occlusion and the response to an intracoronary bolus of adenosine (60 μg) were prominent at a low P_{CO_2} but absent at a high P_{CO_2}. Beta-adrenergic blockade did not abolish the increase in coronary flow that occurred at increased P_{CO_2}. Thus, progressive elevations of regional coronary P_{CO_2} produced substantial increases in coronary blood flow and maximal or near maximal coronary vasodilation.

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Coronary occlusion results in a decrease in vascular resistance in the ischemic myocardium (1). The mechanism or mechanisms that are responsible for this decrease in resistance remain poorly understood. Recently, the myocardial partial pressure of carbon dioxide (P_{CO_2}) has been shown to increase rapidly and substantially in ischemic myocardial tissue (2–4). After coronary occlusion, myocardial P_{CO_2} may rise to levels greater than 200 mm Hg (2–4). The possibility that increases in myocardial P_{CO_2} might contribute to decreases in vascular resistance in the ischemic myocardium has not been considered for two reasons: 1) a controversy exists about whether moderate elevations of P_{CO_2} produce significant coronary vasodilation (5–15); and 2) the effects of marked increases in P_{CO_2} to levels achieved distal to a coronary occlusion have not been previously studied.

The present experiments were designed to determine whether increases in P_{CO_2} to levels reached during myocardial ischemia result in changes in coronary vascular tone. An experimental model of selective regional perfusion of a coronary artery branch was chosen for these experiments. This model permits selective elevation of coronary artery P_{CO_2} in one coronary artery branch and thus avoids the systemic hormonal and hemodynamic effects produced by systemic hypercapnia and acidosis (16–19). The effects of carbon dioxide on coronary blood flow were studied at different levels of P_{CO_2} by determining the relation between coronary perfusion pressure and flow over a wide range of perfusion pressures. In addition, coronary vascular reactivity at a high P_{CO_2} was assessed by measuring the coronary vascular responses to brief periods of coronary occlusion (reactive hyperemia) and to intracoronary administration of adenosine.

Methods

Experimental preparation. Sixteen mongrel dogs of either sex weighing between 25 and 35 kg were anesthetized with intravenous pentobarbital (30 mg/kg). Tracheal intubation was performed and respiration was achieved with a Harvard respirator using room air. A left thoracotomy was performed and the heart was elevated in a pericardial cradle. The left anterior descending coronary artery was dissected free of adjacent tissue in its proximal portion, cannulated

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and perfused. The perfusion cannula was placed in the coronary artery so that no obstruction to flow occurred at the cannula tip. Blood was pumped from the left femoral artery to a reservoir, heat exchanger (39°C) and gas exchanger. Blood from the gas exchanger was pumped into a perfusion line connected to the perfusion cannula. The perfusion line contained an overflow column with a variable resistor, a warming coil which passed through a warm water bath maintained at 39°C, an extracorporeal flow probe (Carolina Instruments Inc.) and a side arm near the heart to measure perfusion pressure. Using this perfusion system, changes in coronary perfusion pressure were produced by changing either the inflow pump rate, the resistor in the overflow column, or both. In 10 of the 16 animals a catheter for blood sampling was passed into the great cardiac vein by way of the right jugular vein and coronary sinus. Catheter position was verified by palpation of the catheter tip. Before each experiment, the perfusion system was primed with the experimental animal's blood. Normal saline solution was administered intravenously as necessary throughout each experiment to maintain constant mean arterial pressure.

Coronary perfusion pressure, coronary flow, aortic pressure and lead II of the electrocardiogram were continuously recorded on a Grass polygraph recorder (Grass Instrument Co.).

Protocol. Different levels of coronary artery P_{CO_2} were obtained by equilibrating the blood perfusing the left anterior descending coronary artery with gases containing between 0 and 40% carbon dioxide, the remainder of each mixture being oxygen. Perfusion line partial pressure of oxygen (P_{O_2}), P_{CO_2} and pH were determined from blood samples obtained from the perfusion line after equilibration with each gas mixture at each level of P_{CO_2}. Left anterior descending artery blood flow at different levels of coronary artery pressure was obtained in each experiment at each of several levels of coronary artery P_{CO_2}. The first pressure-flow relation in each experiment was obtained at 3% carbon dioxide. In most experiments, the final pressure-flow relation was also obtained at 3% carbon dioxide to document stability of the preparation and the reversibility of coronary flow changes produced by high P_{CO_2}. All pressure-flow relations in all experiments were found to be highly linear (all r values greater than 0.9). For the presentation of the data, coronary flows at perfusion pressures of 60, 80, and 100 mg were obtained from each linear pressure-flow relation.

In 5 of the 16 dogs, pressure-flow relations were obtained at several levels of P_{CO_2} after the administration of propranolol (2 mg/kg body weight) into the coronary perfusion line. Adequacy of beta-adrenergic receptor blockade was evident from a substantial decrease in heart rate in each animal after propranolol administration.

After determination of the pressure-flow relation at each level of P_{CO_2}, the coronary vascular response to a 30 second occlusion of the perfusion line (reactive hyperemia) was measured. Coronary vascular responses to an injection of 60 μg of adenosine into the perfusion line were then obtained. In these studies, the changes in coronary blood flow and coronary artery pressure during the intervention were measured. Coronary vascular resistance (in arbitrary units) was calculated by dividing mean coronary artery pressure by blood flow.

In 10 dogs (5 without and 5 with propranolol pretreatment), great cardiac vein oxygen saturation was measured at the lowest and highest coronary perfusion pressures at each level of arterial P_{CO_2}. Samples were obtained through the catheter in the great cardiac vein and were measured using an American Optical oximeter.

Coronary pressure correction and blood flow calibration. The extracorporeal flow probe was calibrated at the completion of each experiment by pumping the experimental animal's blood through the perfusion system at several pump rates and measuring flow at each rate by timed collection. The pressure drop that occurred between the point of pressure measurement in the perfusion line and the distal tip of the perfusion cannula was also determined at the end of each experiment over the range of flows observed during the experiment. This pressure drop was found to vary linearly with flow. Accordingly, the pressures measured in the perfusion line during the experiment were corrected to obtain the coronary perfusion pressure at the tip of the perfusion catheter. P_{CO_2}, P_{O_2} and pH were measured in blood obtained from the coronary perfusion line and from the femoral artery after equilibration with each gas mixture. Changes in coronary artery P_{CO_2} had no effect on systemic arterial P_{CO_2} or pH. Systemic P_{CO_2}, P_{O_2} and pH were maintained in the physiologic range. Hematocrit was measured frequently and did not change significantly throughout the experimental period.

All studies were performed in accordance with animal welfare regulations of Columbia University and with the guiding principles of the American Physiological Society.

Statistical analysis. Throughout the text, figures and tables, data are given as mean values ± SEM. Statistical analysis was performed using analysis of variance, Duncan's multiple range test and linear regression using the method of least squares.

Results

Pressure-flow data. Figure 1 presents data from 1 of the 11 animals not pretreated with propranolol. Equilibration of coronary blood with 3% carbon dioxide yielded an arterial P_{CO_2} of 20 mm Hg. As coronary artery pressure was increased at this P_{CO_2}, there was a linear increase in anterior descending artery blood flow. Similar pressure-flow data were obtained at levels of P_{CO_2} ranging from 7 to 36 mm Hg. A linear pressure-flow relation was also observed when P_{CO_2} was increased to 108 and 186 mm Hg. At a perfusion

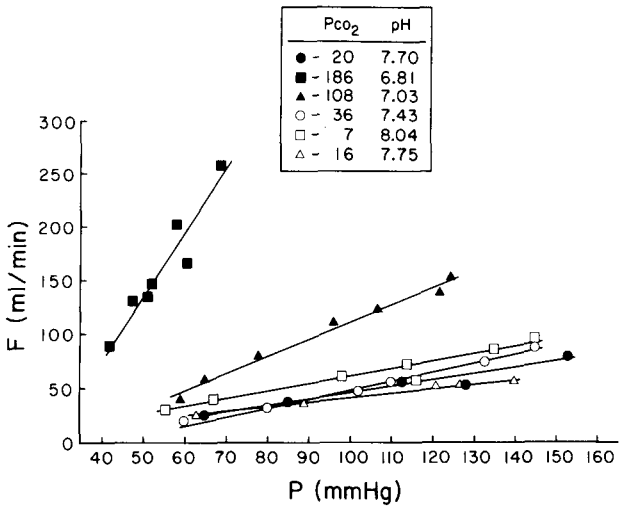

Figure 1. Coronary pressure (P)-flow (F) data from a single experiment. Coronary artery partial pressure of carbon dioxide (P_{CO_2}) and pH for each of the six pressure-flow relations are given in the **box.**

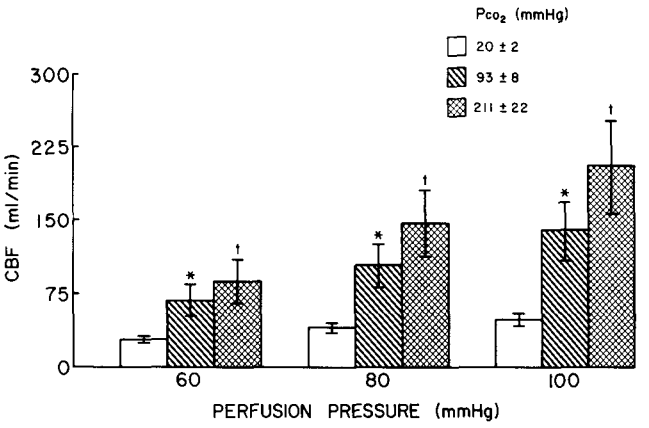

Figure 2. Coronary blood flow (CBF) at perfusion pressures of 60, 80, and 100 mm Hg at the three respective levels of coronary artery partial pressure of carbon dioxide (P_{CO_2}). *Significant difference in flow compared with flow at a P_{CO_2} of 20 ± 2 mm Hg ($p < 0.01$); †significant difference in flow compared with flow at a P_{CO_2} of 20 ± 2 and 93 ± 8 mm Hg ($p < 0.01$).

pressure of 65 mm Hg, increasing coronary artery P_{CO_2} from 20 to 186 mm Hg resulted in an increase in coronary flow from 25 to 220 ml/min (a 780% increase).

Mean data from all 11 experiments were grouped into 1) those obtained after coronary artery equilibration with 0 to 5% carbon dioxide, yielding a coronary artery P_{CO_2} of 20 ± 2 mm Hg, 2) those obtained after equilibration with 10 to 20% carbon dioxide (arterial P_{CO_2} = 93 ± 8mm Hg), and 3) those obtained after equilibration with 40% carbon dioxide (arterial P_{CO_2} = 211 ± 22 mm Hg). The increases in P_{CO_2} produced substantial increases in coronary flow over the entire perfusion pressure range studied (Fig. 2). At a perfusion pressure of 100 mm Hg, these respective increases in coronary P_{CO_2} increased coronary flow from 49 ± 6 to 139 ± 30 to 206 ± 48 ml/min (all increases $p < 0.01$). Pressure-flow data obtained at a physiologic P_{CO_2} (35 to 45 mm Hg) in five experiments were not significantly different from those obtained at a P_{CO_2} of 20 ± 2 mm Hg, although at a given perfusion pressure coronary flow tended to be greater at the higher, physiologic P_{CO_2} (83 ± 36 ml/min at a perfusion pressure of 100 mm Hg).

Heart rate and aortic pressure. Heart rate remained nearly constant at the three levels of coronary artery P_{CO_2} (140 ± 5, 133 ± 5 and 140 ± 7 beats min, respectively). Similarly, mean aortic pressure was unchanged (59 ± 3, 62 ± 3 and 62 ± 6 mm Hg, respectively, at the three levels of coronary P_{CO_2}). The final pressure-flow relation obtained at a low P_{CO_2} at the end of each experiment was similar to the first obtained at a low P_{CO_2} at the beginning of each experiment. Thus, the relatively low mean aortic pressures maintained in these experiments did not abolish autoregulation in the perfused coronary arteries. Systemic arterial pH, P_{O_2} and P_{CO_2} remained nearly constant throughout each experiment.

Effect of reactive hyperemia and adenosine. Coronary reactive hyperemia, which was substantial at a low P_{CO_2}, was absent at a high P_{CO_2} (Fig. 3); at a P_{CO_2} of 21 ± 2 mm Hg (n = 19), coronary resistance decreased from 2.42 ± 0.24 to 1.04 ± 0.11 mm Hg/ml per min after a 30 second coronary occlusion ($p < 0.01$). Reactive hyperemic responses at a P_{CO_2} of 35 to 45 mm Hg in four experiments were similar to those observed at a P_{CO_2} of 21 ± 2 mm Hg (2.25 ± 0.34 to 1.05 ± 0.35 mm Hg/ml per min). In contrast, at a P_{CO_2} of 198 ± 17 mm Hg (n = 17) no significant reactive hyperemic response occurred. Similarly, substantial responses occurred to intracoronary adenosine at a P_{CO_2} of 19 ± 2 mm Hg (n = 18) with a decrease in coronary resistance from 2.75 ± 0.35 to 1.58 ± 0.21 mm Hg/ml per min ($p < 0.01$) (Fig. 3). However, at a P_{CO_2} of 191 ± 20 mm Hg (n = 7), no response to 60 μg of intracoronary adenosine was observed. Furthermore, in three animals studied at a P_{CO_2} of 201 ± 30 mm Hg, additional doses of intracoronary adenosine of either 120 or 180 μg produced no change in coronary resistance.

Coronary venous oxygen saturation. In five experiments, the effect of changes in coronary artery P_{CO_2} on coronary venous oxygen saturation was examined. Table 1 contains mean perfusion pressure, coronary flow and great cardiac vein oxygen saturation data obtained at the lowest and highest perfusion pressures studied in each experiment. Great cardiac vein oxygen saturations were significantly greater at a P_{CO_2} of 208 ± 23 mm Hg than at a P_{CO_2} of 32 ± 3 mm Hg at low and high perfusion pressures.

Propranolol pretreatment. In five additional animals, pressure-flow relations were obtained at several levels of coronary artery P_{CO_2} after propranolol pretreatment. Propranolol administration resulted in a decrease in heart rate

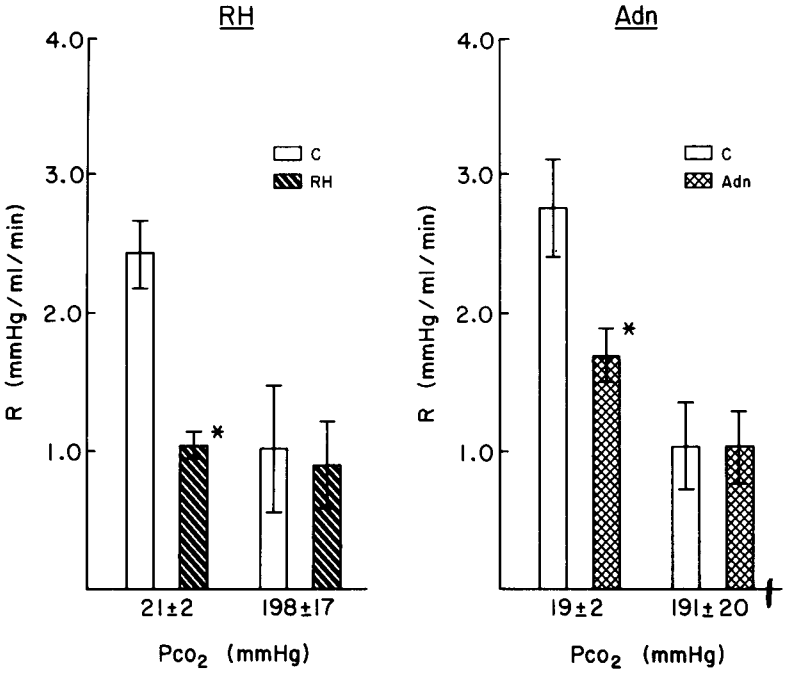

Figure 3. Coronary resistance (R) at the peak of the reactive hyperemia response (RH) and after the intracoronary administration of adenosine (Adn) at low and high coronary artery partial pressure of carbon dioxide (P_{CO_2}). C = control (resistance before reactive hyperemia or adenosine administration). *Significant change in resistance from control, $p < 0.05$.

from 130 ± 6 to 93 ± 3 beats/min ($p < 0.01$); mean arterial pressure was maintained constant. Increases in coronary artery P_{CO_2} from 31 ± 2 to 82 ± 6 to 152 ± 23 mm Hg in these experiments resulted in increases in coronary flow over the entire range of perfusion pressures studied (40 ± 8 to 63 ± 8 to 78 ± 19 ml/min at 60 mm Hg, 65 ± 11 to 96 ± 12 to 133 ± 32 ml/min at 80 mm Hg and 90 ± 13 to 130 ± 16 to 185 ± 44 ml/min at 100 mm Hg, respectively; all increases $p < 0.05$). Thus, beta-adrenergic blockade did not abolish the vasodilator effect of elevations in coronary artery P_{CO_2}.

Discussion

Previous work from this (4) and other (2,3) laboratories has demonstrated that myocardial P_{CO_2} increases to a value of greater than 200 mm Hg distal to a coronary artery occlusion. Similar elevations in P_{CO_2} have been observed in the human myocardium during ischemia produced at the time of heart surgery and cardiopulmonary bypass (20). In the present experiments increases in coronary artery P_{CO_2} were studied over a wide range of perfusion pressures to test whether increases in P_{CO_2} might contribute to the changes in coronary vascular resistance that occur during myocardial ischemia (1). The present study demonstrates that progressive elevations of coronary artery P_{CO_2} at a given level of coronary artery pressure result in progressive increases in coronary blood flow. Marked elevation of coronary artery P_{CO_2} increased coronary flow more than fourfold at a perfusion pressure of 100 mm Hg. Furthermore, the reactive hyperemic response after a brief coronary occlusion and the vasodilator response to an intracoronary bolus of adenosine were absent at a high coronary artery P_{CO_2}. The substantial increases in coronary flow observed at moderate and high P_{CO_2} levels suggest that changes in myocardial P_{CO_2} may contribute importantly to decreases in vascular resistance in the ischemic myocardium.

Table 1. Effect of Elevations of Coronary Artery Partial Pressure of Carbon Dioxide on Coronary Venous Oxygen Saturation

Coronary P_{CO_2} (mm Hg)	Coronary Pressure (mm Hg)	Coronary Flow (ml/min)	$GCVO_2$ (% SAT)
32 ± 3	62 ± 4	37 ± 7	56 ± 5
	137 ± 8	84 ± 12	68 ± 5
208 ± 23*	57 ± 7	56 ± 15*	69 ± 5*
	103 ± 23*	156 ± 39*	87 ± 4*

*Different from data obtained at a partial pressure of carbon dioxide (P_{CO_2}) of 32 ± 3 mm Hg ($p < 0.05$).
$GCVO_2$ = great cardiac vein oxygen saturation (SAT).

Effect of moderate elevations of P_{CO_2} on coronary blood flow. In the present study, selective increases in coronary artery P_{CO_2} without changes in systemic P_{CO_2} or pH were investigated. Previous investigators (8–15) studying the effects of moderate elevations of systemic arterial P_{CO_2} on coronary vascular resistance have obtained conflicting results. Because systemic hypercapnia and acidosis result in systemic hemodynamic changes (17,18) and sympathoadrenal activation (16,19), differences in the results of previous studies may be due, in part, to differences in activation of the sympathetic nervous system produced by increases in systemic arterial P_{CO_2}. A recent study by Rooke and Sparks (14) examining changes in coronary blood flow produced by changes in systemic P_{CO_2} concluded that carbon dioxide is a weak vasodilator. However, in their experiments, decreases in coronary resistance produced by increases in P_{CO_2} may have been attenuated by sympathoadrenal activation or the increases in coronary venous P_{O_2} that occurred in their experiments (7), or both. Case and coworkers (6,7) demonstrated substantial decreases in coronary resistance when coronary but not systemic arterial P_{CO_2} was increased to a moderate degree. Our data obtained over a wide range of coronary perfusion pressures demonstrate a substantial increase in coronary blood flow when P_{CO_2} is increased to 93 mm Hg. Thus, our data at moderately increased P_{CO_2} are in agreement with the data of Case et al. and demonstrate that increases in P_{CO_2} to levels less than 100 mm Hg result in substantial increases in coronary blood flow.

Effect of marked increases in P_{CO_2} on coronary blood flow. In addition to examining the effects of moderate elevations of P_{CO_2}, we studied the effects of marked P_{CO_2} increases. No previous study has examined the effect of these marked increases in P_{CO_2} on coronary blood flow. Our data demonstrate that arterial carbon dioxide at this level is a powerful vasodilator. Furthermore, under conditions of high coronary flow produced by a high P_{CO_2}, reactive hyperemia and responses to intracoronary adenosine were no longer observed. The absence of reactive hyperemic and adenosine responses appears to be the result of the profound vasodilation produced by carbon dioxide. These data indicate that carbon dioxide at a high arterial concentration is a maximal or near maximal coronary vasodilator.

Mechanism of effect of carbon dioxide on coronary blood flow. Increases in coronary blood flow produced by elevations of coronary artery P_{CO_2} cannot be explained by increases in myocardial oxygen demand. Aortic pressure and heart rate, two important hemodynamic determinants of myocardial oxygen demand, were constant in our experiments. Furthermore, increases in coronary flow produced by increases in coronary artery P_{CO_2} were associated with increases in coronary venous oxygen saturation over the entire range of perfusion pressures examined. This increase in coronary venous oxygen saturation indicates that increases in P_{CO_2} increased coronary blood flow relative to myocardial oxygen consumption. The increases in coronary blood flow produced by increases in coronary artery P_{CO_2} in our experiments were not abolished by beta-adrenergic receptor blockade. Although two early studies (10,21) demonstrated decreases in coronary resistance at a high P_{CO_2} despite the prior administration of beta-adrenergic blocking drugs, a recent study (15) concluded that systemic hypercapnia had no significant effect on coronary vascular resistance after beta-blockade. Our data are in agreement with the earlier studies and suggest that the effects of carbon dioxide on coronary blood flow do not depend on myocardial or coronary vascular beta-adrenergic receptor stimulation.

Our experiments did not attempt to dissociate the effects of carbon dioxide on coronary vascular resistance from the effects of acidosis. Previous work in isolated perfused hearts (9) has demonstrated that increases in arterial P_{CO_2} produce decreases in coronary resistance when perfusate pH is maintained constant by the infusion of buffers. In addition, in perfused hearts decreases in arterial pH at constant P_{CO_2} have relatively little effect on coronary vascular resistance (9,21). These results suggest that the increases in coronary flow at the high P_{CO_2} observed in the present experiments were due to changes in P_{CO_2} rather than to associated changes in coronary artery pH. In contrast, relaxation of isolated arterial segments may occur when acidosis is produced either when P_{CO_2} is increased or when P_{CO_2} is maintained constant (22–24). Thus, both blood P_{CO_2} and blood pH may affect coronary resistance and may have influenced coronary flow in the present experiments.

Critique of methods. Several points concerning the methods of this study deserve comment: 1) Perfusion pressure was measured in the perfusion cannula, and not directly in the coronary artery, requiring a correction of each pressure measurement for the pressure drop across the cannula. This correction allowed for an assessment of intracoronary pressure and thus removed any possibility that resistance in the perfusion apparatus had any influence on our results. 2) Autoregulatory reserve at low P_{CO_2} was maintained throughout each experiment. This preservation of autoregulatory reserve is demonstrated by similar coronary pressure-flow relations at similar low levels of P_{CO_2} at the beginning and end of each experiment. 3) Mean aortic pressure was maintained at approximately 60 mm Hg. This mean pressure was adequate to maintain a normal and constant systemic pH throughout all experiments. This level of systemic pressure and the trauma of the experimental preparation as well as anesthesia may have had effects on levels of circulating vasoactive substances such as catecholamines. However, it is apparent that any systemic effects on coronary tone remained constant throughout each experiment since coronary pressure-flow relations performed at low P_{CO_2} were similar at the beginning and end of each experimental period. 4) Calculations of coronary vascular resistance are subject to

certain limitations. Precise calculations of resistance may require knowledge of downstream zero-flow or waterfall pressure. However, the determinants of this downstream pressure in the coronary circulation are not fully understood (25–29). In addition, changes in coronary perfusion pressure almost certainly changed the extent of the perfused vascular bed (30) and, even if the extent of the vascular bed is constant, coronary resistance changes with changes in perfusion pressure (26). Nevertheless, in the present experiments, at any given perfusion pressure at which effects of pressure on the extent of the perfusion bed and on coronary resistance would be constant, increases in arterial P_{CO_2} produced substantial increases in coronary blood flow.

Coronary artery and venous P_{O_2} and oxygen saturation were maintained at a high level during the present experiments so that hypoxia would not occur and therefore not contribute to increases in coronary blood flow under conditions of increased P_{CO_2}. The work of Case et al. (7) demonstrated that increases in coronary venous P_{O_2} increase coronary vascular resistance and limit the decrease in coronary resistance that occurs at high coronary venous P_{CO_2}. In the present experiments, increases in coronary blood flow produced by increases in P_{CO_2} might have been even greater than those observed if coronary artery and venous P_{O_2} had not been maintained at high levels.

Mechanism of increased P_{CO_2} during myocardial ischemia. The substantial rise in tissue P_{CO_2} that occurs during ischemia develops in association with substantial intracellular and extracellular acidosis (31). The mechanisms responsible for the changes in P_{CO_2} and pH in the ischemic myocardium have not been defined. Some aerobic carbon dioxide production may persist in the ischemic myocardium. In addition, hydrogen ions may be produced by a number of metabolic processes in ischemic tissue and result in the conversion of bicarbonate ion to carbon dioxide (32). Decreased washout of carbon dioxide due to decreased tissue blood flow may also be an important contributor to increases in myocardial P_{CO_2} during periods of ischemia (4).

Conclusion. The determinants of coronary vascular resistance within the ischemic myocardium remain incompletely explored. The present study demonstrates profound coronary vasodilation at levels of P_{CO_2} attained in the ischemic myocardium after coronary occlusion. The lack of reactive hyperemia and adenosine responses at a high P_{CO_2} suggests that other vasodilators released in the ischemic myocardium may have relatively little additional effect on coronary resistance during extreme elevations of myocardial P_{CO_2}. Our results suggest the possibility that carbon dioxide is an important contributor to the fall in coronary resistance in the ischemic myocardium.

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