CIRCULATORY AND VISUAL EFFECTS OF OXYGEN AT 3 ATMOSPHERES PRESSURE\textsuperscript{1}

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In dogs anesthetized with sodium barbital, oxygen at a pressure of 4 atmospheres produces a fall in blood pressure and convulsive seizures which terminate in paralysis of respiration (Shaw, Behnke, and Messer, 1934). Since these phenomena are rapidly reversed when air replaces oxygen, the inference may be drawn that oxygen acts directly on the central nervous system, and possibly reflexly through the carotid sinuses.

In man oxygen at a pressure of 4 atmospheres induces either sudden syncope or convulsive seizures followed by complete recovery when air is again breathed (Behnke, Johnson, Poppen and Motley, 1935). In view of these striking phenomena, the question arose concerning the symptoms of oxygen toxicity for man at pressures less likely to produce sudden collapse.

The results reported in this paper indicate that oxygen at a pressure of 3 atmospheres brings about definite but rapidly reversible changes in man, namely, concentric contraction of the visual field, diminution of visual acuity, dilatation of the pupils, a rise in blood pressure, constriction of the facial vessels, and increased pulse rate.

EXPERIMENTAL METHOD. Four healthy young men breathed oxygen from either a closed or open system equipped with mask (4 experiments) or helmet (5 experiments) for periods up to 4 hours at a pressure of 3 atmospheres (30 lb. gauge). To accomplish this they were placed in the large pressure chamber described by Thomson, Yaglou and Van Woert (1932). The observations include records of the leucocyte count, blood pressure, heart rate, respiratory rate and minute volume, acuity of vision, area of the visual field, and the appearance time of a negative after-image. The visual field of each eye was measured on a perimeter immediately before and after oxygen breathing. Visual acuity was tested by the ability to distinguish two black lines drawn parallel on white piece of cardboard and separated by a distance of 0.35 mm. The negative after-

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image was induced by allowing the subject to fix on a red and green cross held at a distance of 1 meter from the eye for a period of 20 seconds.

Results. The period of oxygen breathing can be divided into two intervals. The first covers 3 hours during which oxygen was well tolerated. The second comprises a period of impending collapse which comes on abruptly during the 4th hour. The detailed results of a representative experiment are given in table 1.

**Oxygen breathing up to the 4th hour.** The usual symptoms were moderate facial pallor and dilatation of the pupils, a rise in diastolic blood pressure of about 10 points, and impairment in visual acuity up to 25 per cent. In

<table>
<thead>
<tr>
<th>TIME</th>
<th>BLOOD PRESSURE</th>
<th>PULSE RATE</th>
<th>VISUAL ACUITY DECREASE</th>
<th>TIME OF NEGATIVE AFTER-IMAGE</th>
<th>REMARKS</th>
</tr>
</thead>
<tbody>
<tr>
<td>a.m.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10:40—air</td>
<td>132/86</td>
<td>96</td>
<td>0</td>
<td>10:50 to 2:15, subject felt well.</td>
<td></td>
</tr>
<tr>
<td>10:50—O₂</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Facial pallor noted at 1:04</td>
</tr>
<tr>
<td>11:10</td>
<td>128/84</td>
<td>90</td>
<td>3</td>
<td></td>
<td>2:15, subject stated that his field of vision was decreased and that his fingers and toes felt numb</td>
</tr>
<tr>
<td>11:45</td>
<td>115/90</td>
<td>75</td>
<td>8</td>
<td></td>
<td>2:19, feeling of dizziness and impending collapse. Sense of precordial oppression, and inability to cough. Numness of fingers and toes. Intense facial pallor. Dilated pupils</td>
</tr>
<tr>
<td>p.m.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12:47</td>
<td>114/88</td>
<td>63</td>
<td>20</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1:15</td>
<td>124/84</td>
<td>57</td>
<td>28</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1:47</td>
<td>138/102</td>
<td>57</td>
<td>26</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2:00</td>
<td>120/94</td>
<td>63</td>
<td>10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2:10</td>
<td>150/104</td>
<td>75</td>
<td>60</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2:22</td>
<td></td>
<td>81</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2:23</td>
<td>Off O₂</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2:35—air</td>
<td>140/92</td>
<td>81</td>
<td>40</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

several experiments vision and blood pressure were not appreciably affected. There were usually no abnormal subjective symptoms during this period.

**Oxygen breathing during the 4th hour.** Progressive contraction of the visual field was a constant symptom during the 4th hour. Measurements on the perimeter immediately following removal of oxygen showed a concentric contraction for each eye ranging from one-half the initial area down to the 10° circle, as shown in figure 1. In a single experiment the contracted field suggested left temporal hemianopsia, and the right pupil was dilated to a greater degree than the left. Central vision for form and color was impaired but not seriously until the period of impending collapse,
when visual acuity was reduced as much as 60 per cent or even temporarily lost during the transfer from oxygen to air. A delay of 50 to 100 per cent in the time of appearance of the negative after-image paralleled the reduction of visual acuity. At the end of 2 out of 4 experiments the colors red and green were not recognized. An intense pallor of the face was present during the 4th hour, accompanied by wide dilatation of the pupils which reacted to light and accommodation. Both systolic and diastolic blood pressure readings were increased. In one experiment, however, in which

![Fig. 1. Perimetric measurements made before and after 3 ½ hours' oxygen breathing at 3 atmospheres' pressure (30 lb. gauge). A, normal field limits; determinations made with the Ferree-Rand perimeter and exposure method with 7 foot-candles illumination. B, C, and D, field limits 5, 25, and 50 minutes, respectively, following 3 ½ hours' oxygen breathing; observations made at atmospheric pressure with a black perimeter of 25 cm. radius illuminated by a blue bulb placed behind and above the observer's head; moving stick stimuli were used and checked by the exposure method; test object was a white disc 6 mm. in diameter.](http://ajplegacy.physiology.org/)

the blood pressure did not change the subject was in good condition at the end of 4 hours although contraction of the visual fields and facial pallor were present. Usually the abrupt onset of dizziness, nausea, and a feeling of impending collapse terminated the experiments in the fourth hour. Impending collapse was always signalized by an increase in pulse rate, rise of both systolic and diastolic pressure of 15 to 20 points, rapid contraction of the field of vision and failure in visual acuity for form and color. Although consciousness was retained at the end of all experiments the subjects looked dazed, and the delay in answering questions suggested partial stupor.
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In two examinations retinal ischemia or constriction of vessels could not be detected.

The respiratory rate and minute volume were constant in all experiments. The leucocyte and differential counts did not show any unusual changes, and there were no subjective symptoms pointing to pulmonary injury.

In one experiment, after the subject breathed oxygen for 3 hours and 56 minutes without discomfort, the blower was stopped and the subject rebreathed the gas in the helmet. Within two minutes he approached a condition of collapse. It is believed that the increased carbon dioxide tension was responsible for the abrupt change.

The period of recovery. Gradual recovery took place within 20 to 60 minutes after air replaced oxygen. Nausea and dizziness disappeared within a few minutes but the return of blood pressure, pulse rate, size of the pupils, visual acuity, and facial color to normal took place concurrently over a considerably longer period of time. The contracted visual fields usually regained their initial limits within an hour (fig. 1). The period of recovery was roughly proportional to the time between the onset of visual field contraction and the termination of the experiment. The significant point about recovery was the feeling of alertness and stimulation.

Calibre of the pial vessels of the cat in relation to oxygen at a pressure of 4 atmospheres and to increased carbon dioxide tension. In order to determine the effect of oxygen and of oxygen and carbon dioxide on blood vessels the pial arteries of the cat were observed through a window placed in the skull according to the method of Forbes (1928). The observations indicated that oxygen breathing at a pressure of 4 atmospheres did not appreciably alter the calibre of the pial arteries. The action of carbon dioxide (approximately 60 mm. tension) in combination with oxygen resulted in a dilatation of the arteries followed by constriction when carbon dioxide was removed (fig. 2). While the experiments are too few for conclusions to be drawn with respect to the action of oxygen at high pressure on pial vessels, the dilating effect of carbon dioxide in combination with a high pressure of oxygen is definite and in accord with the results of other investigators working with normal oxygen tensions.

Discussion. Severe functional disturbances similar to those associated with high oxygen pressure are without parallel in pharmacologic reactions in regard to the complete and rapid recovery which invariably follows. Temporary oxygen deprivation or withdrawal of cerebral blood supply for very short periods of time perhaps most closely simulate the oxygen effects.

Oxygen toxicity in relation to circulatory changes. Tolerance for oxygen at a pressure of 3 atmospheres is closely related to the stability of blood pressure and pulse rate. In the experiments of 4 hours' duration, which were symptomless except for contraction of the visual field, the blood pressure
remained constant. The circulatory disturbance in man associated with the toxic action of oxygen is essentially a peripheral vasoconstriction. At a pressure of 3 atmospheres the period of impending collapse was always signalized by the abrupt rise of both diastolic and systolic blood pressure, increased pulse rate, facial pallor, and dilatation of the pupils—symptoms which suggest stimulation of the sympathetic nervous system. At a pressure of 4 atmospheres, a rise in blood pressure (not previously reported) from 116/86 to 130/104 immediately preceded a violent convulsive seizure (Behnke et al., 1935).

Whether the circulatory changes are direct effects of the high oxygen pressure or compensatory reactions remains to be determined. The experimental results, however, bring up the fundamental question whether oxygen acts directly on nervous tissue to produce at 4 atmospheres the convulsive seizure and at 3 atmospheres contraction of the visual field, or whether these phenomena are the result of cerebral and retinal angiospasm induced by oxygen. Aid in answering this question is afforded by a consideration of the effect of carbon dioxide on cerebral vessels in relation to oxygen toxicity. The constriction of blood vessels would not, of course, deprive the brain of oxygen in view of the high partial pressure of this gas in the arterial blood (23 times the normal tension), but would tend to limit the supply of other necessary substances and hinder the removal of metabolites.

Action of carbon dioxide on cerebral vessels. The experiments of Gibbs, Gibbs, and Lennox (1935) indicate that human cerebral blood flow is

Fig. 2. Changes in the diameter of a pial arteriole of a cat breathing a 2 per cent carbon dioxide (equivalent to 8 per cent carbon dioxide at 1 atmosphere) and 98 per cent oxygen mixture at 4 atmospheres' pressure. Ordinate, diameter in microns; abscissa, time in minutes.
increased by raising the alveolar carbon dioxide tension. In cats, increased carbon dioxide tension dilates the pial vessels (Forbes, 1928; Wolff and Lennox, 1930) and increases the blood flow in the medulla and hypothalamus (Schmidt and Picson, 1934; Schmidt, 1934-1935). Conversely, decreased carbon dioxide tension constricts pial vessels and decreases blood flow.

**Carbon dioxide in relation to high oxygen pressure.** From the observations reported in this paper on the pial vessels of the cat, the dilating action of carbon dioxide on arterioles is not altered by high oxygen pressure. The effect of carbon dioxide on cerebral vessels and blood flow offers, therefore, a partial explanation of the finding of Shaw et al. (1934) that with an oxygen pressure of 4 atmospheres, convulsive seizures and a fall in blood pressure can be rapidly induced in anesthetized dogs by raising the alveolar carbon dioxide tension to 65 mm., or prevented by lowering the carbon dioxide tension to 22 mm. From this fact it is inferred that carbon dioxide renders a given oxygen tension more toxic by increasing cerebral blood flow, and that decreasing cerebral blood flow by lowering the alveolar carbon dioxide tension will render the given oxygen tension less toxic.

That carbon dioxide increases oxygen toxicity in man is inferred from the condition of impending collapse which was rapidly brought about by stopping the circulation of oxygen during the 4th hour and allowing re-breathing to take place for a period of 2 minutes. If carbon dioxide dilates retinal and cerebral vessels in man and increases blood flow when oxygen is breathed at a pressure of 3 and of 4 atmospheres, then it can be concluded that cerebral and retinal angiospasm are not responsible under these circumstances for the toxic action of oxygen. The inference follows that oxygen acts directly on nervous tissues, and that peripheral vasconstriction is probably a compensatory reaction.

In a study of the physicochemical reactions brought about in the nerve cell by high oxygen pressure, certain essential facts should be kept in mind: a, the action of oxygen is characterized by severe functional disturbances without apparent structural injury to nervous tissue; b, a latent period of about 3 hours at a pressure of 3 atmospheres and of 45 minutes at a pressure of 4 atmospheres precedes severe toxic symptoms in man; c, the circulatory, visual, and convulsive symptoms which lead to the collapse of the individual appear rather abruptly during the course of oxygen breathing; d, complete recovery is promoted by the substitution of air for oxygen, and requires a period of time roughly proportional to the duration of the toxic symptoms, i.e., 10 to 60 minutes; e, in man the sympathetic division of the autonomic nervous system is apparently stimulated since a rise in blood pressure, increase in pulse rate, and dilatation of the pupils accompany visual loss and mental impairment at a pressure of 3 atmospheres, while at a pressure of 4 atmospheres a rise in blood pressure pre-
cede a convulsive seizure; recovery, moreover, is attended by a feeling of stimulation; $f$, in dogs anesthetized with sodium barbital, a fall in femoral or carotid blood pressure is the constant and early sign of oxygen toxicity and always precedes the convulsive seizure; $g$, increased carbon dioxide tension hastens the fall in blood pressure and the convulsive seizure, while decreased carbon dioxide tension delays or prevents these symptoms.

**SUMMARY**

Oxygen at a pressure of 3 atmospheres (30 lb. gauge) can be breathed by healthy men for 3 hours without distressing symptoms. During the 4th hour a progressive contraction of the visual field with dilatation of the pupils and some impairment in central vision is the most constant criterion of oxygen toxicity.

Circulatory changes indicative of peripheral vascular constriction are associated with the visual impairment, and culminate during the 4th hour in an abrupt rise of systolic and diastolic blood pressure, increase in pulse rate, and extreme pallor of the face. At this stage the subjects experience dizziness and a feeling of impending collapse. A condition of partial stupefaction is indicated by the facial expression and the slowed mental responses.

Rapid and complete recovery attended by a feeling of alertness and stimulation takes place within an hour after air is substituted for oxygen.

We wish to express our appreciation and thanks to Dr. Marion R. Stoll of the Massachusetts Eye and Ear Infirmary for the perimetric studies, figure 1.

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