Synergistic Action of Myocardial Oxygen and Carbon Dioxide in Controlling Coronary Blood Flow

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A two-part experiment was designed to test the hypothesis that myocardial oxygen and carbon dioxide tensions, as measured by coronary venous oxygen and carbon dioxide tensions, determine coronary blood flow during increases in myocardial oxygen consumption. The left main coronary artery was pump-perfused at constant pressure in closed-chest, anesthetized dogs. Oxygenators in the perfusion circuit permitted control of coronary arterial gas tensions. The steady-state relation between coronary venous oxygen and carbon dioxide tensions and coronary flow at a constant myocardial oxygen consumption was determined by locally altering coronary arterial oxygen and carbon dioxide tensions. Values of coronary venous oxygen and carbon dioxide tensions and coronary flow were also obtained at normal coronary arterial gas tensions during pacing-induced increases in myocardial oxygen consumption. The data yielded a hyperbolic relation among coronary venous oxygen and carbon dioxide tension and coronary flow during constant myocardial metabolism, suggesting a synergistic interaction between myocardial oxygen and carbon dioxide tensions in determining coronary flow. This relation was then used to predict the coronary flow change during pacing-induced increases in myocardial metabolism. Approximately 40% of the flow response during pacing-induced increases in myocardial oxygen consumption was predicted. In conclusion, coronary venous oxygen and carbon dioxide tensions synergistically interact to produce steady-state changes in coronary flow at a constant myocardial oxygen consumption. Changes in myocardial oxygen and carbon dioxide tensions can account for about 40% of the change in coronary flow during moderate changes in myocardial oxygen consumption. (Circulation Research 1991;68:531–542)

There is a remarkable matching of coronary blood flow to myocardial metabolism over a wide range of myocardial oxygen consumption. It has often been proposed that a depletion of a substrate such as oxygen or the accumulation of a metabolite such as carbon dioxide is the stimulus to coronary vasodilation during functional hyperemia resulting from increases in myocardial metabolism. Many investigators have reported that varying arterial oxygen and carbon dioxide tensions affect coronary blood flow; however, the tissue oxygen and carbon dioxide tensions are probably the critical variables. Case and colleagues used coronary venous oxygen and carbon dioxide tensions as an estimate of tissue values. They also varied coronary arterial oxygen and carbon dioxide tensions separately in a constant-flow perfused preparation and observed that coronary vascular resistance was well correlated with coronary venous oxygen and carbon dioxide gas tensions. Such a correlation suggests a role for tissue oxygen and carbon dioxide in the local metabolic control of coronary blood flow but does not constitute a sufficient test of such a hypothesis for functional hyperemia that occurs during tachycardia.

A two-part study was designed to test the hypothesis that a combination of myocardial oxygen and carbon dioxide tensions uniquely determines coronary blood flow during functional hyperemia resulting from cardiac pacing. In the first part, the steady-state three-dimensional relation among coronary venous oxygen and carbon dioxide tensions and the resulting coronary blood flow was determined by altering coronary arterial blood gases at a constant myocardial oxygen consumption. A hyperbolic relation among coronary venous oxygen and carbon dioxide tensions and coronary flow was observed,
indicating a synergism between low oxygen and high carbon dioxide tensions. In the second part, this relation was then used to predict flow changes during pacing-induced increases in myocardial oxygen consumption. The hyperbolic relation obtained in the first part predicted about 40% of the increase in flow caused by pacing-induced increases in myocardial oxygen consumption.

Materials and Methods

General Preparation

Adult mongrel dogs (25–30 kg) were sedated with morphine sulfate (2.5 mg/kg s.c.) and anesthetized 1 hour later with 100 mg/kg α-chloralose. Anesthesia was maintained with an α-chloralose infusion (5 mg/kg/hr) and 500-mg supplements, as needed. The metabolic acidosis commonly associated with α-chloralose anesthesia was treated with an intravenous infusion of 1.5% sodium bicarbonate solution (1 ml/min) and bolus injections of an 8.4% sodium bicarbonate solution, as required. The dogs were intubated and ventilated with oxygen-enriched room air by a positive displacement respiration pump (model 607, Harvard Apparatus, South Natick, Mass.). End-expiratory carbon dioxide content was monitored continuously (model LB-2, Beckman Instruments, Inc., Fullerton, Calif.) and maintained between 4.5% and 5% by appropriate adjustments of the ventilatory rate. A heating pad and controller (model 73A, Yellow Springs Instrument Co., Yellow Springs, Ohio) were used to regulate esophageal temperature at 37°C. Aortic pressure was measured by a strain gauge manometer (Statham P23Dd, Gould Inc., Cleveland, Ohio) connected to a polyethylene catheter placed in the aorta via a femoral artery. Heparin (750 units/kg i.v.) was administered to prevent coagulation.

Heart Block and Ventricular Pacing

Closed-chest atrioventricular heart block was produced as described by Ito and Feigl. A cannula was inserted into the right external jugular vein and, with the aid of fluoroscopy, advanced to the region of the atrioventricular node. A hollow needle, housed within the cannula, was advanced to the nodal region, and formalin was injected. After successful completion of the block, the cannula was replaced by a pacing wire (No. 5651, USCI, Billerica, Mass.) that was advanced to the apex of the right ventricle. The ventricles were paced at a constant rate (70 or 80 beats/min for different animals).

Left Main Coronary Artery Perfusion

The experimental preparation is shown in Figure 1. The left main coronary artery was cannulated, closed-chest, with a stainless-steel, balloon-tipped cannula6,7 via the common carotid artery. Coronary artery pressure was measured at the tip of the cannula via an inner steel tube connected to a strain gauge manometer (Statham P23Id). A servo-controlled roller pump maintained mean coronary artery perfusion pressure constant at 90 mm Hg.8 Coronary blood flow was measured with a cannulating electromagnetic flow transducer (model SWF-5RD, Zepeda Instruments, Seattle) placed in the extracorporeal circuit. The source of the coronary arterial perfusate was blood drawn from a femoral artery and passed through a series of three membrane oxygenators (pediatric type VPCML 050-103, Cobe Laboratories, Lakewood, Colo.). A heat exchanger (pediatric model P7-14, Sci-Med, Minneapolis, Minn.) in the circuit maintained blood temperature at 37°C. The oxygenator circuit was primed with a 1:1 solution of heparinized Rheomacrodex (10% dextran 40; Pharmacia Laboratories, Piscataway, N.J.) and 0.9% saline. The total prime volume was approximately 800 ml, and the additional heparin dose was 250 units/kg. The femoral blood was withdrawn at a constant rate that was always greater than the coronary flow. The overflow from the oxygenator was returned to a femoral vein. Varying the amount of oxygen, nitrogen, and carbon dioxide gas supplying the oxygenators permitted local control of the coronary arterial gas tensions.

![Figure 1. Schematic diagram of the closed-chest experimental preparation. Heart rate was controlled via a pacing wire advanced to the right ventricular apex after atrioventricular heart block. The left main coronary artery was cannulated and pump-perfused at a constant pressure of 90 mm Hg with blood drawn from a femoral artery (Fem. a.). Coronary flow was measured by an electromagnetic (EM) flowmeter placed in the extracorporeal circuit. A series of three oxygenators placed in the perfusion circuit permitted local control of coronary arterial blood gases. Coronary sinus blood was withdrawn at a constant rate for the determination of coronary venous oxygen tension. Fem. v., femoral vein.](image-url)
At the end of the experiment, coronary perfusion pressure was set 50 mm Hg greater than aortic pressure and a crystal violet dye–10% ammonia solution was injected into the coronary cannula. Upon postmortem examination, dye found staining the aorta was an indication of an inadequate seal of the cannula around the coronary ostium, and these experiments were discarded. The stained regions of the myocardium were excised and weighed to determine the total myocardial tissue perfused by the left main coronary artery. All coronary flow values were calculated as the quotient of flow and perfused myocardium and were expressed as milliliters per minute per gram. The flow transducer was calibrated at the end of each experiment by timed volume collection of blood.

**Measurement of Blood Gas Tensions and Lactate**

A Sones catheter (No. 5423, USCI) was inserted into the right external jugular vein and, with the aid of fluoroscopic visualization, placed in the coronary sinus. Coronary sinus blood was withdrawn at a constant rate and returned to the animal via a femoral vein. An in-line oxygen electrode continuously measured coronary sinus oxygen tension (Figure 1). Right atrial admixture was avoided by maintaining coronary sinus blood withdrawal to less than 15 ml/min and placement of the Sones catheter not less than 15 mm beyond the coronary sinus ostium as verified postmortem.

Steeply coronary arterial and venous blood samples were collected simultaneously in glass syringes for the determination of pH, P_{O_2}, and P_{CO_2} (No. 1302, Instrumentation Laboratories, Lexington, Mass.). Some of these samples were also analyzed for oxygen content (Lex-O_2-Con, Waltham, Mass.) and hemoglobin content (cyanmethemoglobin method). For all samples, the oxygen content was calculated from the pH, P_{O_2}, and P_{CO_2} by using a computer subroutine. The Lex-O_2-Con oxygen content values were used to construct a calibration curve for the computer subroutine. Myocardial oxygen consumption was calculated as the product of coronary flow and the arteriovenous oxygen content difference and was expressed as microliters O_2 per minute per gram.

Steeply coronary arterial and venous blood samples were collected for the determination of blood lactate concentration when the myocardium was thought to be at risk due to hypoxia. Blood samples were immediately pipetted into iced perchloric acid to inhibit lactate production by the blood cells. The samples were then centrifuged, and the lactate concentration of the supernatant was determined by an enzymatic method. Data were calculated as percent lactate extraction by using the quotient of the arteriovenous lactate difference and the arterial lactate concentration.

**Drugs**

Adrenergic and cholinergic blockade was used so that functional hyperemia could be studied in the absence of autonomic effects. All animals received the β-receptor blocking agent propranolol (0.5 mg/kg plus 0.2 mg/kg/hr i.v.) and the α-receptor blocking agent phenoxybenzamine (0.1 mg/kg i.c.; Dibenzyline, Smith Kline & French Laboratories, Philadelphia) to mitigate adrenergic effects. Each dog received atropine (0.5 mg/kg i.v.) or a bilateral vagotomy to eliminate cholinergic effects. Ibuprofen (12.5 mg/kg i.v.) was administered to prevent complement and white cell activation caused by blood–oxygenator interactions. In addition, five of the seven dogs received methylprednisolone (Solu-Medrol, Upjohn Co., Kalamazoo, Mich.; four dogs received 30 mg/kg i.m. and one dog received 5 mg/kg i.v.) as an adjunct to the ibuprofen treatment.

**Experimental Protocol**

A two-part experiment was designed to test the hypothesis that myocardial oxygen and carbon dioxide tensions determine coronary blood flow. For the first part of the experiment, heart rate (and myocardial oxygen consumption) was held constant while coronary arterial gas tensions were independently varied. The steady-state relation describing coronary venous P_{O_2}, P_{CO_2}, and coronary blood flow at a constant myocardial oxygen consumption was thus determined.

In the second part of the experiment, coronary arterial gas tensions from the oxygenator were held constant in the normal range (P_{O_2} 90–120 mm Hg, P_{CO_2} 34–41 mm Hg, pH 7.36–7.45), myocardial oxygen consumption was increased by a step increase in heart rate, and the resulting steady-state changes in coronary venous P_{O_2}, P_{CO_2}, and coronary blood flow were recorded. The previously determined mathematical relation describing coronary venous P_{O_2}, P_{CO_2}, and flow during constant myocardial oxygen consumption was then used to predict the change in flow elicited by a pacing-induced increase in myocardial oxygen consumption, given the resultant coronary venous P_{O_2} and P_{CO_2} values. The rationale was that if only P_{O_2} and P_{CO_2} determine coronary flow, then this relation should predict 100% of the functional change in flow observed during the increase in myocardial metabolism.

Figure 2 depicts the time protocol for the experiment. The two parts of the experiment were run in an alternating manner for each dog. Initially, heart rate was held at 70 or 80 beats/min (depending on the animal) and step changes in the gas composition supplying the oxygenators were produced, yielding a change in the local coronary arterial P_{O_2} and P_{CO_2}. Once steady state was achieved (~5 minutes), simultaneous coronary arterial and venous blood samples were collected. This was repeated four or five times with different changes in the oxygenator gas composition. In the second portion of the protocol, coronary arterial blood gases were maintained in the normal physiological range and two periods of pacing tachycardia were produced when heart rate was increased from 70 or 80 beats/min to 140 or 160 beats/min, depending on the experimental animal.
FIGURE 2. Schematic diagram of the experimental protocol. The experiment consisted of two parts conducted in an alternating manner for each dog. First, the relation between coronary venous oxygen and carbon dioxide tension and coronary flow during constant myocardial oxygen consumption was determined. The heart was paced at a constant rate (70 or 80 beats/min) while step changes in coronary arterial oxygen and carbon dioxide tension were performed. For the second part, the relation between coronary flow and coronary venous oxygen and carbon dioxide tensions was determined during pacing-induced increases in myocardial oxygen consumption. While coronary arterial gases were maintained in the normal physiological range, heart rate was increased from 70 or 80 beats/min to 140 or 160 beats/min. The entire protocol was repeated two or three times per animal.

Steady-state coronary venous and arterial blood samples were collected simultaneously before, during, and after each step increase in heart rate.

Data Analysis

Coronary blood flow is known to change in response to alterations of blood hemoglobin content. Therefore, to compensate for changes in blood hemoglobin content that occurred among dogs and during the course of an experiment, coronary blood flow values were normalized to the oxygen carrying capacity of the blood as given by

\[ \text{flow} \times \text{O}_2 \text{ capacity} = \text{flow} \times (\text{Hb} \times 1.36) \]

where flow is coronary blood flow (milliliters per minute per gram) and the O₂ capacity is calculated as the product of the hemoglobin content (Hb; grams per deciliter) and the oxygen-binding capacity of hemoglobin (1.36 ml O₂/g Hb). This normalized flow is expressed as microliters O₂ per minute per gram.

Nonlinear regression analysis (STATGRAPHICS, STSC, Inc., Rockville, Md.) was used to determine the mathematical relation among flow × O₂ capacity and coronary venous oxygen and carbon dioxide tensions during constant myocardial metabolism. Separate equations were fit for each dog and used an average of 23 (range, 13–28) data points per dog.

Regression analysis revealed that the relation among flow × O₂ capacity and coronary venous oxygen and carbon dioxide tensions was described by the hyperbolic function

\[ \text{flow} \times \text{O}_2 \text{ capacity} = \frac{b_1}{\text{PO}_2 - b_2 \text{PCO}_2 + b_3} \]

where \( b_1, b_2, \) and \( b_3 \) are the fitting constants.

Even with the heart paced at a constant rate, small changes in myocardial oxygen consumption were observed. Therefore, the relation described above does not truly represent the independent effects of coronary venous oxygen and carbon dioxide tensions on flow. To correct for the small changes in metabolism, which necessarily affect flow, a regression analysis was performed according to

\[ (\text{flow} \times \text{O}_2 \text{ capacity})_u = \frac{b_1}{\text{PO}_2 - b_2 \text{PCO}_2 + b_3} + b_4 \text{MVO}_2 \]

where \( u \) is uncorrected and \( b_4 \) is the sensitivity of flow to the observed small changes in metabolism. The coefficient \( b_4 \) was then used to correct each flow × O₂ capacity value to a fixed myocardial oxygen consumption according to the equation

\[ \text{flow} \times \text{O}_2 \text{ capacity} = (\text{flow} \times \text{O}_2 \text{ capacity})_u + b_4 (\text{MVO}_2 - (\text{MVO}_2)_{obs}) \]

where MVO₂ is the mean myocardial oxygen consumption from an individual dog for all data used in the regression analysis, and \((\text{MVO}_2)_{obs}\) is the observed myocardial oxygen consumption for that data point. In this way, flow × O₂ capacity was adjusted to MVO₂. The average correction of flow × O₂ capacity for MVO₂ fluctuations was 5% of the measured flow × O₂ capacity. The corrected flow × O₂ capacity was then used in the final regression analysis. This correction made the test of the hypothesis more rigorous, since covariance between oxygen consumption and coronary venous gas tensions was removed (see “Discussion”).
Experimental Criteria

Criteria were established, a priori, to ensure that the data to be analyzed were within the normal range of local metabolic control. Coronary venous oxygen tensions were restricted to the range of 10–25 mm Hg. The upper limit was set to avoid data from vasodilated preparations, since coronary venous oxygen tension is normally below 20 mm Hg20 and autoregulation is diminished above 25 mm Hg.21 The lower limit is an estimate of when the myocardium is ischemic.22,23 For the first part of the experiment, when myocardial oxygen consumption was to be constant, any data associated with myocardial oxygen consumptions greater than ±2 SD from the mean myocardial oxygen consumption (for that individual) were treated as outliers and excluded from analysis. Four points from three dogs were excluded because of outlying myocardial oxygen consumptions. In addition, post hoc evaluation of the data yielded five points from three dogs that were excluded because the values of coronary venous oxygen and carbon dioxide tensions were far removed from the other data points, requiring extrapolation of the nonlinear regression model. When low arterial oxygen tensions were associated with myocardial lactate production (negative extraction), indicating ischemia, the data were excluded from subsequent analysis.

Results

Relation Between Flow×O2 Capacity and Coronary Venous Oxygen and Carbon Dioxide Tensions During Constant Myocardial Metabolism

The overall ranges of coronary venous gas tensions obtained by varying local coronary arterial gas tensions were PO2 10–25 mm Hg, PCO2 34–70 mm Hg, and pH 7.236–7.540. Each dog exhibited a unique range of coronary venous gas tensions, but no individual dog exhibited coronary venous gas tensions spanning the overall range. Regression analysis was restricted to the range of coronary venous gas tensions obtained for each dog to avoid extrapolation of the data. In all cases, the range of coronary venous PO2 and PCO2 obtained during changes in coronary arterial gas tensions encircled the values obtained during pacing and normal arterial gas tensions. This permitted testing of the synergistic interaction of coronary venous PO2 and PCO2 during pacing without extrapolating.

The three-dimensional relation between the corrected flow×O2 capacity and coronary venous oxygen and carbon dioxide tensions for one dog is shown in Figure 3. The regression equation for this relation is

\[
\text{flow} \times \text{O}_{2} \text{ capacity} = \frac{1605.8}{\text{PO}_2 - 0.34 \cdot \text{PCO}_2 + 16.6}
\]

with a multiple correlation coefficient \(r^2\) of 0.631. The data points used to derive the surface are included to illustrate the range of data obtained. For this dog, coronary venous oxygen tension ranged from 14 to 22 mm Hg, coronary venous carbon dioxide tension ranged from 40 to 64 mm Hg, and coronary venous pH ranged from 7.236 to 7.424. The flow×O2 capacity values were corrected to a fixed myocardial oxygen consumption of 65.2 μl O2/min/g. The plot of the observed versus predicted flow×O2 capacity (Figure 4) demonstrates the goodness of fit of this regression model. The regression and multiple correlation coefficients for each of the seven dogs are given in Table 1.

An average regression surface was calculated by averaging the regression coefficients from the seven dogs (Table 1) and is shown in Figure 5. The surface is restricted to the overall range of coronary venous oxygen and carbon dioxide tensions obtained. The average equation for the surface is

\[
\text{flow} \times \text{O}_2 \text{ capacity} = \frac{1820.3}{\text{PO}_2 - 0.39 \cdot \text{PCO}_2 + 23.9}
\]

with an \(r^2=0.596\).

Note that the hyperbolic relation reflects a synergistic interaction between coronary venous oxygen and carbon dioxide tensions with respect to controlling coronary flow. The response of coronary flow to changes in coronary venous oxygen tension is less at a low coronary venous carbon dioxide tension than at a high coronary venous carbon dioxide tension. Likewise, the sensitivity of coronary flow to changes in coronary venous carbon dioxide tension is less at a high coronary venous oxygen tension than at a low coronary venous oxygen tension.

Relation Between Flow×O2 Capacity and Coronary Venous Oxygen and Carbon Dioxide Tension During Increases in Myocardial Metabolism

A response of coronary blood flow and coronary venous oxygen tension to pacing tachycardia is shown in Figure 6. Increasing heart rate from 80 to 140 beats/min elicited a rapid rise in coronary flow from 0.58 to 0.82 ml/min/g and a decrease in coronary venous oxygen from 23 to 19 mm Hg. Coronary venous carbon dioxide tension, not shown, increased from 48 to 50 mm Hg. Average changes in myocardial oxygen consumption were modest, with a mean increase of 53% (range, 45–64%). The associated changes in coronary venous oxygen and carbon dioxide tension were also small.

The mathematical relation derived from the first part of the experimental protocol, when myocardial oxygen consumption was fixed, was used to predict the coronary flow change elicited by pacing tachycardia. The prediction value of this relation was calculated as

\[
\text{predictive value} = \frac{\Delta \text{flow (predicted)}}{\Delta \text{flow (observed)}} \times 100(\%)
\]

\[
= \frac{\bar{Y}_{\text{high}} - \bar{Y}_{\text{low}}}{Y_{\text{high}} - \bar{Y}_{\text{low}}} \times 100(\%)
\]
where \( \hat{Y}_{\text{high}} \) is the flow×O\(_2\) capacity predicted from the regression model given the observed coronary venous gas tensions at the high heart rate; \( \hat{Y}_{\text{low}} \) is the mean predicted flow×O\(_2\) capacity from the low heart rate points immediately preceding and following the high heart rate point; \( \hat{Y}_{\text{high}} \) and \( \hat{Y}_{\text{low}} \) are the high and low observed flow×O\(_2\) capacity, respectively. An example of this calculation, based on the data shown in Figure 6, is shown in Figure 7. A predictive value of 100% would indicate that the regression equation perfectly predicted the change in coronary flow during pacing tachycardia.

Predictive values for the regression equations were evaluated in two ways: first, a paired analysis for which regression equations from individual dogs were tested against their respective individual pacing tachycardia data; second, on an overall basis for which the average regression equation was tested against each dog's pacing tachycardia data. The paired analysis yielded an average predictive value of 37%, while the overall average predictive value was 42% (Table 1).

**Discussion**

Myocardial oxygen and carbon dioxide tensions have been hypothesized to be involved in the local metabolic control of coronary blood flow. If the hypothesis is correct, then 1) changing myocardial oxygen and carbon dioxide tensions, independent of changes in myocardial oxygen consumption, should alter coronary flow and 2) similar changes in myocar-
A unique aspect of the present study is the two-part design for which both components of the hypothesis are tested within the same experimental animal. The data indicate that myocardial oxygen and carbon dioxide tensions, as estimated by coronary venous measurements, interact in a synergistic manner to produce changes in coronary blood flow during constant myocardial oxygen consumption (r²=0.596). However, this hyperbolic relation predicted only ~40% of the functional hyperemia observed during pacing tachycardia.

To determine the local metabolic effects of oxygen and carbon dioxide tension on coronary flow, the
other major determinants of coronary vascular resistance were controlled. Perfusing the left main coronary artery at a constant pressure of 90 mm Hg avoided any influence of autoregulatory adjustments on coronary vascular resistance. Systemic chemoreflex activation and subsequent neural modulation of coronary vascular tone were minimized by locally altering coronary arterial gases and by the administration of the autonomic blocking agents atropine, phenoxybenzamine, and propranolol. Variations in myocardial metabolism were mitigated by constant cardiac pacing. Because all variables affecting myocardial metabolism cannot be absolutely controlled, the small coronary flow changes caused by variations in myocardial metabolism observed during the course of the experiment were determined at each data point. The coronary flow values were then mathematically adjusted to the mean myocardial oxygen consumption for the individual animal. Therefore, the relation for coronary venous oxygen and carbon dioxide tension and coronary flow was determined at a constant myocardial metabolism. It is important that there not be any change in myocardial oxygen consumption in the first part of the experiment, because then coronary venous oxygen and carbon dioxide tensions would covary with myocardial metabolism. Such a covariance would artificially improve the prediction of functional hyperemia during changes in myocardial oxygen consumption from venous gas tension measurements in the second part of the experiment.

A consistent, hyperbolic relation among coronary venous oxygen and carbon dioxide tensions and coronary flow, without changes in myocardial oxygen

![Pacing Tachycardia Graph](https://example.com/pacing_tachycardia_graph.png)

**FIGURE 6.** An example of the hemodynamic response to pacing tachycardia in one dog. An increase in heart rate from 80 to 140 beats/min caused a rapid increase in coronary flow and a decrease in coronary sinus oxygen tension (PO2) from 23 to 19 mm Hg. Coronary sinus carbon dioxide tension, not shown, increased from 48 to 50 mm Hg.
consumption, was found for each of the seven dogs in this study. The hyperbolic relation suggests a synergistic interaction between coronary venous oxygen and carbon dioxide tension and coronary flow. The synergistic interaction of oxygen and carbon dioxide tension is also supported by the observation that the relation among coronary venous oxygen and carbon dioxide tensions and flow could not be well described by a linear equation (e.g., \( \text{flow} = b_1 \text{PO}_2 + b_2 \text{PCO}_2 + b_3 \)). Qualitatively similar synergistic interactions between oxygen and carbon dioxide have been described in the control of skeletal muscle blood flow and chemoreceptor activation.

The relative sensitivity of coronary flow to changes in coronary venous oxygen tension as compared with changes in coronary venous carbon dioxide tension can be estimated by the ratio of the respective regression coefficients (slopes). For the average equation \((n = 7)\), the ratio of the coronary venous oxygen and coronary venous carbon dioxide coefficients is 0.39, indicating that coronary flow is 39% as sensitive to changes in coronary venous carbon dioxide as to changes in coronary venous oxygen tension. Case et al. reported a linear relation among coronary vascular resistance and coronary venous oxygen and coronary venous carbon dioxide tensions in a constant-flow perfused preparation. Solving that relation for coronary flow, assuming a constant coronary pressure of 90 mm Hg and a hemoglobin concentration of 12 g/dl, yields the following equation:

\[
\text{flow} \times \text{O}_2 \text{ capacity} = \frac{2485.3}{\text{PO}_2 - 0.44 \times \text{PCO}_2 + 25.5}
\]

The relative sensitivity of coronary flow to changes in coronary venous carbon dioxide tension as compared with changes in coronary venous oxygen tension is remarkably similar to the present findings (0.44 as compared with 0.39). Mohrman and Regal\(^{24}\) described a qualitatively similar hyperbolic relation among venous oxygen and carbon dioxide tensions and blood flow in a constant-pressure, pump-perfused muscle preparation in which both muscle oxygen consumption and arterial blood gas composition were changed.

Inspection of the relation between oxygen and carbon dioxide tensions and coronary flow described in the present study (Figure 5) reveals that the gain (slope) of the oxygen–coronary flow or carbon dioxide–coronary flow relation depends on the prevailing coronary venous gas tensions. For example, if coronary venous carbon dioxide tension is altered when coronary venous oxygen tension is high (e.g., 25 mm Hg), then only a small response in coronary flow will be observed. However, if the same change in coronary venous carbon dioxide is induced when coronary venous oxygen is low (e.g., 10 mm Hg), then a large change in coronary flow will be observed. Similarly, the oxygen–coronary flow relation is steep at high venous carbon dioxide tensions and relatively flat at low carbon dioxide tensions (Figure 5). A consistent increase in coronary flow during arterial or coronary venous hypoxia has been reported by many investigators; however, there has been some disagreement on the vasoactive potency of carbon dioxide. Systemic hypercapnia in \(\beta\)-blocked and unblocked preparations caused little or no increase in coronary flow, while others attribute substantial vasodilatory activity to carbon dioxide. \(3^3,4,28-32\) However, van den Bos et al.\(^{27}\) reported that coronary venous oxygen tension significantly increased in response to hypercapnia, most likely resulting from a rightward shift of the oxyhemoglobin dissociation curve. These investigators suggested that the increased venous oxygen tension may have induced a vasodilator response that masked the vasoactive response to carbon dioxide.

The hyperbolic relation described in the present study between coronary venous oxygen and carbon dioxide tensions supports that interpretation. Rooke and Sparks\(^{28}\) did not report coronary venous oxygen tension but did report an increase in coronary venous oxygen content during hypercapnia. The presumed accompanying increase in coronary venous oxygen tension could account for the lack of carbon dioxide–induced vasodilation reported in that study. Thus, the apparent discrepancies in the literature may be explained by the synergistic action between oxygen and carbon dioxide shown in Figure 5, that is, little carbon dioxide sensitivity with high

![Graph](attachment:image.png)
venous oxygen tensions but good carbon dioxide sensitivity with low oxygen tensions. Changes in arterial carbon dioxide tension or hydrogen ion concentration (pH) will shift the oxyhemoglobin dissociation curve,33 affecting oxygen delivery to the myocardial tissue. Mehmel et al34 reported that a leftward shift in the oxyhemoglobin dissociation curve induced by increasing arterial pH caused an increase in coronary blood flow. In the present study, a decrease in carbon dioxide tension was associated with an increase in pH and a decrease in coronary flow. The common denominator that may reconcile these seemingly discordant results is coronary venous oxygen tension. Mehmel et al35 reported that a slight decrease in coronary sinus oxygen tension (from 19 to 17 mm Hg) was associated with the increase in coronary flow. The increase in coronary flow in response to a decrease in coronary sinus oxygen tension is consistent with the results of the present study.

The mechanism of action of oxygen and carbon dioxide tensions on coronary flow was not specifically addressed in this study. Wexels et al36 reported that the increase in coronary flow induced by hypercapnia was abolished when pH was normalized by sodium carbonate infusion, suggesting that the mechanism of the hypercapnic increase in coronary flow was via hydrogen ions. Because hydrogen ion concentration covaried with carbon dioxide tension in the present study, the hyperbolic relation was nearly as well described when hydrogen ion concentration was substituted for carbon dioxide tension. The observed relation is also consistent with a mechanism involving an intermediary effector such as adenosine, but that was not tested in the present experiment.

The critical test of the hypothesis is not whether coronary venous oxygen and carbon dioxide tensions are correlated with coronary blood flow independent of changes in myocardial oxygen consumption, but whether this relation accounts for the change in coronary flow during functional hyperemia. The latter question was addressed by using the mathematical relation between coronary venous oxygen and carbon dioxide tensions derived during constant myocardial oxygen consumption to predict the change in coronary flow observed when myocardial oxygen consumption was increased by pacing. The data indicate that approximately 40% of the functional hyperemic response to pacing tachycardia was predicted by the observed changes in coronary venous oxygen and carbon dioxide tensions, regardless of whether the individual (paired design) or average (n=7) regression relation was used (Table 1). Previous studies have suggested a role for oxygen and carbon dioxide tensions in the regulation of flow. Drake-Holland et al36 constructed a mathematical model that assigned the control of coronary vascular resistance to myocardial (venous) oxygen tension. This model qualitatively described changes in coronary vascular resistance to changes in coronary perfusion pressure (autoregulatory adjustments) and to increases in heart rate. Case et al37 reported a linear relation between coronary vascular resistance and flow during local alterations in coronary arterial gas tension. Mohrman and Regal24 reported that there was a consistent hyperbolic relation among skeletal muscle blood flow and venous oxygen and carbon dioxide tensions in exercising muscle even in the presence of hypocapnia or hypercapnia. These studies are correlative in nature and support a role for oxygen and carbon dioxide tensions in the control of flow but do not constitute a sufficient test of such a hypothesis.

It should be emphasized that the functional hyperemia in the present experiments was modest, since myocardial oxygen consumption was increased by only about 50%. This is far below the fourfold to fivefold increase in myocardial oxygen consumption and coronary flow associated with maximal exercise.37,38 Under such circumstances, the described relation among coronary venous oxygen and carbon dioxide tensions and coronary flow would predict less than 40% of the functional hyperemia, since the changes in coronary venous oxygen and carbon dioxide tensions are no greater than observed in the present study. During physiological conditions, coronary blood flow will be under autonomic control, as well as local metabolic control, which is the topic of the present investigation.2

The assumption underlying the present study is that coronary venous oxygen and carbon dioxide gas tensions may be used to estimate myocardial gas tensions. Any type of shunting will adversely affect the relation between coronary venous and myocardial gas tensions. Experiments with various diffusible indicators indicate that countercurrent diffusional shunting occurs in the myocardium39;40; however, Katz and Feigl41 found that the magnitude of countercurrent diffusional shunting of carbon dioxide is quite small. Thus, countercurrent diffusional shunting of carbon dioxide or oxygen probably does not affect the results of the present study. Any heterogeneity in the match between local metabolism and microvascular flow (including nonexchanging shunts) will result in a disparity between tissue and venous oxygen tensions analogous to alveolar ventilation/flow (VA/Q) heterogeneity in the lung, causing an alveolar–arterial difference. Metabolism/flow heterogeneity will produce a mixed coronary venous oxygen tension that is higher than the average tissue value in the myocardium, and this could be a reason that changes in coronary blood flow cannot be completely predicted from venous measurements. Microelectrode studies in saline-perfused cat hearts and blood-perfused dog hearts indicate that there is a wide range of tissue oxygen tension values.42,43 The tissue distribution of oxygen tensions is skewed toward low oxygen tensions with 60% of the myocardial oxygen tension values below coronary venous oxygen tension. Case et al44 found good agreement between myocardial carbon dioxide tension measured with a tissue electrode and the venous carbon dioxide tension.
The simple explanation why only 40% of functional hyperemia could be predicted from the venous oxygen and carbon dioxide tensions in the present experiment is that other controlling factors, such as adenosine or potassium, are involved. The effects caused by oxygen and carbon dioxide could be mediated by adenosine; the present study is not a test of the adenosine hypothesis. Also, the independent effects of arterial oxygen and carbon dioxide tensions on coronary conductance cannot be excluded by the present experiments. The present results do not indicate what other factors might be involved in functional hyperemia.

In conclusion, steady-state myocardial oxygen and carbon dioxide tensions, as measured by coronary venous oxygen and carbon dioxide tensions, synergistically interact to alter coronary flow at a constant myocardial oxygen consumption during changes in arterial oxygen and carbon dioxide tensions. This relation predicts approximately 40% of the functional hyperemia observed in response to pacing tachycardia.

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Synergistic action of myocardial oxygen and carbon dioxide in controlling coronary blood flow.

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