Reduction of Infarct Size by Oxygen Inhalation Following Acute Coronary Occlusion

By Peter R. Maroko, M.D., Paulo Radvany, M.D., Eugene Braunwald, M.D., and Sharon L. Hale, B.S.

SUMMARY
This study was carried out in order to determine the effects of the inspiration of O2-enriched air on the size of myocardial infarction. In 15 anesthetized dogs, epicardial electrograms were recorded from 10 to 14 sites on the anterior surface of the left ventricle before and after intermittent occlusion of the left anterior descending coronary artery or one of its major branches. In each dog, one occlusion was carried out while the fraction of inspired oxygen (FIO2) was 0.20 and the other while the FIO2 was 0.40. With an FIO2 of 0.20 the average ST-segment elevation (ST) was 4.0 ± 0.6 mV (SEM) and the number of sites exhibiting ST-segment elevations exceeding 2 mV (NST) 15 minutes following occlusion was 6.2 ± 0.7 sites; comparable values following occlusion with an FIO2 of 0.40 were 1.8 ± 0.4 mV (P < 0.01) and 2.7 ± 0.7 sites (P < 0.01), reflecting reduction in acute myocardial ischemic injury. An FIO2 of 1.0 did not decrease myocardial injury further. In 24 other dogs, occlusion was maintained for 24 hours. In nine dogs in which FIO2 was increased from 0.20 to 0.40 30 minutes after occlusion, myocardial creatine phosphokinase activity (CPK) was less depressed in sites having comparable levels of ST-segment elevation at 15 minutes than in dogs that respired an FIO2 of 0.20 during the entire 24 hours. All (54) sites with ST-segment elevations > 3 mV in the 0.20 FIO2 group showed early signs of myocardial infarction, while only 49% of such specimens showed infarction in the 0.40 FIO2 group. Thus, it is concluded that 0.40 FIO2 following an experimental coronary artery occlusion decreases acute ischemic injury and reduces the eventual development of necrosis, as evaluated by enzymatic and histological techniques.

THE MAJORITY OF IN-HOSPITAL DEATHS subsequent to acute myocardial infarction result from cardiogenic shock or "pump failure"11 and a close correlation exists between this clinicophysiologic syndrome and the findings of massive infarction of myocardial tissue at postmortem examination.5, 12 Consequently, in an effort to reduce the high mortality associated with pump failure, efforts have been directed to reducing infarct size following coronary occlusion.4-10 Interventions that favorably alter the balance between myocardial oxygen supply and demand have also been found to reduce myocardial damage following coronary artery occlusion.11-21 Enrichment of oxygen in the inspired gas is easily achieved and widely used in the treatment of patients with acute myocardial infarction but its potential value in limiting infarct size is not clear. While innocuous in modestly increased concentrations, the prolonged and continuous inhalation of very high concentrations of O2 has been demonstrated to be hazardous.22 Accordingly, the goal of this investigation, carried out in anesthetized open chest dogs with experimentally induced coronary occlusions, was to ascertain whether and to what extent the doubling of inspired O2 concentration reduces ischemic injury, as well as whether or not the inhalation of 100% O2 provides any additional benefits.

Methods
The effect of hyperoxia on myocardial damage following coronary artery occlusion was studied using two protocols.
Protocol A: Thirty-six dogs, weighing between 18 and 25 kg, were anesthetized with sodium thiamylal (25 mg/kg) with respiration maintained by a Harvard respirator. The heart was exposed through the fifth left intercostal space and was suspended in a pericardial cradle. The left anterior descending coronary artery (LAD), or its apical branch, was dissected free from the adjacent tissue and occluded intermittently when desired, using a Schwartz intracranial arterial clamp. As previously described,11 epicardial electrograms were obtained from ten to 14 sites on the anterior surface of the left ventricle, distributed in areas supplied by the occluded artery as well as in areas remote to it and presumably adequately perfused. Two occlusions of 20 min each were carried out with an interval of 60 min for reflow. In 15 dogs two successive occlusions using a fraction of inspired oxygen (FIO2) of 0.20 (20% O2 concentration) were carried out. In another 15 dogs the first occlusion was with an FIO2 of 0.20 and the second with an FIO2 of 0.40 (40% O2 concentration). In six additional dogs, the effects of an FIO2 of 0.40 during one occlusion were compared to those

From the Departments of Medicine, Harvard Medical School and Peter Bent Brigham Hospital, Boston, Massachusetts.
Supported in part by NIH-NHLI Contract 72-2949 and a grant from the John A. Hartford Foundation.
Address for reprints: Peter R. Maroko, M.D., Harvard Medical School, Building A, 25 Shattuck Street, Boston, Massachusetts 02115.
Received August 5, 1974; revision accepted for publication March 10, 1975.
HYPEROXIA AND INFARCT SIZE

during an occlusion in which the FIO₂ was 1.0 (100% O₂ concentration). Epicardial electrograms were recorded prior to each occlusion and at 5 min intervals during the 20 min occlusions. These changes in acute myocardial ischemic injury were analyzed using the average ST-segment elevation over the epicardium (ST) and the number of sites showing ST-segment elevation exceeding 2mV (NST). Changes in ST and NST show alterations in injury in the same animal, but the absolute values do not allow a comparison of the severity of injury between dogs. Any site which exhibited a QRS duration exceeding 0.065 sec on any single tracing (the average normal value equals 0.040 seconds) and therefore showing secondary lowering of ST-segment levels (QRS-STT gradient effect) was excluded from analysis for the entire experiment. The paired t-test was used to examine the differences between ST and NST in consecutive occlusions.

Protocol B: In 24 dogs the effects of inhalation of 0.20 FIO₂ and 0.40 FIO₂ mixtures on the size of myocardial infarctions, as defined histologically, and on myocardial necrosis, as reflected in myocardial creatine phosphokinase (CPK) activity, were compared. The surgical procedure was identical to the one used in Protocol A. However, in these dogs, coronary artery occlusion was maintained for 24 hours. Epicardial maps were recorded at 5 min intervals following coronary occlusion for 20 min, as described in Protocol A. The dogs’ chests were then closed, they were extubated and allowed to awaken. Their arterial pressure was recorded by a Statham P23DB gauge through a polyethylene catheter inserted into the carotid artery and an electrocardiographic lead (aVR) was monitored constantly. Twenty-four hours following occlusion, the dogs were again anesthetized, their chests re-opened and the hearts excised immediately and washed in cold saline. Transmural specimens were obtained from the same sites at which epicardial electrograms had been recorded 24 hours earlier. The specimens were excised in the shape of rectangular blocks involving the thickness of the entire left ventricular wall. These specimens were analyzed for CPK activity, as previously described. The specimens were coded and prepared using Bouin’s fixation and hematoxylin and eosin stain. They were examined without previous knowledge of the origin of the biopsy for signs of early myocardial infarction, as reflected in a deeper eosinophilic appearance, karyorrhexis, karyolysis, polymorphonuclear infiltrate and membrane rupture, as described previously.

Fifteen of the 24 animals served as controls, i.e., they were maintained on room air for the 24 hour period. In the nine experimental animals, beginning 50 min following occlusion, i.e., 15 min following the epicardial mapping, the inhaled gas mixture was changed to one with an FIO₂ of 0.40. After extubation the dogs were placed in a chamber in which an FIO₂ of 0.40 was maintained until they were sacrificed 24 hr later. Although the investigator knew which dogs were controls and which were experimental, the myocardial specimens for histological appearance and CPK content were coded and were analyzed without previous knowledge of their site of origin or whether they were obtained from a control or experimental dog. The data were analyzed by relating ST-segment elevation at each site 15 min following occlusion to the transmural myocardial CPK activity and histological appearance 24 hr later.

Results

Protocol A: The effect of FIO₂ of 0.40 and 1.00 on acute myocardial ischemic injury.

In 15 dogs, the average ST-segment elevation (ST) and number of sites showing ST-segment elevations over 2 mV (NST) were similar following two consecutive occlusions with an FIO₂ of 0.20; STs after 15 min of each occlusion were 4.3 ± 0.7 and 4.0 ± 0.8 mV (NS) and the NSTs were 5.0 ± 2.0 and 5.0 ± 2.0 sites.

When the FIO₂ was raised from 0.20 to 0.40, the arterial pO₂ rose from 99 ± 5 to 185 ± 5 mm Hg. When the occlusion was carried out with an FIO₂ of 0.40, ST and NST were both lower than when the FIO₂ was 0.20 (fig. 1). In the 15 dogs so studied, ST 15 min following control occlusion was 4.0 ± 0.6 mV and was reduced to 1.8 ± 0.4 mV (P < 0.01) during the occlusion with an FIO₂ of 0.40 (fig. 2, left); NST decreased from 6.2 ± 0.7 to 2.7 ± 0.7 sites (P < 0.01) (fig. 2, right). It should be noted that although the interventions were not randomized, no difference was expected between the two occlusions as documented in the previous group of dogs.

In an additional group of dogs, when FIO₂ was increased from 0.40 to 1.00, the arterial pO₂ rose from 206 ± 14 to 550 ± 18 mm Hg. There were no significant differences in ST and NST 15 min following the two occlusions (fig. 3). In all six dogs so studied, STs were 4.9 ± 1.6 and 5.6 ± 2.0 mV (NS) and NSTs were 6.3 ± 1.4 and 6.3 ± 1.5 sites (NS), respectively, as FIO₂ was elevated from 0.40 to 1.00. At the same time heart rate and mean arterial pressure did not change significantly (from 140 ± 15 to 138 ± 15 beats/min and from 114 ± 10 to 122 ± 10 mm Hg). The ST and NST were purposely set at higher levels (by using dogs with larger infarcts) when comparing an FIO₂ of 0.40 with an FIO₂ of 1.00 than they were when comparing an FIO₂ of 0.20 with an FIO₂ of 0.40 in order to be able to detect decreases in injury with an FIO₂ of 1.00, if they did, in fact, occur.

Protocol B: The effect of FIO₂ 0.40 on infarct size.

In the control dogs, in which the FIO₂ was maintained at 0.20 throughout the 24 hr of coronary artery occlusion, CPK activity was depressed in sites with ST-segment elevations (figs. 4, 5 and table 1). There was an inverse relationship between ST-segment elevations at 15 min after occlusion and CPK activity 24 hr later: log CPK = −0.06 ST + 1.5 (r = 0.8). In these control dogs, all 54 sites with ST-segment elevations > 3 mV showed early signs of myocardial necrosis, as reflected by deepened eosinophilic appearance, karyorrhexis, karyolysis, polymorphonuclear cell infiltrate and disruption of the sarcolemma (fig. 4). In contrast, all sites with no or minimal ST-segment elevations 15 min following coronary artery occlusion revealed a normal histological appearance 24 hr later (fig. 4). Also, there was a good correlation between the histologic findings and

Circulation, Volume 52, September 1975
Example of the effect of respiring 40% O₂ on the number of sites showing ST-segment elevation (NST) and on the average ST-segment elevation (ST). Right) Schematic representation of the heart. Lined area = area of ST-segment elevation 15 min following occlusion with FIO₂ of 0.20. Starred area = area of ST-segment elevation 15 min following occlusion with FIO₂ of 0.40. LAD = left anterior descending coronary artery. • = sites from which epicardial electrograms were recorded. Left) Comparison between the average ST-segment elevation (ST) in the same animal after two occlusions. □ = ST just before and after occlusion with FIO₂ of 0.20. ⋄ = ST just before and after occlusion with FIO₂ of 0.40. Time = minutes after coronary artery occlusion.

myocardial CPK concentration in sites which exhibited early myocardial necrosis histologically; the CPK concentration averaged just less than half of that noted in sites which showed no histologic evidence of myocardial necrosis (fig. 6).

In dogs in which the FIO₂ was raised to 0.40 30 min following occlusion (i.e., 15 min following the epicardial mapping) and in which this level of FIO₂ was maintained throughout the 24 hr of occlusion, many sites which exhibited ST-segment elevations 15 min after occlusion — and thus in control dogs would have shown signs of myocardial necrosis as reflected by CPK depression and histological appearance of early myocardial infarction — exhibited a normal histologic appearance (figs. 5 and 7, sites C and F). In all nine dogs exposed to an FIO₂ of 0.40, myocardial CPK activity was less depressed in sites having comparable levels of ST-segment elevation at 15 min than in dogs exposed to an FIO₂ of 0.20 (fig. 5 and table 1). The relationship between ST-segment elevation and CPK depression, in this group, was log CPK = −0.02 ST + 1.5 (r = 0.7). The slope of this line was

Circulation, Volume 52, September 1975
HYPEROXIA AND INFARCT SIZE

Figure 3
A comparison of the effects of 40% and 100% oxygen inhalation. Right) Schematic representation of the heart. Lined area is the area of ST-segment elevations 15 min following occlusion with FIO2 of 0.40. Starred area = area of ST-segment elevations 15 min after occlusion with FIO2 of 1.0. LAD = left anterior descending coronary artery. • = sites from which epicardial electrograms were recorded. Left) Average ST-segment elevation at 15 min following occlusion (ST15) while breathing 40% oxygen (lined column) and while breathing 100% O2 (starred column).

Figure 4
The relation between ST-segment elevation 15 min after occlusion and CPK activity and histological appearance 24 hr later in an experiment in the control group (FIO2 = 0.20). Left) A schematic representation of the anterior surface of the heart and its arteries. The shaded area represents the area of ST-segment elevation 15 min after occlusion. The circles represent sites from which biopsies were taken. Right) Comparison of ST-segment elevations 15 min after coronary artery occlusion with CPK and histological analysis 24 hr later at the same sites.

<table>
<thead>
<tr>
<th>SITE</th>
<th>ST15 (mV)</th>
<th>CPK (I.U./mg prot.)</th>
<th>HISTOLOGY</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>0</td>
<td>34.9</td>
<td>NORMAL</td>
</tr>
<tr>
<td>B</td>
<td>0</td>
<td>29.1</td>
<td>NORMAL</td>
</tr>
<tr>
<td>C</td>
<td>3</td>
<td>23.3</td>
<td>ABNORMAL</td>
</tr>
<tr>
<td>D</td>
<td>6</td>
<td>8.9</td>
<td>ABNORMAL</td>
</tr>
<tr>
<td>E</td>
<td>5</td>
<td>8.5</td>
<td>ABNORMAL</td>
</tr>
<tr>
<td>F</td>
<td>4</td>
<td>9.4</td>
<td>ABNORMAL</td>
</tr>
<tr>
<td>G</td>
<td>7</td>
<td>11.2</td>
<td>ABNORMAL</td>
</tr>
<tr>
<td>H</td>
<td>0</td>
<td>31.3</td>
<td>NORMAL</td>
</tr>
</tbody>
</table>

Circulation, Volume 52, September 1975
significantly less steep than that of the control group ($P < 0.005$). In sites with moderate ST-segment elevation (4–5 mV), CPK activity was significantly less depressed in the dogs in which FIO$_2$ was increased to 0.40 (fig. 5 and table 1) indicating that elevating the FIO$_2$ to 0.40 reduced myocardial necrosis, as reflected

Table 1

<table>
<thead>
<tr>
<th>Dog</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>11</th>
<th>12</th>
<th>13</th>
<th>14</th>
<th>15</th>
<th>Mean ± SEM†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sites with ST-segment elevations of 0–3 mV</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of specimens*</td>
<td>7</td>
<td>5</td>
<td>6</td>
<td>5</td>
<td>7</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>2</td>
<td>4</td>
<td>5</td>
<td>3</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>CPK‡</td>
<td>25.6</td>
<td>33.5</td>
<td>33.2</td>
<td>26.7</td>
<td>25.2</td>
<td>34.2</td>
<td>22.7</td>
<td>29.7</td>
<td>27.5</td>
<td>38.0</td>
<td>31.4</td>
<td>33.8</td>
<td>22.7</td>
<td>35.2</td>
<td>29.8</td>
<td>29.9</td>
</tr>
<tr>
<td>±0.3</td>
<td>±5.8</td>
<td>±4.2</td>
<td>±2.9</td>
<td>±3.8</td>
<td>±4.0</td>
<td>±4.4</td>
<td>±2.4</td>
<td>±1.3</td>
<td>±3.0</td>
<td>±4.7</td>
<td>±1.2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sites with ST-segment elevations of 4–5 mV</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of specimens*</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>3</td>
<td>1</td>
<td>3</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>3</td>
<td>4</td>
<td>3</td>
<td>3</td>
<td>1</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>CPK‡</td>
<td>13.1</td>
<td>11.0</td>
<td>17.6</td>
<td>17.8</td>
<td>15.5</td>
<td>14.5</td>
<td>10.5</td>
<td>9.0</td>
<td>12.1</td>
<td>15.5</td>
<td>16.9</td>
<td>14.0</td>
<td>13.8</td>
<td>16.7</td>
<td>16.0</td>
<td>14.3</td>
</tr>
<tr>
<td>±0.7</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sites with ST-segment elevations ≥ 6 mV</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of specimens*</td>
<td>0</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>3</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>4</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>CPK‡</td>
<td>8.8</td>
<td>11.8</td>
<td>15.8</td>
<td>8.2</td>
<td>10.2</td>
<td>14.2</td>
<td>15.5</td>
<td>14.4</td>
<td>9.5</td>
<td>17.7</td>
<td>9.7</td>
<td>12.3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>±1.4</td>
<td>±1.0</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Dog</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>Mean ± SEM†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sites with ST-segment elevations of 0–3 mV</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of specimens*</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>2</td>
<td>6</td>
<td>7</td>
<td>2</td>
<td>2</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>CPK‡</td>
<td>41.3</td>
<td>27.9</td>
<td>37.9</td>
<td>34.8</td>
<td>17.6</td>
<td>17.6</td>
<td>36.8</td>
<td>31.2</td>
<td>27.8</td>
<td>30.3</td>
</tr>
<tr>
<td>±3.4</td>
<td>±3.3</td>
<td>±5.9</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sites of ST-segment elevations of 4–5 mV</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of specimens*</td>
<td>1</td>
<td>3</td>
<td>0</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>3</td>
<td>21.8</td>
</tr>
<tr>
<td>CPK‡</td>
<td>42.2</td>
<td>17.3</td>
<td>23.1</td>
<td>9.6</td>
<td>12.4</td>
<td>27.2</td>
<td>24.3</td>
<td>18.5</td>
<td>3.6</td>
<td></td>
</tr>
<tr>
<td>Sites with ST-segment elevations ≥ 6 mV</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of specimens*</td>
<td>4</td>
<td>2</td>
<td>3</td>
<td>3</td>
<td>1</td>
<td>0</td>
<td>4</td>
<td>4</td>
<td>0</td>
<td>17.4</td>
</tr>
<tr>
<td>CPK‡</td>
<td>34.8</td>
<td>13.8</td>
<td>19.0</td>
<td>13.5</td>
<td>8.7</td>
<td>15.5</td>
<td>16.9</td>
<td>3.1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Number of specimens in each dog with the above ST-segment elevations.
†CPK activity in international units/mg of protein. Mean value ± 1 standard error when N ≥ 4.
‡The average of the mean values of CPK concentration at sites having stated ST-segment elevations for each dog. Each dog is weighted equally regardless of the number of sites sampled.

Figure 5

Relationship between ST-segment elevations 15 min following occlusion and CPK activity in myocardial biopsies from the same sites 24 hr later in dogs breathing 20% oxygen (lined columns) and in dogs breathing 40% oxygen (dotted columns). Note that with no or minimal (0–3 mV) ST-segment elevations, CPK activity was similar in the two groups but with moderate (4–5 mV) ST-segment elevations and with marked ST-segment elevations (≥ 6 mV) there was less CPK depression in dogs treated with 40% oxygen. Numbers in the columns represent the number of dogs. Each dog is weighted equally regardless of the number of sites sampled. Columns indicate the average of the mean values of CPK concentration at sites having stated ST-segment elevations for each dog. *P = 0.08 (two tails), **P < 0.01 (20% vs 40% O$_2$ inhalation). The CPK concentrations in the specimens with 4–5 mV and those ≥ 6 mV in either the control dogs or those treated with 40% O$_2$ did not differ significantly (4–5 mV vs ≥ 6 mV ST-segment elevation).
HYPEROXIA AND INFARCT SIZE

in tissue CPK content; in sites with marked ST-segment elevation (≥ 6 mV) the directional changes were similar, but the difference in CPK concentration between the groups receiving 0.20 and 0.40 oxygen were of borderline significance (P = 0.08).

Sites that exhibited ST-segment elevations > 3 mV 15 min following occlusion, i.e., prior to commencing an FIO₂ of 0.40, exhibited signs of early myocardial infarction in only 49% (18/37) of specimens; thus histological signs of early myocardial necrosis were not present in half of the specimens in which it would have been expected had the FIO₂ remained at 0.20 (fig. 7). Just as was the case in the dogs that received an FIO₂ of 0.20 for 24 hrs, in the dogs that were exposed to an FIO₂ of 0.40, those sites that exhibited abnormal histological findings of early myocardial necrosis had significantly lower CPK concentration than sites with normal histologic appearance (fig. 6).

There was no difference between mean arterial pressure, heart rate and the time of development of arrhythmias between the two groups of dogs (table 2). In this series of dogs, as well as in all of our previous experiments, the animals exhibited a lower arterial pressure 24 hr after occlusion than initially (table 2);

Figure 6

Relationship between CPK activity and histology 24 hr following coronary occlusion in dogs on FIO₂ of 0.20 (lined columns) and in dogs in which FIO₂ was increased to 0.40 (dotted columns). Note that there was a good correlation between myocardial CPK levels and histology in both groups. Level of CPK activity in normal specimens was on the average double those with abnormal histology in both groups. Numbers in the columns represent the number of specimens.

<table>
<thead>
<tr>
<th>SITE</th>
<th>ST</th>
<th>CPK</th>
<th>HISTOLOGY</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>0</td>
<td>40.1</td>
<td>NORMAL</td>
</tr>
<tr>
<td>B</td>
<td>0</td>
<td>34.6</td>
<td>NORMAL</td>
</tr>
<tr>
<td>C</td>
<td>4</td>
<td>29.2</td>
<td>NORMAL</td>
</tr>
<tr>
<td>D</td>
<td>6</td>
<td>14.1</td>
<td>ABNORMAL</td>
</tr>
<tr>
<td>E</td>
<td>12</td>
<td>10.8</td>
<td>ABNORMAL</td>
</tr>
<tr>
<td>F</td>
<td>4</td>
<td>25.2</td>
<td>NORMAL</td>
</tr>
<tr>
<td>G</td>
<td>13</td>
<td>20.1</td>
<td>ABNORMAL</td>
</tr>
<tr>
<td>H</td>
<td>14</td>
<td>17.1</td>
<td>ABNORMAL</td>
</tr>
</tbody>
</table>

Figure 7

Effect of FIO₂ of 0.40 on the relationship between ST-segment elevation (recorded while FIO₂ was 0.20) and CPK activity and histologic structure 24 hr later. Left) Schematic representation of the anterior surface of the heart and its arteries. LAD = left anterior descending coronary artery. Shaded area = area of ST-segment elevation 15 min after coronary occlusion (prior to switch from 0.20 to 0.40 FIO₂). Right) Comparison between ST-segment elevation 15 min after occlusion on FIO₂ of 0.20 and CPK activity and histological structure 24 hr later.

Circulation, Volume 52, September 1975
the mechanism of this reduction is not clear. In this model, ST-segment elevations decline with elevations of arterial pressure, and on the basis of earlier studies it is believed that arterial pressure is an important determinant of the extent of ischemic injury following coronary occlusion. Therefore, it is likely that if the arterial pressure had been held constant, infarcts both in the control and experimental groups would have been even smaller. Actually, arterial pressure declined even more in the group with an FIO2 of 0.40 as compared to that respiring 0.20 and the finding that the former group had smaller infarcts, despite greater reductions of pressure, strengthens the conclusion that an FIO2 of 0.40 reduced ischemic damage in dogs with coronary occlusion. Prior to occlusion and three and 24 hours after occlusion, the PO2 in the FIO2 0.20 and FIO2 0.40 groups were, respectively, 85 ± 2, 82 ± 3, and 79 ± 2 mm Hg and 85 ± 3.6 (NS), 191 ± 12 (P < 0.001), and 171 ± 4 (P < 0.001) mm Hg.

**Discussion**

Interventions which favorably affect the balance between myocardial oxygen supply and demand can significantly reduce the size of an infarction following coronary artery occlusion. Thus, beta-adrenergic blockade with propranolol and practolol as well as intra-aortic balloon counterpulsation and nitroglycerin by reducing myocardial oxygen requirements, reduce myocardial damage and/or necrosis following coronary occlusion; on the other hand, interventions which presumably increase coronary artery flow to the ischemic area, either through collaterals or reperfusion of the occluded artery, reduce myocardial injury by increasing oxygen availability. In this investigation it was demonstrated that the inhalation of 40% O2 reduced electrocardiographic evidence of acute myocardial ischemic injury as well as the extent of myocardial necrosis. Sites at the periphery of the damaged zone of myocardium, which showed lesser degrees of ST-segment elevation 15 min following coronary occlusion, were completely protected by an FIO2 of 0.40, while sites in the center of the damaged zone, with more severe ischemic injury, were partially protected. The histologic findings were consistent with this interpretation that in half of the sites which would have been expected, on the basis of studies in animals receiving FIO2 of 0.20, to exhibit early signs of myocardial necrosis were protected by an FIO2 of 0.40 and exhibited a normal histologic appearance. This finding, that enrichment of inspired O2 content reduced electrocardiographic evidence of ischemic injury, as noted in the epicardial ST segment following acute coronary occlusion, is reflected also in biochemical evidence of reduced myocardial injury (less CPK reduction).

The histologic and biochemical findings are internally consistent in that in dogs which were exposed to an FIO2 of 0.40: 1) as stated above, many sites which, on the basis of the ST-segment elevation, would have been expected to exhibit myocardial necrosis showed no histologic changes; 2) these same sites exhibited significantly less reduction of CPK concentration than if they had been exposed to an FIO2 of 0.20 (fig 5); and 3) the concentration of CPK was significantly lower in the sites with histologic evidence of myocardial necrosis than in sites with normal histologic appearance (fig 6), although the histologic assessment apparently is not sensitive enough to detect early necrosis in every site in which there was some reduction of CPK activity.

It is not known whether the reduction in myocardial CPK concentration represents CPK loss from the injured myocardium or decreased production. At least in part it represents loss into the plasma since a correlation exists between loss of myocardial CPK activity and the appearance of CPK in the plasma. Also, it has been shown that CPK leaks from the injured area through the lymphatics. The observed correspondence between depression of tissue CPK activity and histologic necrosis is consistent with earlier studies.

Our conclusions concerning the beneficial effects of an FIO2 of 0.40 are further strengthened by the observation that epicardial ST-segment elevation following coronary occlusion reflects reduction of cellular PO2 as well as alterations in the lactate, ATP and creatine phosphate concentrations of the subjacent heart muscle.

A number of possibilities should be considered in the explanation of these findings. Oxygen administra-
tion increases total peripheral resistance which, in turn, may elevate arterial pressure and thus augment coronary artery perfusion pressure, decreasing myocardial damage. However, in these experiments, an FIO2 of 0.40 did not produce a significant change in systemic arterial pressure, effectively excluding this explanation. Recently, Ishikawa et al. demonstrated that oxygen administration can reduce myocardial contractility in the ischemic zone following partial coronary artery occlusion and therefore, since myocardial contractility is a major determinant of myocardial O2 consumption, it might be postulated that the reduction in infarct size with an FIO2 of 0.40 is related to a decrease in myocardial oxygen needs. However, in two dogs the inhalation of 40% oxygen did not change left ventricular dp/dt or dp/dt/developed pressure, an index of myocardial contractility. While not excluding the possibility that regional contractility could be decreased by an FIO2 of 0.40, this does not seem to be the most plausible mechanism, since a complete occlusion (in contrast to a partial occlusion) results in a noncontracting segment of myocardium, and thus contractility cannot decrease further.

With an elevation of FIO2 from 0.20 to 0.40, arterial pO2 increased from 99 to 185 mm Hg; this does not result in a substantial increase in the oxygen content of the blood and thus the marked reduction of ischemic injury cannot be explained simply on the basis of augmented oxygen delivery. This increase in arterial pO2 also does not augment substantially the quantity of O2 delivered to normal tissue, according to the considerations developed by Krogh and Kety. However, the possibility that an increased arterial pO2 may enhance the diffusion of O2 through an increase in the gradient between the normal and ischemic tissue cannot be excluded. Moreover, since the distribution of blood to the myocardium distal to an occlusion is often quite heterogeneous, the interface between normally perfused and ischemic tissue is much greater than the gross boundary of the infarct; thus, it is postulated that a deeper penetration of oxygen by only a small distance into the ischemic tissue might result in a substantial increase in the quantity of tissue that is sufficiently oxygenated to allow survival and that it might thereby decrease myocardial damage. If it is considered that the level of pO2 required for function of the mitochondria is between 1 and 2 mm Hg, it becomes reasonable to consider that a minimal increase in pO2 can favorably affect the energetic mechanism of myocardial cells, thus permitting their survival. Also, considering that oxygen may constrict the coronary arteries in normal tissue, there may be an increase in the pressure gradient between the normal and the ischemic area, diverting more blood to the injured zone. Therefore, it is postulated that increased availability of oxygen to the ischemic areas constitutes the mechanism by which an FIO2 of 0.40 reduced damage following coronary occlusion. The finding that oxygen therapy is beneficial in decreasing infarct size is in accordance with the observation in patients with ischemic heart disease in which the threshold to pacing-induced angina and myocardial lactate metabolism have all been shown to improve with inhalation of oxygen enriched mixtures.

In this study the effect of an FIO2 of 1.00 on the extent and severity of ischemic injury was not found to be more beneficial in reducing ischemic injury than an FIO2 of 0.40. The reason for this is not clear, but since an FIO2 of 0.40 as compared to 1.002 presents no danger of oxygen toxicity and since this modestly increased FIO2 can be easily administered through a nasal catheter, it is suggested that an FIO2 of 0.40 might be appropriate in the treatment of patients with acute myocardial infarction.

It is appreciated that extrapolation of these results to the clinical setting must of course be done cautiously, considering the many differences between man and dog, particularly as they relate to the richness of coronary collaterals and the fact that these studies were carried out on dogs with normal coronary vessels and myocardial function whereas most patients with myocardial infarction exhibit diffuse coronary obstructive lesions and myocardial damage. However, considering the substantial beneficial effects of an FIO2 of 0.40 on the severity of ischemic injury and the size of infarcts following coronary occlusion, and its negligible adverse effects, the routine use of this treatment in patients with uncomplicated acute myocardial infarction would appear to be rational.

Acknowledgments

We gratefully acknowledge the technical help of Mr. Daniel White and Mr. Denis Hourihan and the secretarial assistance of Ms. Merrilee Spence.

References

5. Braunwald E, Maroko PR: The reduction of infarct size — An idea whose time (for testing) has come. Circulation 50: 206, 1974


27. MALMBERG P: Time course of enzyme escape via heart lymph following myocardial infarction in the dog. Scand J Clin Lab Invest 30: 405, 1972


36. KROGH A: Anatomy and Physiology of Capillaries. New Haven, Yale University Press, 1936


39. MOSS AJ: Oxygenation of the heart. Hospital Practice 6: 104, 1971


Circulation, Volume 52, September 1973
Reduction of infarct size by oxygen inhalation following acute coronary occlusion.
P R Maroko, P Radvany, E Braunwald and S L Hale

Circulation. 1975;52:360-368
doi: 10.1161/01.CIR.52.3.360

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1975 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/52/3/360

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org//subscriptions/