Reduction by Hyperbaric Oxygenation of the Mortality from Ventricular Fibrillation Following Coronary Artery Ligation

By William M. Chardack, M.D., Andrew A. Gage, M.D., Anthony J. Federico, M.D., John K. Cusick, M.D., Paul J. H. Matsumoto, M.D., and Edward H. Lanphier, M.D.

Smith and Lawson reported in 1958 that in dogs the administration of oxygen at a pressure of two atmospheres absolute (atm abs) reduced the mortality from ventricular fibrillation following experimental occlusion of the circumflex coronary artery from 60 to 10%. The same authors in 1962 substantiated their conclusions by similar results obtained in additional experiments and reported favorable impressions from their initial clinical trial with this form of treatment.

Large variations of mortality rates have been observed following experimental ligation of coronary arteries of the dog. An earlier study by some of us dealt with these discrepancies and their relationship to differences in oxygenation, anesthesia, operative technique, and anatomical distribution of the arterial tree. In subsequent years, further experience with such “test ligations” taught us that age, sex and, most of all, the size of the animal and therefore of the heart have considerable influence on the incidence of ventricular fibrillation in such experiments. That larger hearts fibrillate more easily seems well established. Our interest in experimental coronary occlusion, the experience of one of us with experimentation under hyperbaric conditions (E. H. L.), and the important therapeutic implications of Smith’s studies prompted us to undertake experimentation along similar lines.

Methods

Mongrel dogs weighing 17 kg or more were used for these experiments. The animals were anesthetized without premedication by intravenous administration of pentobarbital sodium, 30 mg/kg of body weight. A cuffed endotracheal tube was introduced and ventilation was maintained by 100% oxygen delivered through a positive pressure demand valve. A thoracotomy was performed through the left fourth intercostal space, the circumflex coronary artery was exposed and a silk ligature passed around it between 5 and 10 mm from its origin. The limbs of this sling were passed through a plastic catheter brought out through the incision. The lumen of the catheter was filled with silicone stopcock grease to maintain an air seal. The wound was closed tightly with attention to complete reinfation of the lungs. All those who did these operations had had experience with the procedure prior to participating in this study; the operative technique was standardized and the duration of the operation was kept within narrow limits.

After preliminary surgical procedures were completed, the animals were allowed to regain...
spontaneous respiration on room air and were then observed for ten minutes. In the control group, the coronary artery was then occluded by tightening the sling and the animals continued to breathe room air. The experimental groups were given 100% oxygen at an ambient pressure of 1, 2, or 4 atm abs. Oxygen was administered by connecting the endotracheal tube to a large bore oxygen line in a T-configuration. For experiments on the animals treated in the hyperbaric chamber, a breathing bag was placed into the oxygen line a few centimeters distal to the endotracheal tube and oxygen flow was adjusted to keep the bag well-inflated throughout inspiration. For the animals receiving oxygen at 1 atm abs, the T-tube device was used with very high flow rates so that 100% oxygen was inspired and the expired air was carried by the oxygen stream into the atmosphere. Placement of the animals into the chamber and/or connection of the endotracheal tube to the oxygen line required between one and two minutes. The sling was then tightened and compression was begun immediately thereafter. Full pressure was reached in the chamber within one minute.

Continuous recordings of the electrocardiogram were made in all animals. In about half of the experiments, blood pressure was also recorded continuously through a catheter placed into a femoral artery and connected to a Statham strain gauge or a Sanborn transducer. An observer was always present in the pressure chamber.

Admission of the animals into the groups treated in the chamber was determined by availability of chamber time and by availability of animals of adequate size. Because of limitations, with respect to both chamber time and availability of suitable animals, the experiments covered a period of months and animals were added to groups A, B, and C at the rate of two to three dogs per week. After ligation of the coronary artery, the animals and experiments presented the following distribution:

- Group A: 50 control dogs, breathed room air at 1 atm abs.
- Group B: 43 dogs, breathed 100% oxygen at 1 atm abs for one hour.
- Group C: 50 dogs, breathed 100% oxygen for one hour in the chamber pressurized with air to 2 atm abs.
- Group D: 18 dogs, breathed 100% oxygen for one hour in the chamber pressurized with air to 4 atm abs.

Group D was added in the last three months of experimentation. Although the administration of 100% oxygen at 4 atm abs may not be practical for clinical purposes, it was selected in order to test at higher pressures an already apparent trend toward a dose-response effect. An attempt was made to raise the challenge in this group by using very large animals.

Since ventricular fibrillation, if it does occur, is nearly always observed within the first hour, the experiments were terminated at that time and the survivors were sacrificed shortly thereafter. Autopsies were performed on all animals and the artery was found occluded in every instance. The distance between the origin of the circumflex and the site of occlusion was recorded as well as the number of branches remaining patent proximal to the ligature. Only two experiments were excluded from the series as reported. In one of these, death, presumably from anesthesia, had occurred prior to ligation. In the other, an additional dose of anesthetic was required and marked respiratory depression was evident.

**Results**

The results of individual experiments in the four groups are given in table 1 according to weight and then summarized in figure 1. In the control group, 52.5% of the animals survived the challenge of coronary ligation. With inhalation of 100% oxygen at 1, 2, and 4 atm abs, survival rates increased to 60.4, 70, and 77.8% respectively. Groups A, B, and C were comparable in regard to body weight, the means being 21.2, 20.9, and 20.5 kg (table 2). The mean weight in group D was 23.3 kg. The mean weights of the survivors and of the animals which fibrillated are also compared in table 2. The average weights of the survivors were lower in groups A and B, the averages were comparable in group C, and the weight of the survivors was somewhat higher in group D.

The female animals had a higher survival rate. Of eight females in group A, six survived; of seven in group B, five survived; and of 13 in group C, ten survived. The two females in group D survived. Although the number of females in group C was higher, the survival trend was not altered by this factor (fig. 2).

The administration of oxygen under high pressure did not delay the appearance of ventricular fibrillation. The mean time which elapsed between occlusion of the artery and the onset of fibrillation was 13.7, 11.7, 14, and 15.2 minutes in groups A, B, C, and D, respectively.
TABLE 1
Effects of Hyperbaric Oxygen on Survival After Ligation of Coronary artery (and according to weight)

<table>
<thead>
<tr>
<th>Groups, conditions, no. of animals</th>
<th>Weight (kg)</th>
<th>Outcome</th>
<th>17</th>
<th>18</th>
<th>19</th>
<th>20</th>
<th>21</th>
<th>22</th>
<th>23</th>
<th>24</th>
<th>25</th>
<th>26</th>
<th>27-34</th>
<th>Total</th>
<th>Per cent survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Room air 1 atm 49</td>
<td>Lived</td>
<td></td>
<td>3</td>
<td>5</td>
<td>3</td>
<td>2</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>21</td>
<td></td>
<td>52.5%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Died</td>
<td></td>
<td>1</td>
<td>3</td>
<td>4</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>3</td>
<td>1</td>
<td>19</td>
<td></td>
<td></td>
</tr>
<tr>
<td>100% O2 1 atm 43</td>
<td>Lived</td>
<td></td>
<td>5</td>
<td>8</td>
<td>6</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td></td>
<td></td>
<td>26</td>
<td></td>
<td>60.4%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Died</td>
<td></td>
<td>2</td>
<td>1</td>
<td>3</td>
<td>3</td>
<td>2</td>
<td>2</td>
<td>3</td>
<td>1</td>
<td></td>
<td>17</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>100% O2 2 atm 50</td>
<td>Lived</td>
<td></td>
<td>3</td>
<td>8</td>
<td>10</td>
<td>5</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>3</td>
<td>1</td>
<td>35</td>
<td>70%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Died</td>
<td></td>
<td>7</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td>15</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>100% O2 4 atm 18</td>
<td>Lived</td>
<td></td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>14</td>
<td></td>
<td></td>
<td>77.8%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Died</td>
<td></td>
<td>1</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>4</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The site of ligation ranged from 5 to 10 mm from the origin of the circumflex artery with an average location at 8 mm. The four groups were evenly matched in this regard and no differences existed between the groups with respect to the number of patent branches proximal to the ligature.

No consistent trend was observed toward depression of blood pressure in the dogs that fibrillated. Most often, the pressure was normal up to the time of fibrillation. Myocardial irritability, indicated by premature ventricular contractions and by runs of ventricular tachycardia, was present in all animals and reached a maximum approximately 12 minutes following occlusion. In the survivors, the period of arrhythmia usually lasted between 5 and 15 minutes. Thereafter, only occasional extrasystoles were noted.

TABLE 2
Mean Weight (kg) of Dogs by Groups and by Survival

<table>
<thead>
<tr>
<th>Group</th>
<th>All dogs</th>
<th>Fibrillated</th>
<th>Survived</th>
</tr>
</thead>
<tbody>
<tr>
<td>A: room air</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 atm abs</td>
<td>21.2</td>
<td>21.9</td>
<td>20.6</td>
</tr>
<tr>
<td>B: 100% oxygen</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 atm abs</td>
<td>20.9</td>
<td>22.7</td>
<td>19.6</td>
</tr>
<tr>
<td>C: 100% oxygen</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 atm abs</td>
<td>20.5</td>
<td>20.3</td>
<td>20.5</td>
</tr>
<tr>
<td>D: 100% oxygen</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 atm abs</td>
<td>23.3</td>
<td>21.8</td>
<td>23.7</td>
</tr>
</tbody>
</table>

FIGURE 1
Per cent survival of dogs after coronary arterial ligation, showing stepwise increase in survival when exposed to increasing pressures of inhaled oxygen.

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The results of the experiments show a trend of proportions in four well-defined and ordered groups. Survival rates increase as the pressure of inhaled oxygen is raised. Although no significant difference was found between the groups (chi square: 4.98, 3 df, 0.10 < P < 0.20), the trend is impressive and approaches significance when subjected to statistical analysis. The degree of significance differs depending upon the position one assigns to group D in the tabulation of the results. The mean weight of the animals in this group was higher and therefore it may be presumed that the challenge of the "test ligation" was greater. On the other hand, the pressure of inhaled oxygen was 4 atm abs or twice that of group C. If the results are tabulated, as in figure 2, taking into account only the oxygen pressure and the proportion of survivors (with each unit increase on the X-scale corresponding to approximately 1 atm of pressure), the trend falls short of significance (0.20 < P < 0.30). The same is true if group 4 is omitted altogether from consideration (0.05 < P < 0.10). If the larger mean weight of the animals and the greater challenge in group D are taken into account by assigning equidistant positions to all groups on the X-axis (fig. 1), the trend of the increase of survival rate is indicated by a slope of +0.086, yielding a chi square value of 4.74 with 1 df. The chances of obtaining such a slope from random sampling are small (0.02 < P < 0.05).

Discussion

Death after coronary arterial occlusion can occur from ventricular fibrillation arising in focal areas of localized ischemia while the major portion of the myocardium still retains its potential for adequate mechanical function. It was postulated by Smith,² that hyperbaric oxygenation might confer protection against this "accidental" disruption of the synchronized activity of the heart by preserving viability of areas in which circulation has been critically reduced. His initial experiments tested this hypothesis on 30 dogs, 20 of which were controls. His subsequent report dealt with an additional 50 animals, of which 30 were controls. Occlusion of the circumflex coronary artery 1 cm from its origin resulted in a mortality of 60%. In the treated group administration of 100% oxygen at 2 atm abs lowered the mortality to 10%. The range of body weight (10 to 30 kg) was stated to be comparable in the three groups of his first series but details as to the distribution of weights in regard to survival were not given. The weights of the animals in the second 50 experiments were not reported.

The mechanism of ventricular fibrillation following occlusion of a coronary artery remains a subject of controversy. A lower fibrillation threshold in the area of ischemia,⁹ the existence of hyperexcitable cells in the narrow boundary zone between the ischemic and normal myocardium,¹⁰ and "currents of injury" caused by the oxygen differential between these zones²² have been implicated in the

† We are indebted to Edward Dowd, Ph.D., Department of Biostatistics, Roswell Park Memorial Institute, Buffalo, New York, for the statistical analyses of these data.
genesis of fibrillation. However, some evidence raises questions as to the role played by the oxygen differential between adjacent zones of normal and ischemic myocardium\textsuperscript{12} and fibrillation has been reported to occur from uniform myocardial anoxia due to asphyxia.\textsuperscript{6} The protective effect of hyperbaric oxygenation has been ascribed by Smith\textsuperscript{1,2} to a broadening of the border zone between normal and ischemic myocardium or to some unidentified mechanism which renders the normal myocardium more resistant to stimuli initiating fibrillation arising from the area of ischemia.

It is fair to state that the nature of the mechanism which leads to ventricular fibrillation remains conjectural. Moreover, the pathways through which hyperbaric oxygenation affects this mechanism also remains to be elucidated. Our experiments were not designed to identify these relationships further but to verify the existence of a protective effect of hyperbaric oxygenation in a larger series of animals. For this reason, instrumentation was kept to the minimum.

Our results are less dramatic than those obtained by Smith, but in general confirm his observations. There is some divergence in detail. In his series, perhaps because of the small number of animals in each group (ten), there was no apparent effect from inhalation of 100% oxygen at 1 atm abs. In our experiments, a stepwise increase in survival occurred in proportion to the partial pressure under which the oxygen was administered, suggesting a dose-response effect. This orderly trend in the results, added to the evidence obtained by Smith,\textsuperscript{1,2} lends weight to the conclusion that hyperbaric oxygenation confers some protection against the occurrence of ventricular fibrillation following experimental coronary artery occlusion.

Parameters other than the incidence of ventricular fibrillation have been studied to evaluate the effects of hyperbaric oxygenation on coronary arterial occlusion. Some reports have described favorable alterations of the electrocardiographic\textsuperscript{18} and biochemical changes\textsuperscript{14} induced by experimental ligation as well as a reduction in the size of the infarct produced.\textsuperscript{15} Recent studies by Moon et al.\textsuperscript{16} and Meijne et al.\textsuperscript{17} suggest that hyperbaric oxygenation may be of value in the treatment of cardiogenic shock following coronary occlusion.

The evidence so far obtained from experiments on animals and from the very few clinical trials to date\textsuperscript{2,16,17} is encouraging but does not warrant the uncontrolled clinical use of this therapy for coronary occlusion. Hyperbaric oxygen therapy carries risks and hazards, even in the normal subject. Its effect upon the pathophysiology of disease and on the pharmacologic effect of agents routinely used in clinical practice remains unexplored. The results of our experiments suggest that the effects of hyperbaric oxygen on the course of experimental coronary artery occlusion have an order of magnitude such that immediately obvious alterations of the mortality in clinical trials probably cannot be expected. These considerations emphasize the need for extended and careful clinical evaluation in rigidly controlled series. The procurement of early and decisive results from clinical trials might well be considerably accelerated by a coordinated effort of facilities staffed not only by clinicians but also by investigators experienced in the difficult techniques required for the acquisition of valid physiologic and other data under altered pressure conditions.

**Summary**

The effect of the inhalation of hyperbaric oxygen on the incidence of ventricular fibrillation following ligation of the circumflex coronary artery was studied in 151 dogs weighing 17 kg or more.

Fifty-two per cent of the animals in the control group (room air, 1 atm abs) survived the challenge of this ligation. Survival increased to 60.4, 70, and 77.8% in the groups given 100% oxygen at an ambient pressure of 1, 2, and 4 atm abs, respectively. The orderly progression in the proportion of survivals is impressive but only approaches statistical significance.
The results of these experiments are less dramatic than those previously reported by others. They do point out the need for cautious clinical trial in rigidly controlled series.

Acknowledgment

We are indebted to Dr. Herman Rahn for his valuable advice and the use of the facilities of his department and to R. A. Morin for his technical assistance including the operation of the hyperbaric chamber.

References