Effect of Arterial Hypoxia on Myocardial Oxygen Consumption

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ABSTRACT
To evaluate the effect of arterial hypoxia on myocardial oxygen consumption (MVO₂) under controlled conditions of stable or decreased contractility and tension, 18 anesthetized, adrenergically blocked dogs on right heart bypass were studied. Heart rate, cardiac output, pH, and Pco₂ were constant. In 9 dogs, progressive decreases in arterial oxygen content were associated with progressive significant increases in MVO₂ to a peak of 1.5 ± 0.5 ml/min 100 g⁻¹ left ventricle (P < 0.005) above the control level at an arterial oxygen content of 7-9 ml/100 ml blood (Po₂ = 30 mm Hg). This value represents a 19% increase from a control MVO₂ of 7.9 ml/min 100 g⁻¹ left ventricle (arterial oxygen content 15-18 ml/100 ml blood, Po₂ > 200 mm Hg). Progressive decreases occurred in mean aortic pressure (P < 0.001) and tension-time index (P < 0.001) with no significant change in mean ejection rate, left ventricular dP/dt, or left ventricular end-diastolic pressure. Quantitatively similar increases in MVO₂ with controlled hemodynamics were found when coronary flow was held constant (5 dogs), after catecholamine depletion with reserpine (2 dogs), and in the beating, empty ventricle (2 dogs). Thus, arterial hypoxia results in (1) an increase in MVO₂ despite no change or a decrease in the magnitude of the hemodynamic parameters correlated with MVO₂ and (2) a decrease in myocardial efficiency.

KEY WORDS
determinants of myocardial oxygen consumption dog hypoxemia myocardial efficiency coronary blood flow contractility reserpine hemodynamic variables

To date, hemodynamic studies (1, 2) have suggested that the change from full arterial oxygenation to hypoxia is associated with a decrease in myocardial oxygen consumption (MVO₂). It has been suggested that this decrease represents a favorable metabolic response of the myocardium in which the heart decreases its oxygen demand to match oxygen delivery (1). However, these experiments were not hemodynamically controlled, and it is not clear to what extent decreases in the hemodynamic correlates of MVO₂ might have been responsible for the observed results. Furthermore, the importance of the contractile state in determining myocardial oxygen demand had not been elucidated at the time these studies were undertaken.

Recent morphologic (3, 4) and biochemical (5-9) observations have identified several direct effects of ischemia and hypoxia which might influence MVO₂ independently of hemodynamic changes. These effects include alterations in mitochondrial structure and function (3-5), intramyocardial accumulation of free fatty acids (6-8), and intramitochondrial accumulation of calcium (4, 9). All three phenomena have been associated with either uncoupling of oxidative phosphorylation or stimulation of nonphosphorylation-linked oxygen consumption. These observations suggest that oxidative metabolism may be sensitive to oxygen supply and that even relative oxygen insufficiency (arterial hypoxia) may lead to an increase in MVO₂.

Thus, a physiological investigation of the effect of hypoxia on MVO₂ under controlled hemodynamic conditions was undertaken. This study attempted to identify the effect of progressive decreases in arterial oxygen content on MVO₂, to determine at what level of hypoxia the observed effects are maximal, and to examine the influence of deliberate alterations in cardiac hemodynamics on the relationship between MVO₂ and arterial oxygenation.
Methods

Mongrel dogs of either sex weighing 25–35 kg were anesthetized with chloralose (60 mg/kg, iv) and urethane (600 mg/kg, iv). Tracheal intubation was performed, and respiration was achieved with a Harvard respirator using various gas mixtures. A medial sternotomy was performed, and a modified right heart bypass preparation was used (Fig. 1). After administration of heparin (3 mg/kg, iv), the superior and inferior venae cavae were cannulated, and the azygos vein was divided. The caval return was directed to a reservoir through a bubble oxygenator and heat exchanger (37 ± 0.5°C) and was returned through a variable speed, calibrated roller pump to the pulmonary artery. This flow was held constant throughout each experiment, thus maintaining a constant left ventricular output. The use of the bubble oxygenator allowed deliberate alterations in arterial oxygen content. A ligature placed around the pulmonary artery completed the isolation of the right heart, which then received only coronary venous drainage. Total coronary flow minus left ventricular thebesian flow was led by siphon drainage from the cannulated right atrium and ventricle to the venous reservoir, which was situated at least 20 cm below the level of the atrium and ventricle. Timed 1-minute volumetric collections of coronary venous blood allowed total coronary blood flow to be quantified. Right ventricular and right atrial pressures were not monitored, but both chambers remained flaccid without visible distention throughout all experiments.

Aortic pressure was controlled by a second separate roller pump from the heat exchanger which pumped blood into or out of the femoral arteries depending on whether the aortic pressure was to be raised or lowered. This procedure allowed deliberate decreases in aortic pressure so that all of the hemodynamic parameters correlated with MVO₂ could be kept constant or decreased. Thus, whenever left ventricular end-diastolic pressure tended to rise with the development of hypoxia, aortic pressure was lowered sufficiently to maintain end-diastolic pressure at the control level. Left ventricular pressure, left ventricular end-diastolic pressure, and the peak first derivative of left ventricular pressure (dP/dt) were measured through a short, wide-bore, Y-shaped polyethylene catheter inserted through the apex of the left ventricle. The proximal aortic pressure was measured through a short, wide-bore polyethylene catheter inserted into the aortic arch through the left carotid artery. All pressures were measured with Statham P23Db pressure transducers; the frequency response of the pressure measurement system was linear up to 30 cycles/sec. The rate of rise of left ventricular dP/dt was obtained by a resistance-capacitance electronic differentiator of the full left ventricular pressure. Calibration of the left ventricular dP/dt differentiator was accomplished by supplying a wave form of known slope to a differentiating circuit, which had a time constant of 0.001 seconds and a cutoff at 160 cycles/sec.

All measured variables were recorded on a multi-channel Sanborn direct-writing oscillograph. After the sinoatrial node was crushed, heart rate was controlled by atrial pacing at a constant rate throughout each experiment. Mecamylamine hydrochloride (Inversine) (100 mg in 10 ml of normal saline) was given intravenously during a 1-minute infusion to the experimental dogs prior to study. All dogs, except those used in the norepinephrine studies and in one of the catecholamine-depletion experiments, received 15—25 mg of propranolol in 15 ml of normal saline intravenously during a 1-minute infusion prior to the experiment. Maintenance of β-receptor blockade was checked by injecting isoproterenol (2–5 µg in 1–3 ml of saline into the pulmonary artery or 0.20 µg directly into a left coronary perfusion line) at the end of every experiment. Prior to the administration of propranolol this amount of isoproterenol produced a 50% increase in left ventricular dP/dt and a lowering of left ventricular end-diastolic pressure. After β-receptor blockade there was no response to the injection of isoproterenol.

To achieve arterial hypoxia, the bubble oxygenator and the Harvard respirator were ventilated with various mixtures of oxygen and nitrogen, all containing 5% CO₂; 15 minutes were allowed for equilibration with different gas mixtures. A steady state of coronary blood flow and arteriovenous oxygen difference was achieved in 8–10 minutes. The steady state was confirmed using an online Guyton arteriovenous oxygen difference analyzer and repetitive coronary blood flow measurements. The arteriovenous oxygen difference analyzer received
arterial blood from the aortic root or the left coronary perfusion line, when one was in use; it received coronary venous blood from the catheter draining the right atrium and ventricle close to the point at which this catheter left the heart. After 15 minutes the hemodynamic data were recorded and arterial and coronary venous blood were obtained for determination of oxygen content (by the method of Van Slyke and Neill [10]). PO₂, PCO₂, pH, hematocrit, and electrolyte concentrations. Total coronary flow was measured, and MVO₂ was calculated as total coronary flow/100 g left ventricle times the coronary arteriovenous oxygen difference. All measurements were done in duplicate. Duplicate determinations differed by 0.2 ml/100 ml blood or less in 98% of all measurements. No difference greater than 0.3 ml/100 ml blood was considered acceptable. Data were collected with ventilation with gas mixtures which ranged from 95% O₂ to 5% O₂; the precontrol and the postcontrol runs of every experiment were conducted with 95% O₂. Precontrol and postcontrol data were averaged and the mean was compared with the hypoxic data (nine dogs).

A second series of experiments (five dogs) was conducted with the above preparation and protocol but with left coronary blood flow held constant. This procedure was accomplished by ligating a Gregg cannula into the ostium of the main left coronary artery and perfusing this artery with a separate calibrated roller pump.

In four dogs the effects of norepinephrine infusion were studied. With left coronary blood flow held constant, 0.2–0.8 μg/min of norepinephrine was infused into a Gregg cannula during the final 10 minutes of a 20–25-minute period of equilibration with each of several gas mixtures. Data collected before the administration of norepinephrine and data collected during infusion of norepinephrine were obtained as they were in the previously described experiments. In these experiments coronary venous blood was returned to a second reservoir, oxygenator, and heat exchanger separate from the reservoir, oxygenator, and heat exchanger to which systemic venous blood was returned. This procedure allowed the total isolation of the left coronary circulation. Thus, in these experiments hypoxia was created only in the left coronary circulation while the remainder of the dog was perfused with well-oxygenated blood. This process eliminated the possible influence of peripherally released metabolites on MVO₂.

Two experiments in two dogs were conducted with a second wide-bore polyethylene catheter inserted into the apex of the left ventricle with the dog on total cardiopulmonary bypass. This catheter allowed continuous siphon drainage of the left ventricle and maintained left ventricular pressure at less than zero during systole and diastole. Experiments with uncontrolled coronary flow similar to those above were performed.

Two dogs were treated with reserpine (0.5 mg/kg/day, im) for 2 days prior to study. One of these dogs was studied with uncontrolled coronary blood flow and with ganglionic (mecamylamine HCl) and β-receptor blockade (propranolol). The second dog was studied with left coronary blood flow held constant and an isolated left coronary system; this experiment was conducted without β-receptor blockade. Adequacy of catecholamine depletion was tested by injecting tyramine (30 mg) into the pulmonary artery in the experiment without coronary cannulation and directly into the left coronary artery (5 mg) in the experiment with coronary cannulation. No response was seen in the reserpinized dogs. A similar dose of tyramine in nonreserpinized dogs resulted in at least a 50% increase in left ventricular dp/dt and a decrease in left ventricular end-diastolic pressure.

The tension-time index was obtained by visually integrating the area under the systolic portion of the aortic pressure tracing. This time interval was taken from the initial point of aortic ejection to the dicrotic notch. Statistical analysis was performed using Student's t-test (11).

**Results**

Progressive decreases in arterial oxygen content resulted in progressive increases in MVO₂ despite no change or a decrease in the hemodynamic parameters correlated with MVO₂. The MVO₂ data for nine dogs are shown in Figure 2. These mean values were obtained at corresponding points from the best-fit plot of each experiment. MVO₂ was plotted as the absolute change from the mean of the precontrol and postcontrol values. The postcontrol values returned to or toward the precontrol values in every experiment. There was a progressive

![Figure 2](https://example.com/figure2.png)

**FIGURE 2**

Mean myocardial oxygen consumption (MVO₂) data for nine experiments. The mean change from control oxygen consumption is plotted as a function of arterial oxygen content and arterial Po₂. Note the progressive increase in MVO₂ peaking at an arterial oxygen content of 7.9 ml/100 ml blood. Mean control MVO₂ equaled 7.9 ± 0.6 ml/min 100 g⁻¹ left ventricle. Asterisks indicate statistical significance (P < 0.05).
increase in MVO₂ with increasing hypoxia, which became significant at an arterial oxygen content of 12-13 ml/100 ml blood (Po₂ = 40 mm Hg). A peak in MVO₂ of 1.5 ± 0.5 (SE) ml/min 100 g⁻¹ left ventricle above control occurred at an arterial oxygen content of 7-9 ml/100 ml blood (Po₂ = 30-35 mm Hg). The mean control MVO₂ equaled 7.9 ± 0.6 ml/min 100 g⁻¹ left ventricle. The peak in oxygen consumption was followed by a decline in MVO₂ at lower arterial oxygen contents, presumably because, at these very hypoxic levels, oxygen delivery limited MVO₂.

The associated changes in coronary blood flow and venous oxygen content are shown in Figure 3. Progressive hypoxia led to a progressive rise in coronary blood flow and a progressive narrowing of the coronary arteriovenous oxygen difference. At an arterial oxygen content of 8 ml/100 ml blood, the point at which oxygen consumption peaked, coronary blood flow rose to 230 ml/min 100 g⁻¹ left ventricle from a control of 100 ml/min 100 g⁻¹ left ventricle, and the arteriovenous oxygen difference decreased to 3.9 ml/100 ml blood from 7.9 ml/100 ml blood.

The associated hemodynamic data for these experiments are shown in Figure 4. There was a progressive significant decrease in tension-time index, mean aortic pressure, and peak left ventricular pressure with hypoxia. Left ventricular end-diastolic pressure, left ventricular dP/dt, and mean ejection rate did not change significantly at any hypoxic level.

Two dogs not included in these mean data were treated with reserpine prior to study (Table 1). In the experiment with uncontrolled coronary blood flow there was no change in any of the measured hemodynamic parameters with hypoxia. In the experiment with constant coronary flow, hypoxia was associated with decreases in mean aortic pressure, peak left ventricular pressure, left ventricular end-diastolic pressure, left ventricular dP/dt, and mean ejection rate. MVO₂ increased progressively with progressive decreases in arterial oxygen content in both experiments. The peak hypoxic increases in oxygen consumption for these two experiments were 1.8 ml/min 100 g⁻¹ left ventricle.

![Figure 3](image)

**Figure 3**
Response of total coronary blood flow and venous oxygen content to hypoxia in the nine experiments of Figure 2.

![Figure 4](image)

**Figure 4**
Mean hemodynamic data for the nine experiments shown in Figure 2. The change in each hemodynamic parameter from control is plotted as a function of arterial oxygen content. Control values are: tension-time index (TTI) = 2400 ± 110 mm Hg sec/min, mean aortic pressure (MAP) = 80 ± 3 mm Hg, peak left ventricular pressure (LVP) = 99 ± 3 mm Hg, left ventricular end-diastolic pressure (LVEDP) = 6.4 ± 0.5 cm H₂O, left ventricular dP/dt = 3100 ± 300 mm Hg/sec, and mean ejection rate (MER) = 89 ± 6 ml/sec. Heart rate was maintained constant at a mean value of 127 ± 3 beats/min. Asterisks indicate statistical significance (P < 0.05).
and 1.7 ml/min 100 g⁻¹ left ventricle, respectively.

To investigate the possibility that increases in MV0₂ were secondary to increases in coronary blood flow which occurred with hypoxia, five dogs were studied with left coronary blood flow maintained constant (Table 2). Left coronary blood flow in these experiments was maintained at 145 ± 7 ml/min 100 g⁻¹ left ventricle. The small increment in total coronary flow which occurred with hypoxia probably represented a small change in right coronary artery blood flow. MV0₂ rose with hypoxia to a peak of 2.6 ± 0.3 ml/min 100 g⁻¹ left ventricle (P < 0.005) above a control value of 5.8 ± 0.7 ml/min 100 g⁻¹ left ventricle. The coronary arteriovenous oxygen difference increased 1.7 ± 0.1 ml/100 ml blood (P < 0.0005) at the peak of MV0₂ from a control of 3.9 ± 1.2 ml/100 ml blood. There was virtually no change in the measured hemodynamic parameters accompanying the increases in MV0₂. Since left ventricular end-diastolic pressure showed little tendency to rise during hypoxia, aortic pressure was maintained nearly constant.

To examine the relationship between MV0₂ and its hemodynamic determinants during hypoxia, four dogs were studied before and during infusion of norepinephrine. Data from a representative experiment are shown in Figure 5. At the levels of oxygenation studied, nearly parallel increases in MV0₂ with infusion of norepinephrine were coupled with nearly parallel increases in left ventricular dP/dt. In all experiments in which infusion of norepinephrine caused nearly parallel shifts in the curves relating the measured hemodynamic parameters to arterial oxygen content, a similar shift in the oxygen consumption curve was also observed (three of four dogs). Aortic pressure was maintained constant throughout each experiment. These experiments were conducted using an isolated left coronary perfusion system, and the left coronary circulation alone was made hypoxic. Prior to infusion of norepinephrine hypoxia was associated with an increase in MV0₂ of 2.3 ± 0.4 ml/min 100 g⁻¹ left ventricle from a control MV0₂ of 5.7 ± 0.6 ml/min 100 g⁻¹ left ventricle (P < 0.05).

To rule out the possibility that hypoxia-induced ventricular compliance changes cause increased intraventricular tension despite constant left ventricular end-diastolic pressure, two dogs were studied with intraventricular pressure maintained at less than zero. There was, therefore, no systolic or diastolic tension developed. Control MV0₂ was 2.8
ml/min 100 g⁻¹ left ventricle and 4.1 ml/min 100 g⁻¹ left ventricle and rose to 5.3 ml/min 100 g⁻¹ left ventricle and 5.8 ml/min 100 g⁻¹ left ventricle at an arterial oxygen content of 6.2 ml/100 ml blood and 7.5 ml/100 ml blood for the two dogs, respectively. Heart rate and aortic pressure were maintained constant in these experiments. Coronary blood flow was uncontrolled and increased 240% and 330%, respectively, at the hypoxic peak of MVO₂.

There was no significant change in arterial pH, Pco₂, hematocrit, or sodium or potassium concentration with progressive hypoxia. The mean data for all experiments are given in Table 3.

**Discussion**

These data establish that a substantial increase in MVO₂ that does not depend on increases in the hemodynamic correlates of MVO₂ occurs with systemic hypoxia. This increase in MVO₂ rises progressively to a peak with progressive systemic hypoxia. Correlation of the increase in MVO₂ with associated hemodynamic variables establishes that a decreased arterial oxygen content is associated with a decreased myocardial efficiency.

In the present study the progressive increases in MVO₂ with hypoxia were associated with either intentional progressive decreases or no change in the hemodynamic parameters correlated with oxygen consumption. These parameters include the
HYPOXIA AND CARDIAC OXYGEN CONSUMPTION

TABLE 3

Effect of Hypoxia on Arterial Plasma pH, Pco2, Hematocrit, and Electrolytes

<table>
<thead>
<tr>
<th></th>
<th>pH</th>
<th>Pco2</th>
<th>Hematocrit (%)</th>
<th>Potassium (mEq/liter)</th>
<th>Sodium (mEq/liter)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>7.32 ± 0.2</td>
<td>52 ± 3</td>
<td>30 ± 1</td>
<td>3.0 ± 0.1</td>
<td>152 ± 1</td>
</tr>
<tr>
<td>Hypoxic peak in MVO2</td>
<td>7.33 ± 0.2</td>
<td>49 ± 3</td>
<td>31 ± 1</td>
<td>3.1 ± 0.1</td>
<td>153 ± 1</td>
</tr>
</tbody>
</table>

All values are means ± SE. There was no significant change with hypoxia.

tension-time index and the left ventricular end-diastolic pressure as indexes of tension development (12–14) and the left ventricular dP/dt and the mean ejection rate as indexes of velocity of contraction (15, 16). The tension-time index decreased with hypoxia, but left ventricular end-diastolic pressure did not change significantly. Assuming no change in ventricular compliance, these changes represent a decrease in systolic tension development. The experiments with the empty ventricles demonstrate that a ventricular compliance change which might increase ventricular tension despite constant or decreasing ventricular pressures does not account for the increase in MVO2 with hypoxia. In these experiments intraventricular pressure was maintained at less than 0 mm Hg so that intracavitary tension was abolished and thus could not be affected by a compliance change.

Although the base-line well-oxygenated MVO2 in the nonejecting, nonworking ventricles was less than half that in the ejecting, working ventricles, the absolute increases in MVO2 with hypoxia were similar in these two preparations. This finding suggests that the rise in MVO2 with hypoxia is independent of the base-line MVO2 and little affected by markedly dissimilar base-line hemodynamic conditions.

Furthermore, the data obtained from more precise alterations in hemodynamic conditions by the administration of norepinephrine to the adren- ergically intact hearts indicate that the relationship between MVO2 and its hemodynamic correlates is unaffected by the level of arterial oxygenation. The increases in left ventricular dP/dt with infusion of norepinephrine at the various levels of oxygenation were paralleled by the increases in oxygen consumption. Thus, the increase in MVO2 with hypoxia does not appear to depend on a distortion of the relationship between MVO2 and its hemodynamic correlates.

In the present study, observed increases in MVO2 during hypoxia cannot be explained by increases in contractility. In Figure 4 and Table 2 a constant stroke volume is associated with a constant left ventricular end-diastolic pressure and, respectively, a decreased and a constant aortic pressure. This finding suggests a mean tendency for contractility to decrease in the first group of experiments and to remain nearly constant in the second group. In a few experiments shown in Figure 4 left ventricular dP/dt remained constant or increased slightly with mild hypoxia, but aortic pressure was decreased. In most experiments (Table 2) these effects were not observed. However, the apparent increase in contractility in some experiments suggests the possibility that hypoxia releases endogenous catecholamines. To eliminate the effect of any catecholamine release on hemodynamic parameters and oxygen consumption, dogs treated with reserpine were studied. These experiments show increases in oxygen consumption similar to those previously observed and an apparently unchanged or decreased contractility.

Previously Katz et al. (1) and Feinberg et al. (2) have concluded that hypoxia is associated with a decrease in MVO2. However, their experiments were not hemodynamically controlled; heart rate, blood pressure, and contractile state were allowed to vary. The discrepancy between their results and those of the present experiments probably is due to hemodynamic variation in their studies.

In the present study the data obtained from the experiments with constant coronary blood flow exclude the possibility that the increases in MVO2 with hypoxia were secondary to increases in coronary blood flow, as suggested by the experiments of Abel and Reis (17). It is also unlikely that changes in the distribution of coronary blood flow are important in the increase in MVO2 during hypoxia. In an ejecting, working ventricle, distribution of coronary blood flow is affected by tension gradients across the ventricular wall. Hypoxia may alter this tension distribution and thus alter coronary blood flow distribution. However, in a nonejecting, nonworking ventricle such tension gradients in the ventricular wall are minimized.
Thus, inequalities in coronary blood flow distribution are similarly minimized, and hypoxia does not alter the distribution of coronary blood flow. Therefore, the increases in $\text{MVO}_2$ in the experiments with nonworking ventricles suggest that changes in coronary flow distribution are not responsible for observed increases in $\text{MVO}_2$.

The possibility that a peripherally released substance might lead to the observed increases in $\text{MVO}_2$ with hypoxia was also investigated. For example, increasing the plasma free fatty acid concentration can increase $\text{MVO}_2$ independently of hemodynamic changes (18). However, the experiments using different perfusion systems for the left coronary artery and the remainder of the circulation demonstrated that this phenomenon was not responsible for the increase in $\text{MVO}_2$ observed in the present study.

This hemodynamic study does not provide insight into the precise biochemical mechanism(s) responsible for the present observations. The range of arterial oxygenation over which oxygen consumption is first increased has not been associated with the conversion to anaerobic metabolism (19, 20). Therefore, the observations of this study do not depend solely on anaerobic metabolism. Detailed biochemical investigation is needed to determine the precise mechanism(s) responsible for the increase in $\text{MVO}_2$ during systemic hypoxia observed in this study.

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References

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