INCREASES IN CORONARY VASCULAR RESISTANCE RELATED TO HIGH ARTERIAL OXYGEN TENSION IN DOGS

Kinji Ishikawa, Ken Kanamasa, Tetsu Yamakado, Yasuyuki Kohashi, Arata Kato, Shohei Otani, Takeo Hayashi, Ryo Katori

It is known that oxygen inhalation induces coronary vessel constriction as well as brings about a reduction in myocardial oxygen consumption. The present study was performed to clarify whether or not this constriction of the coronary vessels resulting from oxygen is secondary to the reduction in myocardial oxygen consumption. The regional myocardium in 12 mongrel dogs was perfused with femoral arterial blood at a constant rate of flow. While maintaining myocardial oxygen consumption equal by adjusting heart rate, coronary vascular resistance was compared under the two following conditions: 1) perfusion of the coronary artery with the dog's own femoral arterial blood (pO₂: 95 ± 14 mmHg) and 2) perfusion with blood with a high level of oxygen tension (pO₂: 497 ± 56 mmHg). Coronary vascular resistance was increased (p < 0.001) from 3.00 ± 1.25 to 3.36 ± 1.28 mmHg/ml/min by increasing the pO₂ in the perfusing blood, even though myocardial oxygen consumption was kept at the same level. This increase in coronary vascular resistance resulting from the increase in oxygen tension was independent of the coronary perfusion rate as well as independent of the presence or absence of myocardial ischemia. This suggests that coronary vasoconstriction due to oxygen is not secondary to decreases in myocardial oxygen demand.

The effectiveness of oxygen inhalation therapy for the treatment of acute myocardial infarction is still controversial.2 One may assume that oxygen inhalation causes an increase in oxygen delivery to the ischemic myocardium, however this has been shown not to be true.3 Although the oxygen content of coronary arterial blood is elevated by oxygen inhalation, the coronary artery is constricted and coronary blood flow is decreased by such inhalation resulting in no net increase in myocardial oxygen delivery.4 Since myocardial oxygen consumption is reduced along with the reduction in coronary blood flow resulting from oxygen inhalation, constriction of the coronary artery may be a secondary response to the reduction in myocardial oxygen consumption. If coronary blood flow is decreased because the myocardium needs less oxygen, oxygen inhalation induced coronary vasoconstriction might not be harmful. However, if coronary blood flow is reduced independent to the need of oxygen in the myo-

Key Words:
Coronary artery
Vasoconstriction
Oxygen inhalation therapy
Myocardium

(Received on January 25, 1980; Accepted on April 18, 1980)
The First Department of Internal Medicine, Kinki University School of Medicine, Sayama, Osaka 589, Japan
Name and address for mailing proofs: Kinji Ishikawa, M.D., The First Department of Internal Medicine, Kinki University School of Medicine, Sayama, Osaka 589, Japan

Japanese Circulation Journal Vol. 44, September 1980 749
cardium, oxygen inhalation therapy might be harmful.

In order to investigate whether or not coronary vasoconstriction due to elevated arterial pO₂ is a secondary response to decreases in myocardial oxygen consumption, the regional myocardium was perfused at a constant flow rate with blood at normal pO₂ and with blood at high pO₂ while maintaining constant myocardial oxygen consumption, and coronary vascular resistance was compared.

MATERIALS AND METHODS

Twelve adult mongrel dogs weighing 25 ± 6 kg (mean ± standard deviation) were intravenously anesthetized with pentobarbital 25 mg/kg and bilateral thoracotomies at the 5th intercostal space were performed under positive pressure breathing (tidal volume: 250–300 ml, respiratory rate 25–35 times/min, end-expiratory pressure 5–10 cmH₂O). Each dog was heparinized (150 unit/kg/hr) and a polyethylene cannula (i.d. 1.2 mm, o.d. 2.0 mm) was inserted into the left anterior descending coronary artery. Blood was perfused from the femoral artery at a constant flow rate (an arbitrary rate of approximately 30 ml/min) using a peristaltic pump (Peristaltic pump model 1203, Harvard Apparatus Co.) (Fig. 1). Coronary perfusion rate was measured using an electromagnetic flowmeter (MF-46, Nihon kohden, Japan) for mean flow, and coronary perfusion pressure was measured using a pressure transducer for mean pressure. An artificial lung was placed on a bypass in the perfusion circuit and blood with a high level of pO₂ (hyperoxic blood) was prepared by mingling the blood with a mixed gas consisting of O₂ (97.5%) and CO₂ (2.5%). A blood oxygenator filter (Temptrol; Bentley, Calif., U.S.A.) was used to prevent embolism from blood clots or air bubbles. The dead space blood volume from the femoral artery to the coronary artery through the artificial lung was about 100 ml. It was confirmed that there was no hemolysis present in the
Coronary Vascular Resistance at High pO₂

Fig. 2. Comparison of coronary vascular resistance between normoxia and hyperoxia under identical myocardial oxygen consumption.

oxygenated blood. A polyethylene tube was inserted into the coronary vein of the perfused region in order to measure the myocardial oxygen consumption in the perfused area and coronary venous blood was drawn for analysis. This method of venous sampling was shown to be superior to coronary sinus blood sampling in verifying regional myocardial metabolism.

A myocardial strain gauge arch (HD-1T, Nihon Kohden, Japan) was sutured into the superficial layer of the myocardium of the perfused area about 2–3 mm in depth in a direction parallel with the muscular fiber, and fixed to extend the initial length of the myocardium by 10–20%. The sinus node was crushed and pacing electrodes were sutured to the right atrial appendage to pace the heart at a constant rate so as to maintain myocardial oxygen consumption. A relatively high pacing rate was used to overcome bouts of spontaneous tachycardia. Aortic pressure was monitored by inserting a catheter into the aorta. Aortic flow was measured by putting an electromagnetic flowmeter (MF-46) at the aortic root. Blood pO₂, pH, and pCO₂ were measured using a blood pO₂ analyzer (ABL-1, Radiometer) and blood oxygen content using an oxygen content analyzer (Lex-O₂CON, Lexington Instruments). Coronary vascular resistance was calculated as the ratio of the mean coronary perfusion pressure to the mean coronary perfusion rate. Cannula resistance was corrected for each flow rate after each experiment. Myocardial oxygen consumption was calculated as the product of the mean coronary perfusion rate and the difference in oxygen content between coronary arterial blood and coronary venous blood. After completion of the experiment, India ink was infused into the polyethylene tube to stain the myocardium. The stained portion was excised in order to measure the weight of the perfused myocardium. The hearts weighed 185 ± 45 g on the average, the left ventricle including the interventricular septum 114 ± 25 g and the perfused myocardium 32 ± 12 g, equivalent to 28 ± 8% of the left ventricle.

The experiment was performed according to the following protocol. Under a given heart rate the myocardium was perfused with femoral arterial blood (normoxia) for 8 minutes. Recordings and blood samplings were made within the last 2 minutes. Then the perfused blood was changed from normoxic blood to blood with a high level of pO₂ (hyperoxia) and the heart rate was fixed at an arbitrary rate for 8 more minutes. Then measurements were performed in the same manner as during the perfusion with normoxic blood. Myocardial oxygen consumption was immediately calculated. If the calculated myocardial oxygen consumptions did not match with each other within a difference of less than ±2% between the two experiments (normoxia and hyperoxia), the heart rate was changed (usually decreased) in hyperoxia so that the myocardial oxygen consumption was equalized to within a difference of 2%. Accordingly, multiple paired experiments at different heart rates were performed in order to obtain a sufficient number of successful experiments. In addition, experiments in which the mean aortic pressure between normoxia and hyperoxia varied more than ±2 mmHg were discarded. To cancel out any effects due to the order of coronary perfusion, the experiment was performed in two different ways; normoxia...
TABLE 1 CHANGES OF CORONARY VASCULAR RESISTANCE AND OTHER PARAMETERS BY PERFUSION WITH BLOOD AT HIGH pO₂

<table>
<thead>
<tr>
<th></th>
<th>Myocardium perfused with</th>
<th>Difference (Hyperoxia) – (Normoxia)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Femoral arterial blood (Normoxia)</td>
<td>Blood at high pO₂ (Hyperoxia)</td>
<td></td>
</tr>
<tr>
<td>Perfusion rate</td>
<td>(ml/min/100g)</td>
<td>108.4 ± 51.4*</td>
<td>0.4 ± 1.9</td>
</tr>
<tr>
<td>Coronary perfusion pressure (mmHg)</td>
<td>98.6 ± 64.3</td>
<td>111.4 ± 69.2</td>
<td>12.8 ± 14.2</td>
</tr>
<tr>
<td>Regional myocardial oxygen consumption (ml/min/100g)</td>
<td>7.27 ± 1.72</td>
<td>7.28 ± 1.74</td>
<td>(0.2 ± 1.1)‡</td>
</tr>
<tr>
<td>Coronary vascular resistance (mmHg/ml/min)</td>
<td>3.00 ± 1.25</td>
<td>3.36 ± 1.28</td>
<td>(13.7 ± 16.2)</td>
</tr>
<tr>
<td>Pacing rate (beats/min)</td>
<td>179 ± 34</td>
<td>159 ± 21</td>
<td>-20 ± 24</td>
</tr>
<tr>
<td>Mean aortic pressure (mmHg)</td>
<td>95 ± 15</td>
<td>94 ± 15</td>
<td>-1 ± 3</td>
</tr>
<tr>
<td>Myocardial contractile force (g)</td>
<td>4.1 ± 3.0</td>
<td>5.2 ± 2.6</td>
<td>1.1 ± 1.7</td>
</tr>
<tr>
<td>Coronary perfusing blood Oxygen content (ml/100ml)</td>
<td>13.8 ± 1.9</td>
<td>15.8 ± 2.0</td>
<td>2.0 ± 0.6</td>
</tr>
<tr>
<td>pO₂ (mmHg)</td>
<td>95 ± 14</td>
<td>497 ± 56</td>
<td>402 ± 56</td>
</tr>
<tr>
<td>pH</td>
<td>7.400 ± 0.118</td>
<td>7.383 ± 0.095</td>
<td>-0.017 ± 0.057</td>
</tr>
<tr>
<td>pCO₂ (mmHg)</td>
<td>29 ± 9</td>
<td>31 ± 8</td>
<td>2 ± 5</td>
</tr>
<tr>
<td>Hb (g/100ml)</td>
<td>15.2 ± 2.9</td>
<td>15.0 ± 3.0</td>
<td>-0.2 ± 0.8</td>
</tr>
<tr>
<td>Coronary venous oxygen content (ml/100ml)</td>
<td>4.3 ± 1.2</td>
<td>6.4 ± 1.3</td>
<td>2.1 ± 0.6</td>
</tr>
<tr>
<td>Myocardial oxygen extraction (%)</td>
<td>56.7 ± 21.5</td>
<td>49.2 ± 18.6</td>
<td>-7.5 ± 3.9</td>
</tr>
</tbody>
</table>

*mean ± one standard deviation  †not significant (p value more than 0.05) ‡( ) indicates that the difference is calculated as (Hyperoxia) – (Normoxia) / (Normoxia) x 100 (%)

preceding hyperoxia and vice versa. The significance of the differences was calculated using the t test for paired samples.

RESULTS

Calculated myocardial oxygen consumptions were equal between paired experiments under perfusion with blood at normal pO₂ (normoxia) and blood at high pO₂ (hyperoxia) in 34 experiments. The coronary perfusion rate was 34–148 ml/min/100 g. The coronary perfusion blood pO₂ level was 95 ± 14 mmHg for normoxia and 497 ± 56 mmHg for hyperoxia, but blood pCO₂ and pH showed no significant variations between the two conditions. Myocardial oxygen consumptions coincided when the heart rate for hyperoxia was on the average 20 ± 24 beats less than for normoxia. Under such a state, coronary vascular resistance increased for hyperoxia in comparison with normoxia in 29 of the 34 experiments (Figure 2), amounting to an increase of 13.7% on the average. There were no consistent changes in systemic arterial pressure, myocardial contractile force or systemic arterial oxygen tension.

In the 20 experiments in which normoxia was first, coronary vascular resistance was elevated by 8.5 ± 8.0% (p <0.001) under hyperoxia, and in the 14 experiments in which normoxia followed hyperoxia it was also elevated under hyperoxia by 21.4 ± 22.6% (p <0.01).

To confirm whether or not this increase in coronary vascular resistance was caused by a decrease in heart rate, the experiments were divided into two groups. In the 23 experiments in which the heart rate was decreased during hyperoxia (by 34 ± 13 beats), coronary vascular resistance increased by 15.6 ± 18.9% (p <0.001). In the other 11 experiments in which the heart rate was increased by 9 ± 14 beats during hyperoxia, coronary vascular resistance still significantly increased during hyperoxia by 8.8 ± 8.0% (p <0.01).

To confirm whether or not coronary vascular resistance response to hyperoxia depends on the coronary perfusion rate, the data was arbitrarily divided into the following three groups according to the rate of perfusion: 5 experiments in which the coronary artery was relatively underperfused (53 ± 11 ml/min/100 gm), 18 experiments in

Japanese Circulation Journal Vol. 44, September 1980
which the coronary perfusion rate was within the normal range \(84 \pm 15\ \text{ml/min/100 gm}\), and 11 experiments in which the coronary perfusion rate was relatively high \((174 \pm 31\ \text{ml/min/100 gm})\). In all three groups the coronary vascular resistance increased; yielding values of \(9.2 \pm 3.2\%\ (p < 0.1), 18.7 \pm 20.1\%\ (p < 0.001),\) and \(7.3 \pm 8.7\%\ (p < 0.05),\) respectively.

Since myocardial oxygen extraction rate is one of the indices demonstrating myocardial ischemia, the results were also divided into three groups according to the myocardial oxygen extraction rate in order to evaluate the grade of ischemia: 11 experiments in which the myocardial oxygen extraction rate was relatively high \((77 \pm 4\%\), suggesting the presence of myocardial ischemia, 11 experiments with a normal myocardial oxygen extraction rate \((64 \pm 3\%\), and 12 experiments in which the myocardial oxygen extraction rate was relatively low \((34 \pm 17\%),\) suggesting excessive oxygen delivery to the myocardium. Coronary vascular resistance increased in these three groups \((7.3 \pm 6.1\%, p < 0.05; 20.0 \pm 22.9\%, p < 0.01; 13.4 \pm 13.9\%, p < 0.001,\) respectively).

**DISCUSSION**

The present study indicated that oxygen inhalation causes coronary vasoconstriction independent to the need to oxygen in the myocardium. Maroko et al.\(^6\) postulated that oxygen may constrict the coronary arteries in normal tissue and increase the pressure gradient between the normal and ischemic areas, diverting more blood to the injured zone. Williams et al.\(^7\) also assumed that oxygen inhalation causes a reduction in coronary blood flow only in a normal myocardium but not in an ischemic myocardium. These assumptions\(^6,7\) seem reasonable since according to the broad meaning of autoregulation an organ may have a capability to regulate its blood supply in accordance with its needs.\(^8\) Rubio et al.\(^9\) demonstrated that a myocardium falling into ischemia delivers vasoactive metabolites to dilate the coronary vessels. These mechanisms\(^8,9\) might be effective in preventing coronary vasoconstriction caused by oxygen inhalation in an ischemic myocardium. However, it has been shown that coronary blood flow in the regional myocardium is reduced by oxygen inhalation in dogs wherein the blood supply has been acutely reduced\(^3\) in patients with coronary artery disease\(^4\) as well as in normal myocardium and in myocardium under various other conditions\(^10–13\) the degree of coronary blood flow reduction being approximately the same in all cases.

Daniell and Bagwell\(^14\) recorded coronary blood flow and myocardial contractile force simultaneously and found that coronary blood flow is decreased by oxygen inhalation prior to the reduction in the myocardial contractile force. If the reduction in coronary blood flow is secondary to the reduction in myocardial contractile force and myocardial oxygen consumption, the decrease in coronary blood flow cannot precede the decrease of myocardial contractile force. Lammerant et al.\(^15\) demonstrated that coronary vasoconstriction by oxygen is induced even when the nerve supply of parasympathetic, alpha- and beta-receptors was blocked. They postulated that a rise in myocardial \(\text{pO}_2\) is not likely to be primarily responsible for an elevation in coronary vascular resistance and suggested that oxygen causes a direct constrictive action on the coronary vessels. The present results favor this concept since regional coronary vascular resistance is increased even when the regional myocardium is relatively underperfused or myocardial oxygen extraction is relatively high, suggesting the presence of myocardial ischemia.

The above reports\(^2,4,14,15\) together with the present study, suggest that oxygen causes coronary vasoconstriction independent of the oxygen need of the supplying myocardium. If oxygen is administered, coronary blood flow in the ischemic myocardium might be reduced further in patients complaining of angina or in patients with acute myocardial infarctions.

**REFERENCES**

5. OWEN P, THOMAS M, YOUNG V, OPIE L: Comparison between metabolic changes in local