THE FAILURE OF OXYGEN BREATHING TO DECREASE
THE MYOCARDIAL CONTRACTILE FORCE IN DENERVATED DOGS

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This study was done to discover whether or not the oxygen-induced depression of sympathoadrenal activity contributes to a reduction of myocardial contractile force during oxygen breathing. In 10 open-chest dogs, myocardial contractile force was measured using a myocardial strain gauge arch during air and oxygen breathing before denervation (intact heart) and after bilateral vagotomies, sympathectomies and adrenalectomies with the intravenous administration of propranolol, phenoxycbenzamine and atropin (denervated heart). One hundred percent oxygen breathing caused similar increases in arterial $pO_2$ in both the intact (from 94 ± 10 to 442 ± 25 mmHg) and the denervated dogs (from 113 ± 11 to 456 ± 15 mmHg). Coronary blood flow measured at the left anterior descending coronary artery was reduced by oxygen breathing from 28.4 ± 3.4 to 21.7 ± 2.3 ml/min in the intact dogs, and from 19.4 ± 3.4 to 14.9 ± 2.6 ml/min in the denervated dogs. Myocardial contractile force was significantly reduced by oxygen breathing in the intact dogs (a reduction of 5.8 ± 1.4%). In the denervated dogs, on the other hand, no significant changes in myocardial contractile force was seen. This study suggests that the reduction in myocardial contractile force is mediated through sympathoadrenal activity, and thus, is abolished by sympathoadrenal blockade.

OXYGEN inhalation has been used in the treatment of patients with acute myocardial infarction.$^{1,2}$ However, its therapeutic usefulness is still in dispute, because the following series of paradoxical phenomena have been noted: Oxygen inhalation does not increase myocardial oxygen availability, because, although arterial oxygen content is elevated by oxygen breathing, coronary blood flow is reduced at the same time and the net effect results in no increase in myocardial oxygen availability.$^{3}$ Also, myocardial contractile force is decreased$^{4-6}$ and cardiac output is decreased by oxygen breathing.$^7$

The effect of oxygen on coronary blood flow has been studied extensively$^{3,8}$ and the mechanisms whereby oxygen induces coronary vasoconstriction and reduces coronary blood flow have been clarified.$^9,10$ The effect of oxygen on myocardial contractile force, on the other hand, has been less well understood$^{4-6,11,12}$ One may assume that oxygen inhalation causes an increase in myocardial contractile force. However, the above studies indicate that hypoxia causes an increase$^{11}$ and hyperoxia causes a decrease in myocardial contractile force$^{4-6,12}$ This unexpected decrease in myocardial contractile force

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Intact heart
[A] Air

[B] O₂

Denervated heart
[A] Air

[B] O₂

200 msec

Fig. 1. Myocardial contractile force traces and electrocardiograms in intact and denervated hearts.

In intact heart, myocardial contractile force measured 20 mm in deflection as shown in the upper left (A). During oxygen breathing, it was reduced to 18 mm (B). In denervated heart (lower panels), the myocardial contractile forces measured during air (A) and oxygen breathing (B) had identical deflections.

due to oxygen inhalation may be mediated through sympathoadrenal activities caused by an elevation in arterial oxygen tension. If this is true, oxygen inhalation in a denervated dog would not cause a decrease in myocardial contractile force.

In the present study, in order to elucidate changes in myocardial contractile force by oxygen breathing, oxygen inhalation was performed first while the dog was intact and then again after the dog was denervated.

MATERIALS AND METHODS

Ten mongrel dogs, weighing 17 ± 2 kg (mean ± SE) were studied. Anesthesia was induced with pentobarbital, 25 mg/kg intravenously, and the chest was opened bilaterally at the 8th intercostal space under positive pressure breathing. The anterior thorax above the 8th intercostal space was excised under blood transfusion from a donor dog and preparations were made to excise the thoracic sympathetic nerves at any time. In this situation, the sympathetic or parasympathetic nerves and the adrenal glands were still intact (intact heart).

The following procedures were used to measure the hemodynamic parameters. A catheter was inserted from the right femoral artery into the descending aorta to measure aortic blood pressure. The left anterior descending coronary artery and aortic root were dissected and the blood flow of each was measured using electromagnetic flowmeters (MF-46, Nihon Kohden, Tokyo, Japan). A myocardial strain gauge arch (HD-1T, Nihon Kohden) was sutured using 3-0 silk sutures, 1-2 mm in depth on the left ventricular free wall parallel to the superficial
### TABLE 1: CHANGES IN MYOCARDIAL CONTRACTILE FORCE AND OTHER PARAMETERS BY 100% OXYGEN BREATHING IN INTACT HEARTS AND DENERVATED HEARTS

<table>
<thead>
<tr>
<th></th>
<th>Intact or Denervated</th>
<th>Air (mean ± SE)</th>
<th>O₂ (mean ± SE)</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Heart rate (beats/min)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intact</td>
<td>151 ± 6</td>
<td>151 ± 6</td>
<td>ns</td>
<td></td>
</tr>
<tr>
<td>Denervated</td>
<td>75 ± 6</td>
<td>74 ± 6</td>
<td>p &lt; 0.05</td>
<td></td>
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<tr>
<td><strong>Mean aortic pressure (mmHg)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intact</td>
<td>92 ± 7</td>
<td>92 ± 7</td>
<td>ns</td>
<td></td>
</tr>
<tr>
<td>Denervated</td>
<td>66 ± 6</td>
<td>68 ± 6</td>
<td>p &lt; 0.01</td>
<td></td>
</tr>
<tr>
<td><strong>Aortic flow (ml/min)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intact</td>
<td>686 ± 35</td>
<td>629 ± 30</td>
<td>p &lt; 0.01</td>
<td></td>
</tr>
<tr>
<td>Denervated</td>
<td>738 ± 131</td>
<td>727 ± 116</td>
<td>ns</td>
<td></td>
</tr>
<tr>
<td><strong>Coronary blood flow (ml/min)</strong></td>
<td></td>
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<tr>
<td>Intact</td>
<td>28.4 ± 3.4</td>
<td>21.7 ± 2.3</td>
<td>p &lt; 0.001</td>
<td></td>
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<tr>
<td>Denervated</td>
<td>19.4 ± 3.4</td>
<td>14.9 ± 2.6</td>
<td>p &lt; 0.01</td>
<td></td>
</tr>
<tr>
<td><strong>Myocardial contractile force (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intact</td>
<td>100</td>
<td>94.2 ± 1.4</td>
<td>p &lt; 0.005</td>
<td></td>
</tr>
<tr>
<td>Denervated</td>
<td>100</td>
<td>99.2 ± 0.9</td>
<td>ns</td>
<td></td>
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<tr>
<td><strong>Arterial blood pO₂ (mmHg)</strong></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Intact</td>
<td>94 ± 10</td>
<td>442 ± 25</td>
<td>p &lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>Denervated</td>
<td>113 ± 11</td>
<td>456 ± 15</td>
<td>p &lt; 0.001</td>
<td></td>
</tr>
<tr>
<td><strong>Arterial blood pH</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intact</td>
<td>7.423 ± 0.044</td>
<td>7.406 ± 0.038</td>
<td>ns</td>
<td></td>
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<tr>
<td>Denervated</td>
<td>7.440 ± 0.010</td>
<td>7.426 ± 0.011</td>
<td>ns</td>
<td></td>
</tr>
<tr>
<td><strong>Arterial blood pCO₂ (mmHg)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intact</td>
<td>37 ± 3</td>
<td>36 ± 3</td>
<td>ns</td>
<td></td>
</tr>
<tr>
<td>Denervated</td>
<td>37 ± 3</td>
<td>37 ± 3</td>
<td>ns</td>
<td></td>
</tr>
</tbody>
</table>

*ns = not significant (p > 0.05)*

Layer of the myocardium to extend approximately 20% of its initial length to measure some force existing in the epicardial layers of the heart. Blood samples were obtained from the aorta to analyze pH, Po₂, Pco₂ and hemoglobin (ABL1 Radiometer, Copenhagen, Denmark). All tracings were recorded on an ink-writing polygraph (RM-85, Nihon Kohden). Sixteen myocardial contractile force traces were synchronized using R waves on electrocardiograms, averaged as a single curve and displayed on an oscilloscope (ATAC-260, Addscope, Nihon Kohden) for measurements (Fig. 1). The positive deflection in millimeter on the myocardial contractile force trace during systole was measured at an arbitrary attenuation and expressed as a percentage of each value measured during air breathing. Measurements were performed first during air breathing and again 7 min after the beginning of oxygen breathing.

Immediately after completion of the measurements with the intact heart, denervation was performed as follows: Bilateral vagal nerves were cut at the level of the 5th cervical vertebra and paravertebral sympathetic chains were excised bilaterally from the stellate ganglia to the 4th sympathetic ganglia. As much as possible the mediastinal tissue around the aortic arch and tissues connecting the heart and sympathetic chains were removed. The esophagus and trachea were cut off transversely at the level of the 2nd thoracic vertebra. Bilateral adrenal glands were excised by bilateral skin incisions. In addition, propranolol (1-3 mg/kg, infused for 30 min), phenoxymethylamine (2 mg/kg, infused for 30 min) and atropin (0.5 mg/kg, a bolus injection) were given intravenously. Within 30 min after completion of these procedures (denervated heart), the same measurements as those in the intact heart were repeated during air and oxygen breathing.

**RESULTS**

Arterial Po₂ was elevated to about 450 mmHg by oxygen breathing under both conditions (intact and denervated hearts) (Table I). Denervated heart rates during air breathing were reduced to approximately one half of the intact heart rates. Aortic flow after denervation increased slightly possibly due to the blood transfusion from the donor dog. In the denervated hearts there was a slight decrease in heart rate and an increase in arterial pressure due to oxygen breathing. Coronary blood flows were reduced by oxygen breathing to the same extent in the intact
and the denervated heart, although the initial value in the denervated heart was reduced on the average (Fig. 2). In all 10 experiments, the myocardial contractile force was reduced by 5.8% (from 35.6 ± 3.4 to 33.2 ± 2.8 mm) on the average by oxygen breathing in the intact heart (Table I and Fig. 3). While in the denervated heart, no consistent change in myocardial contractile force due to oxygen breathing (from 19.3 ± 0.6 to 19.2 ± 0.7 mm) was demonstrated (Table I and Fig. 3). Although myocardial contractile force was markedly reduced after complete denervation, the deflection of myocardial contractile force was still sufficient to evaluate the changes induced by oxygen breathing. Since complete denervation markedly reduced heart rate and aortic pressure, the effects of oxygen after denervation may be masked. However, in 3 experiments where denervation produced only a slight change in heart rate and aortic pressure, oxygen breathing produced no significant change in myocardial contractile force after denervation.

**DISCUSSION**

It has been shown that oxygen breathing reduces coronary blood flow in experimental dogs as well as in patients with coronary artery disease and in patients with valvular or congenital heart disease. It is interesting that this decrease in coronary blood flow is demonstrated in intact as well as in denervated hearts. However, this is not surprising because Lammerant et al have already demonstrated that oxygen-induced coronary vasoconstrictions are not blocked by denervation. The previous study by this laboratory has also demonstrated that oxygen-induced coronary vasoconstriction is not influenced by oxygen demand in the myocardium. There is a marked contrast between the finding that denervation does not block oxygen-induced reductions in coronary blood flow and the finding that it blocks oxygen-induced reductions in myocardial contractile force. It has been shown, in a coronary perfusion study, that regional myocardial contractile force is increased if the regional coronary artery is perfused with hyperoxic blood while the arterial pO2 perfusing the rest of the body remains constant. If the pO2 of the regional coronary perfusing blood is elevated together with the rest of the body, regional myocardial contractile force is decreased. These results indicate that the reduction in myocardial contractile force may be caused by a neurohumoral mechanism.

Woods and Richardson have demonstrated
that arterial hypoxia causes an increase in heart rate and myocardial contractile force, and that these changes are eliminated by adrenalectomy as well as sympathetic blockade. They suggested that numerous circulatory phenomena elicited by hypoxia are mediated through activation of sympathetic nerves or hypersecretion from the adrenal glands. Also, the important role of chemoceptors or the central nervous system in adjusting the body to hypoxia has been recently reviewed and stressed.

For hypoxia, on the contrary, one may assume that sympathoadrenal activity will be suppressed. It is true that oxygen inhalation causes bradycardia, decreases in cardiac output and reductions in myocardial contractile force, all of which are characteristic circulatory manifestations of negative chronotropic and negative inotropic actions induced by depression of sympathetic nerve activity. The study of Hale et al. who have demonstrated that urinary excretions of catecholamines in normal subjects are reduced by oxygen breathing, may support this concept. Also, increases in plasma catecholamine concentrations during exercise were shown to be suppressed by oxygen breathing.

Daniell and Bagwell, assuming that changes in myocardial contractile force due to oxygen are mediated through the autonomic nerve system, conducted a study similar to the present one. Their study indicated that myocardial contractile force was decreased even if the heart was denervated and they postulated that oxygen had a toxic effect on the myocardium which decreases myocardial contractile force. Their results are in contrast to ours. Also, their preparations, in which adrenalectomies were not performed, and alpha-, beta- and para-sympathetic pharmacologic denervations and anatomic denervations were not combined, were different from the present method.

In summary, the mechanism of reducing myocardial contractile force by hypoxia may be explained as follows: The primary effect of oxygen on the myocardium is to increase myocardial contractile force. At the same time, hypoxia causes neurohumoral changes (possibly suppressions of sympathetic nerve activity and adrenal secretion) and thereby reduces myocardial contractile force. The net effect, therefore, is a decrease in myocardial contractile force.

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