RATIONALE AND HAZARDS OF PRESSURE BREATHING AND OXYGEN THERAPY

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Shortly after the first world war oxygen became commercially available for medical use. At present the monthly consumption for this purpose in the United States is 30,000,000 cubic feet (1); this is ten times the figure for 1930. The yearly use of oxygen by a presumably representative general hospital shows a recent acceleration (table 1). In Cincinnati, a Life-Saving Squad in the Fire Department, trained in emergency therapy, is at each citizen’s beck and call. By reason of the availability of portable bottles and efficient masks, every doctor could have oxygen in his car if he thought it desirable.

TABLE 1

NUMBER OF CYLINDERS OF COMMERCIAL OXYGEN OF 220 CUBIC FEET CAPACITY BOUGHT YEARLY FOR USE IN THE CINCINNATI GENERAL HOSPITAL (2)

<table>
<thead>
<tr>
<th>Year</th>
<th>Cylinders</th>
<th>Year</th>
<th>Cylinders</th>
</tr>
</thead>
<tbody>
<tr>
<td>1930</td>
<td>500</td>
<td>1938</td>
<td>1087</td>
</tr>
<tr>
<td>1931</td>
<td>520</td>
<td>1939</td>
<td>1466</td>
</tr>
<tr>
<td>1932</td>
<td>525</td>
<td>1940</td>
<td>1382</td>
</tr>
<tr>
<td>1933</td>
<td>540</td>
<td>1941</td>
<td>1775</td>
</tr>
<tr>
<td>1934</td>
<td>900</td>
<td>1942</td>
<td>2355</td>
</tr>
<tr>
<td>1935</td>
<td>1100</td>
<td>1943</td>
<td>2576</td>
</tr>
<tr>
<td>1936</td>
<td>1181</td>
<td>1944</td>
<td>3852</td>
</tr>
<tr>
<td>1937</td>
<td>1415</td>
<td>1945</td>
<td>4812</td>
</tr>
</tbody>
</table>

Certain questions about this trend may well be raised. Is there justification for this emphasis being placed upon oxygen therapy? Are there hazards from administering oxygen indiscriminately? Are there new technics which will improve upon present methods of administration?

EXPERIMENTAL OBSERVATIONS

To answer these questions it is instructive to review the manner in which the body uses molecular oxygen. The process by which oxygen is transported from the ambient air to the tissues is relatively simple

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and well understood. The complex series of oxidations and reductions, and the complementary reactions that lead to the conversion of food-stuffs into water, carbon dioxide, and certain other compounds, are gradually being elucidated by the biochemists. We know that for the orderly sequence of these reactions there are many essential enzymes and coenzymes; the lack of or the poisoning of any one of them may decrease the consumption of molecular oxygen by the entire system through the inhibition of one or another specific reaction.

There are several ways of determining the cerebral consumption of oxygen. The essential part of the technic is to measure the amounts of oxygen in the blood going to and coming from the brain, and the volume of blood flowing through the brain in a unit of time. Five years ago a group working with Ferris measured the oxygen consumption in the brains of a number of people, ourselves included, by taking samples of femoral arterial and internal jugular blood, and measuring the cerebral blood flow by studying the response of jugular pressure to pressure in a cuff around the neck. The following observations were carried out upon patients suffering from abnormalities of interest in the present discussion.

Tables 2 and 3 give the hydrogen ion concentration of the arterial blood, the arterial oxygen and carbon dioxide tensions, the difference between the oxygen content of the arterial and the venous blood, the cerebral blood flow in arbitrary units, and the cerebral oxygen uptake in percentage of the normal value. The arterial oxygen tension was derived from the degree of oxygen saturation, and the pH of the arterial blood as determined by a glass electrode (3). The carbon dioxide tension was calculated from the pH, carbon dioxide content and hematocrit reading (4). The cerebral oxygen uptake was derived from the arteriovenous oxygen difference in volumes per cent, and the blood flow. The method of determining cerebral blood flow by means of the response of jugular pressure to cuff pressure gives an "index" of such flow, which can be expressed in terms of blood flow in arbitrary units or percentage of the normal value.

The patient with encephalopathy in association with deficiency of Vitamin B complex, was confused when first seen (table 2). There was a slight, partially compensated respiratory alkalosis, and a slightly lowered arterial oxygen tension. The arterio-venous oxygen difference was normal, but the blood flow was only one-third of normal; therefore the cerebral oxygen uptake per minute was a third of normal. After 100 mg. nicotinic acid amide was given intravenously, the cerebral blood flow doubled. Since the brain still extracted the same amount of oxygen from each cubic centimeter of blood while twice as much blood was traveling through, the total oxygen uptake doubled. On the following day, after no further treatment, the oxygen uptake remained unchanged. Ten days later, after massive B complex therapy, the patient was alert, and the cerebral blood flow and oxygen uptake were normal. The observations agree with the idea that treatment directed to a specific deficiency will give rise to a specific response.
TABLE 2
ENCEPHALOPATHY ASSOCIATED WITH VITAMIN B COMPLEX DEFICIENCY

<table>
<thead>
<tr>
<th>Hospital Day</th>
<th>Comment and Therapy</th>
<th>Arterial Blood</th>
<th>Brain</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>$pO_2$ mm. Hg</td>
<td>pH</td>
</tr>
<tr>
<td>2</td>
<td>Confused</td>
<td>68</td>
<td>7.46</td>
</tr>
<tr>
<td></td>
<td>100 mg. niacinamide, i.v.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Confused</td>
<td>60</td>
<td>7.52</td>
</tr>
<tr>
<td>3-13</td>
<td>Massive B complex therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>Alert</td>
<td>62</td>
<td>7.46</td>
</tr>
</tbody>
</table>

TABLE 3
CEREBRAL METABOLISM IN IRREVERSIBLE COMA

<table>
<thead>
<tr>
<th>Patient</th>
<th>Comment</th>
<th>Arterial Blood</th>
<th>Brain</th>
</tr>
</thead>
<tbody>
<tr>
<td>J.M., uremia</td>
<td>Shock</td>
<td>$pO_2$ mm. Hg</td>
<td>pH</td>
</tr>
<tr>
<td></td>
<td></td>
<td>82</td>
<td>7.21</td>
</tr>
<tr>
<td>F.L., head injury</td>
<td>9 hours</td>
<td>60</td>
<td>7.42</td>
</tr>
<tr>
<td></td>
<td>3 days</td>
<td>23</td>
<td>7.30</td>
</tr>
<tr>
<td></td>
<td>Oxygen by nasal catheter</td>
<td>58</td>
<td>7.38</td>
</tr>
<tr>
<td>M.S., pneumonia</td>
<td>Breathing air</td>
<td>32</td>
<td>7.34</td>
</tr>
<tr>
<td></td>
<td>2 days later</td>
<td>26</td>
<td>7.19</td>
</tr>
<tr>
<td></td>
<td>Oxygen tent (24% O₂)</td>
<td>25</td>
<td>7.21</td>
</tr>
<tr>
<td></td>
<td>Air</td>
<td>50</td>
<td>7.10</td>
</tr>
</tbody>
</table>

The next 3 patients were comatose. The experimental observations are shown in table 3. J. M. was pulseless, with blood pressure too low to measure. There was no arterial oxygen deficiency. There was severe uncompensated metabolic acidosis. The rate of cerebral blood flow was extremely low but the
jugular venous blood was nearly completely reduced; therefore the total cerebral oxygen uptake was quite normal. This condition illustrates the expected findings in stagnant anoxia, with the cells quite capable of consuming their normal complement of oxygen.

F. L. had a slight anoxic anoxia on admission, with an oxygen uptake at the lower limit of normal. Three days later the arterial oxygen tension was less than half that usually characterizing mixed venous blood, and the cerebral oxygen uptake had diminished somewhat. On the following day the anoxic anoxia had been nearly corrected by the administration of oxygen by nasal catheter. The arterial oxygen content was higher, but the venous oxygen content was also higher; the cerebral oxygen uptake had not improved. These findings illustrate the fact that a specific deficiency may not respond to nonspecific therapy.

It is a common observation that patients become apneic when effective oxygen therapy is initiated during anoxic anoxia. The third patient, in the terminal stages of pneumonia, was in a state of severe respiratory acidosis, with extreme anoxic anoxia. The cerebral oxygen uptake was deficient. Twenty-four hours later the acid-base response to effective oxygen therapy was studied. The breathing became much quieter, the coma deepened, and a more severe respiratory acidosis developed, when oxygen was given. It would seem that oxygen had depressed the sensitivity of the regulatory respiratory mechanism to carbon dioxide. This patient had adequate molecular oxygen therapy, with a result of dubious clinical value.

Physiologic Effects

In order to discuss the effects of oxygen and positive pressure in various anoxic states, we will outline the physiologic effects of these two procedures in health and illness. Increasing the alveolar oxygen tension increases the arterial oxygen tension. Special techniques are required to demonstrate the effect of this increase in arterial oxygen tension upon the regulation of the respiration of intact human subjects at atmospheric pressures equivalent to or near to that at sea level, because there are so many other more powerful factors that influence respiration. One such method is a study of the factors influencing the breath-holding time. Ferris, Engel, Stevens and Webb have published pertinent data (5). The arterial oxygen tensions have to be inferred from the experimental conditions except in two instances. The alveolar carbon dioxide tensions were assumed equal to the average experimental arterial tensions observed in each instance. The ordinates in figure 1 are oxygen tensions on a logarithmic scale, the abscissae are the carbon dioxide tensions on an arithmetic scale. The regression line drawn by inspection indicates that a change of 100 per cent in oxygen tension is associated with a change of 4 mm. in the tension of carbon dioxide to which the respiratory center is sensitive.

The data of Barach (6) on patients breathing 50 per cent oxygen mixtures over considerable periods of time show a consistent rise in the carbon dioxide combining power of the venous blood. This finding might be interpreted to be a compensating response to an elevated arterial carbon dioxide tension. Increase in the carbon dioxide tension
with increase in the oxygen tension has been noted particularly at superatmospheric oxygen tensions in animal experiments. It has been explained as owing to interference with normal diffusion processes ("disturbed pulmonary diffusion theory"), or inadequate blood carbon dioxide transport because of failure of reduction of oxyhemoglobin ("disturbed transport theory"). The present interpretation is that of retention of carbon dioxide because of lessened sensitivity of the centers controlling respiration to carbon dioxide tension in the presence of high oxygen tension ("disturbed respiratory sensitivity theory").

![GAS TENSIONS AT BREAKING POINT OF BREATH-HOLDING](image)

**Fig. 1.** Relation of logarithm of the alveolar oxygen tension and the alveolar carbon dioxide tension at the breaking point of breath-holding, based on data of Feris et al. (5).

Each of these alternatives is supported by experimental evidence, and that to which we have given preference here may have no more or less evidence in its favor at present than the others. Beau (8) has recently discussed the literature on this complex subject.

There are a few other effects resulting from oxygen administration. According to Barach (7), there is a slight consistent decline in the oxygen combining capacity of the blood after prolonged exposure to atmospheres containing 50 per cent of oxygen at sea level. The effect of high oxygen tension upon erythropoiesis is best shown under special circumstances, such as the response of formed elements in the blood of patients with sickle cell anemia to giving and withdrawing 100 per cent oxygen at normal atmospheric pressures (9).
The circulatory effects of high oxygen tension have not been elaborately studied in normal or sick human subjects as far as we are aware.

The problem of the toxic effects of high oxygen tensions is a curious chapter in respiratory physiology, for much has been done with animals and little with human beings. In general, the animals that have been studied have been fatally injured by continued exposure to oxygen tensions greater than 760 mm. of mercury over periods of hours or days (10). Some animals, including dogs, die within forty-eight hours during continuous respiratory exposure to oxygen at a pressure of 760 mm. of mercury. Behnke, Johnson, Poppen and Motley (11) and Case and Haldane (12) have observed convulsions develop in men at oxygen tensions greater than atmospheric. Recently Comroe, Dripps, Dunke and Deming (13), in a well-controlled experiment, showed that evidence of oxygen poisoning (bronchial irritation and reduction in vital capacity) appears within forty-eight hours in a high percentage of healthy men breathing U.S.P. oxygen at sea-level pressures. Some years ago Evans (14), and Boothby, Mayo and Lovelace (15) reported observations in which no evidences of intoxication by oxygen could be found among several hundred sick patients to whom “100 per cent oxygen” had been administered for as long as forty-eight hours. These are the only extensive data on such patients that we have seen; their limitations have been discussed by Comroe et al. (13).

In summary, increasing the alveolar oxygen tension immediately increases the arterial oxygen tension and thereby depresses slightly the sensitivity to carbon dioxide of the centers controlling respiration. It has little dramatic effect on the circulation and erythropoiesis. When oxygen is given in sufficiently high concentration for hours or days, it depresses slightly the oxygen-carrying capacity of the blood, and has uniformly toxic effects upon animals and certain toxic effects upon representative groups of healthy men.

Pressure breathing received a great stimulus from war research because of two possible applications: increasing the “ceiling” of airmen, and treating the pulmonary edema resultant from irritant gas poisoning. With pressure breathing the lungs can be actively inflated; without this technique much of present day chest surgery would be impractical. The cardiac output of healthy men is uniformly reduced under the conditions of pressure breathing (16). Apparently this is owing to the obstruction in the venous return because of the high intrathoracic pressure, which is partially transmitted to the great veins. Syncope was more easily induced in healthy men while undergoing pressure breathing (17, 18). The arterial oxygen tension is increased, since it follows the alveolar oxygen tension; this increase is of some clinical importance at ground level since it is relatively so small, but at reduced atmospheric pressure such as at a simulated altitude of 45,000 feet it makes a difference of several thousand feet in the “anoxic ceiling” of healthy men. This was of some theoretical tactical importance.
In practice it is somewhat difficult to avoid acapnia during pressure breathing, which may of itself lead to an incapacitating syndrome. Most investigators find that pressure breathing decreases the alveolar transudate in experimental pulmonary edema from drugs or irritant gases (19, 20).

Thus, increasing the intrathoracic pressure by pressure breathing actively inflates the lungs, increases the pressure upon the heart and great veins and thereby decreases the venous return and the cardiac output, increases the alveolar gas tensions slightly and decreases alveolar transudation. Presumably, oxygen therapy and pressure breathing together are additive in their effects.

**Discussion**

The inference that the specific types of anoxia require specific therapy is widely accepted clinically. Two arguments are employed to justify the empirical use of molecular oxygen for the treatment of a wide variety of clinical conditions.

The first argument is itself an inference; it justifies the use of molecular oxygen as the common denominator of anoxic states. Hoff, Grenell and Fulton (21) exemplified this argument in more general terms in a recent paper in which they have emphasized the existence of a common quality in certain changes in the central nervous system induced by diverse clinical states, in that each interferes in some manner with the metabolism of nervous tissue. They infer that “the similar histopathology in these various conditions may serve to elucidate a common etiological background and thus establish a firmer basis for therapy, as well as a deeper understanding of the interrelations between the physiology and pathology of the brain.” Michaelis (22) has pointed out that it is fruitful to define “oxidation as the withdrawal of electrons from a molecule or atom, and reduction... (as) the addition of electrons... The oxidizing agent is the acceptor, the substance to be oxidized the donor of the electron. Oxygen is one of the many substances which act as electron acceptors and is just one of the many oxidizing agents.” Since even oxygen is not a common denominator of all biologic oxidations, and the specificity of enzymes and coenzymes has been shown to be one of the most widely observed of biochemical phenomena, the fruitfulness of this “common denominator” concept remains to be shown.

The second argument is as follows: there is nothing specific that can be done, other than what is being done; oxygen is harmless; why not give it? We hasten to acknowledge that the proof of the efficacy of any method of therapy lies in the experiment that establishes the facts. Until recently, experimentation was limited to indirect observations, because the procedures needed for specific measures were not clinically available. With the development of practical procedures for measuring cerebral oxygen consumption, cerebral functional activity, the func-
tions of the special senses, and changes in the acid-base balance and oxygen tension of the arterial blood, empirical evaluation of these predicted effects can be expected.

Applications

From a knowledge of the effects of breathing oxygen under various conditions, and an understanding of the various types of anoxia that occur clinically, the field of usefulness of oxygen and pressure breathing can be discussed, although the rigid empirical proof by which to define this field precisely is lacking.

There is a large number of clinical states that are thought to be characterized by histotoxic anoxia. The use of superoxygenation in such states has the same rationale as the administration of vitamins for all anoxic states. This statement leads to the inference that such therapy should be judged empirically.

There are many types of stagnant anoxia, from shock following hemorrhage or plasma loss following burns, to peripheral vasoconstriction as a response to cold. The relative importance of specific therapy and such a nonspecific measure as oxygen inhalation should be considered in planning the treatment of the patient. Since pressure breathing diminishes the venous return in normal men, it would seem wise to avoid using it for this type of anoxia.

The anemia of hemoglobin deficiency is partially compensated for physiologically by an increase in the cardiac output. In special types of anemic anoxia as from the methemoglobinemia of aniline poisoning, and carbon monoxide hemoglobinemia, part of the circulating hemoglobin has been oxidized or inactivated so that it can no longer carry oxygen. The reduction of methemoglobin to hemoglobin is not affected by oxygen therapy as far as we are aware. Methemoglobinemia may rapidly disappear when the cause of the disturbance is removed (23).

The reversion of carboxyhemoglobinemia is hastened by increasing the arterial oxygen tension and by hyperventilation (voluntarily, or mechanically as from a pneumolator or artificial respiration, or chemically as from breathing carbon dioxide), but in our experience clinical recovery from the coma seems to be related more to the length of time before therapy was initiated than to the type of therapy.

Oxygen therapy was introduced principally for the rational treatment of the anoxic anoxia that may complicate pneumonia. Oxygen is frequently life-saving. Evans’ previously cited 1930 observations (14) on the toxicity of oxygen were carried out upon 147 patients to whom “pure oxygen” was administered. Seventy-four of the patients recovered and 69 died. More than oxygen therapy was needed by these 69 grievously ill patients. The comparative value to the patient of symptomatic and other types of supportive therapy, and such specific therapy as the use of antibiotics, must be kept in mind.
Pressure breathing is being increasingly advocated for the treatment of pulmonary edema, as from irritant gas poisoning or congestive failure. The rationale usually given for this therapy is that the increased pressure decreases the venous return to the right heart, indirectly relieving pulmonary congestion and lowering the hydrostatic pressure in the pulmonary capillaries.

There is a number of mixed anoxic states of clinical importance. Of these, myocardial infarction may be one of the most difficult to treat properly. If congestive failure is present with pulmonary edema, the usual measures for the relief of heart failure are recommended. Positive pressure respiration decreases the venous return, and is in effect a way of applying tourniquets not only to all four extremities but also to the head and abdomen. In congestive failure this may be salutary, but in the shock that may be associated with myocardial infarction, a procedure capable of inducing further shock is used with caution. The proper clinical treatment can be decided only at the bedside.

In the treatment of asthma there are a number of symptomatic therapies of proven value, such as depressing respiration by administration of oxygen (which has the unique property among all respiratory depressant drugs of simultaneously relieving anoxic anoxia, if it is present), quieting anxiety and its associated hyperventilation by the judicious use of other sedatives such as barbiturates and morphine, and dilating the terminal bronchioles by the inhalation of certain aerosols or smoke or by the parenteral injection of drugs like epinephrine or aminophylline. It is well recognized, however, that the proper treatment of an asthmatic has just begun when the acute attack is relieved.

In the treatment of apnea, giving oxygen by mask is obviously as useless as putting an analeptic in a vein in an attempt to restore the circulation after the heart has stopped. Only by some effective reflex stimulation of the respiratory center, or intermittent positive pressure breathing, or artificial respiration performed by some other technic can pulmonary gas exchange be kept up. It is noteworthy that passive ventilation of the lungs of animals while they continue to breathe the pure nitrogen that stopped their active respiration, may serve to restore the respiratory control to the animal (24).

**Summary**

The inhalation of oxygen is becoming a major item of general therapy. Its intelligent use requires a knowledge of the clinical, physiologic and biochemical actions of oxygen and pressure breathing. These actions are outlined. Certain limitations of the usefulness of oxygen therapy are shown by examples of the response of different types of anoxia to specific therapy and the failure of response to nonspecific therapy. In most anoxic states studied in vitro, the lack of availability of oxygen is not the cause of the disability and does not complicate it. That increasing the availability of oxygen will relieve
clinical anoxia and benefit the patient requires empirical proof. The clinical study of histotoxic anoxia lags far behind biochemical knowledge, but methods are now available to test directly the effect of therapy on the oxygen metabolism in such conditions. When used in conjunction with such procedures as psychomotor and electroencephalographic tests, further clinical understanding of anoxic conditions and their proper treatment should be forthcoming.

CONCLUSIONS

It is recognized that all forms of anoxia are deleterious and should be avoided. The proper treatment of an anoxic state usually requires far more than molecular oxygen therapy.

The principal hazard of oxygen therapy is the neglect of the primary cause of the disability.

The principal clinical value of pressure breathing relates to the therapy of pulmonary edema and such other conditions as are relieved by decreasing the venous return to the right side of the heart. This therapeutic effect is also the principal immediate hazard of pressure breathing.

REFERENCES

7 Ibid., p. 123.


