Proceedings
of the
Society
for
Experimental Biology and Medicine

VOL. 122 JUNE, 1966 No. 2

SECTION MEETINGS

DISTRICT OF COLUMBIA
Naval Medical Research Institute May 19, 1966

MINNESOTA
University of Minnesota May 11, 1966

# Blood Gas and Neurological Responses to Inhalation of Oxygen at 3 Atmospheres.* (31122)

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The recent widespread clinical use of hyperbaric oxygen (OHP) has made a critical evaluation of its toxic effects urgent. Excessive exposure to oxygen produces abnormal central nervous system reactions and severe pulmonary pathology in all mammals(1) but very little is known about the mechanism of these responses. Lambertson(2) has shown that the inhalation of pure oxygen at 3.5 atmospheres (at.) produces hyperventilation in normal human subjects accompanied by a decrease in cerebral blood flow. The central nervous system responses of man to OHP mimic those of anoxia and could therefore be attributed entirely to a decrease in cerebral blood flow. We know of no other study of cerebral blood flow in man exposed to OHP but a recent study of blood gas tensions in normal men breathing oxygen at 3 at. pressure failed to show that hyperventilation occurred(3). It was the purpose of this study to determine whether hyperventilation is produced in men breathing OHP. To detect early signs of pulmonary malfunction the Alveolar-arterial (A-a) differences were measured. The subjects were observed for clinical signs of oxygen toxicity.

*Procedures and methods.* The subjects were 7 normal men between the ages of 21 and 36 who had 6 months previously breathed pure oxygen at atmospheric pressure for 3 hours without showing any signs of toxicity. They were exposed to pure oxygen at 3 atmospheres in a hyperbaric chamber(4). Six were exposed twice for 2 hours and in addition for several shorter periods. At least 3 weeks were allowed between 2-hour exposures to prevent

* Supported by grants from Department of Health and Welfare, Quebec, USPHS and Medical Research Council of Canada.

a possible cumulative effect of oxygen. Three of the subjects were exposed for periods longer than 2 hours until neurological signs appeared. The seventh subject was exposed to 3 at. $O_2$ twice for one hour, twice for half an hour and 2 weeks later for 1 hour and 20 minutes.

The subjects rested in the supine position throughout the exposure to OHP and their pulse rate and blood pressure (sphygmomanometer) were recorded periodically. Oxygen (99.5%) from commercially available cylinders was bubbled through water and then passed through a mask made by modifying a face tent which was fitted with gauze sponges until the mask gas $O_2$ concentration was greater than 98%. A Beckman oxygen analyser with the sensor in the mask was unreliable at 3 atmospheres and we therefore checked the oxygen concentration by analysing mask gas samples on a micro-Scholander analyser outside the hyperbaric chamber. Samples of mask gas from the sampling tube were collected into small bag-bottles which were flushed out 3 times before sampling. The oxygen flow was maintained constant throughout each exposure, at a rate high enough to produce concentrations of at least 98% oxygen in the mask. The high flow helped to prevent accumulation of $CO_2$ in the mask. The $CO_2$ concentration in the mask never rose higher than 0.5%. To obtain an estimate of alveolar oxygen tensions during the exposures to OHP the end expiratory mask gas was sampled during some experiments. Because of the fast oxygen flow the $CO_2$ tension in these samples was much lower than alveolar $P_{CO_2}$ but their oxygen tension was assumed to equal alveolar $P_{O_2}$.

In all but one subject, a Riley needle was inserted into the radial artery before exposures for 2 or more hours and samples of arterial blood were analysed repeatedly during the exposure to oxygen at 3 at. Arterial blood samples were analysed for $P_{O_2}$, $P_{CO_2}$ and pH at 3 atmospheres on an Instrumentation Laboratories gas analyser (with a polypropylene membrane on the oxygen electrode) within 10 minutes from the time drawn. The calibration of the instrument was checked with an appropriate gas prior to each blood analysis but no attempt was made to humidify the calibrating gases nor to correct for oxygen diffusion through the membrane on the oxygen electrode. For this reason the absolute blood gas tensions may not be accurate but changes in $P_{O_2}$ or $P_{CO_2}$ during the exposures cannot be due to errors in measurement.

*Results. Clinical signs of oxygen toxicity.* The pulse tended to decrease during exposure to OHP and heart rate remained low for over 2 hours. Blood pressure on the other hand remained constant throughout the exposure in all our subjects (Fig. 1 and 2). In the 3 experiments in which the subjects were exposed until neurological signs occurred there was a slight increase in both pulse and blood pressure just prior to these signs. In one of

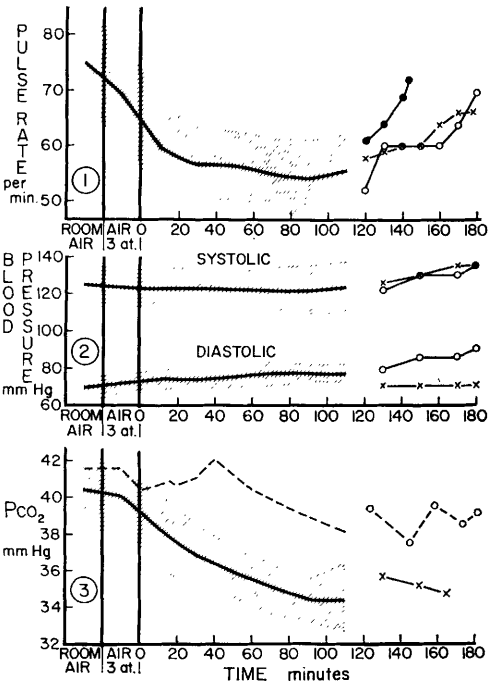



FIG. 1. Effect of inhalation of oxygen at 3 atmospheres on pulse rate.

FIG. 2. Effect of inhalation of oxygen at 3 atmospheres on blood pressure.

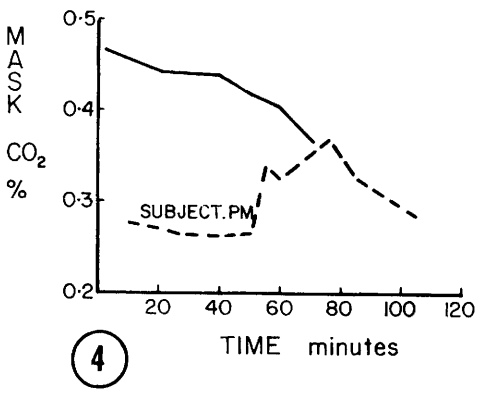
FIG. 3. Effect of inhalation of oxygen at 3 atmospheres on arterial carbon dioxide tension. Oxygen tension in the mask was 98% or more from time zero. Solid lines represent average readings on all subjects, shaded areas plus and minus one standard deviation. Each of the lines after 120 min shows readings from a single experiment. Broken line (Fig. 3) represents average readings for 3 exposures of subject PM, points after 120 min indicate readings during one exposure.

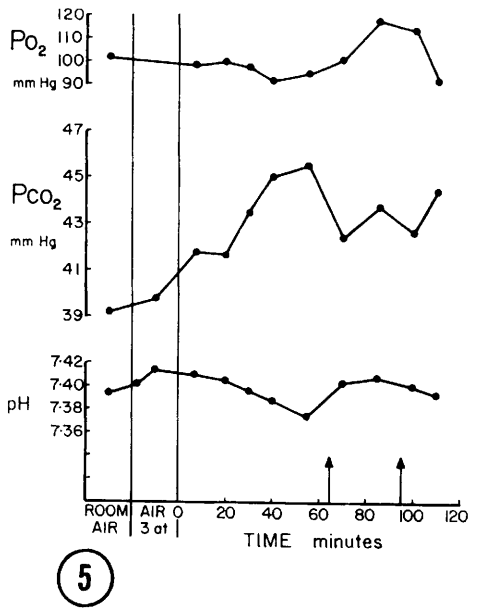
these subjects the experiment was terminated after 2 hours and 23 minutes when the subject complained of substernal pain and dizziness and his arm muscles were seen to twitch during the occlusion of the blood pressure cuff. The other 2 subjects had visual disturbances after 2½ hours of breathing oxygen at 3 at. Lights appeared too bright, objects looked distorted and there was a progressive loss of peripheral vision. In both cases vision had returned to normal 40 minutes after the experiment. One of these subjects (PM) had transient tingling in his fingers and toes earlier in the exposure but had no other symptoms. The other subject had a slight headache, nausea and chest pain during the last 15 minutes of the exposure. All subjects exposed for 2 or more hours said they felt hypersensitive to noise and were slightly dizzy for about 10 minutes after the exposure.

*Evidence of hyperventilation.* In 5 of the 6 subjects in whom arterial blood samples were obtained there was a decrease in arterial $CO_2$ tension ($Paco_2$) which began during the first 5 minutes of $O_2$ breathing and continued until the $Paco_2$ was approximately 35 mm Hg. The $Paco_2$ tended to remain constant at this level throughout the rest of the exposure (Fig. 3). In the one subject in whom arterial bloods could not be obtained the $CO_2$ concentration ($Fco_2$) in the mask gas decreased throughout the 2 hours of oxygen breathing (Fig. 4). Since $Fco_2$ in the same mask tended to increase to 1% within 15 minutes when our subjects breathed oxygen at one atmosphere this decrease must be due to hyperventilation. For exposures of less than 2 hours no arterial punctures were done but $Fco_2$ in the mask decreased in 10 out of 11 cases in a manner similar to that shown in Fig. 4. In our seventh subject, (PM), the $Paco_2$ did not decrease until 40 minutes after exposure was begun and then tended to fluctuate around 39 mm Hg. We were unable to demonstrate decreasing mask $Fco_2$ in this subject (Fig. 3 and 4). Subject PM is an amateur scuba diver. In order to demonstrate that hyperventilation was not due to the mask, 7% oxygen was substituted for the 99% $O_2$ at 3 at. in one experiment without the subject's knowledge. Fig. 5 shows the $Paco_2$, $Pao_2$ and arterial pH observed during this experiment. Arterial $Pco_2$ tended to rise instead of fall as it did when our subjects breathed 99% $O_2$. This rise must be due to the dead space in the mask because the $Pco_2$ fell when the mask was lifted for 10 seconds to flush out the dead space.

*$PAo_2$ and $Pao_2$.* The oxygen concentration in the mask always rose to 98% or more within 5 minutes of beginning the administration of oxygen at 3 atmospheres, *i.e.*, an $O_2$ tension of at least 2200 mm Hg was breathed throughout these exposures. In the 4 experiments in which alveolar gas (see *Methods*) was sampled the alveolar $Po_2$ ranged from 2130 to 2200 mm Hg. In the 11 experiments in which arterial blood samples were analysed the arterial $Po_2$ rose to its maximum value (mean of 1960 mm Hg, range 1880 to 2030) during the first 5 minutes of exposure and remained steady at this value throughout the experiment. Fig. 6 shows the $PAo_2$ and $Pao_2$ in the 2 subjects who were studied for 3 hours. There was no increase in the A-a difference of approximately 160 mm Hg during this period.

*Discussion.* The data presented show that healthy men hyperventilate when exposed to 3 at. of oxygen. This agrees with a previous study(2) in which the hyperventilation was attributed to decreased cerebral blood flow. The low $Pco_2$ produced by hyperventilation may cause widespread vasoconstriction and decreased organ blood flow which would detract from the possible beneficial effects of hyperbaric oxygen therapy. Vasoconstriction has been observed in the retinal vessels of man breathing OHP(5). Another effect of OHP that would decrease organ perfusion is the decrease in pulse rate observed in these experiments. The decrease in pulse rate leads to a decreased cardiac output and increased peripheral resistance(3). Both pulse and blood pressure tended to rise after 2 hours of exposure to hyperbaric oxygen when neurological signs of oxygen toxicity began to appear. The increase in blood pressure is small and the pulse rate may remain below the resting value breathing air at one atmosphere; but these changes seem to precede more serious symptoms of toxicity and an



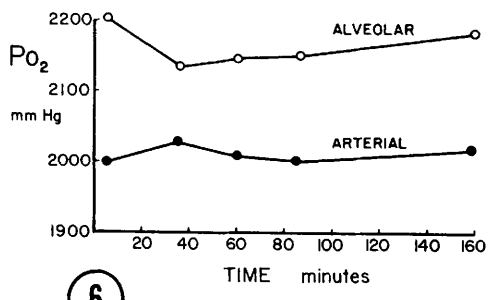




FIG. 4. Concentrations of carbon dioxide in the mask gas. Solid line, average concentrations from 2 exposures of one subject in whom no arterial blood samples were obtained. Broken line, average concentrations during 3 exposures of subject PM. Oxygen tension in the mask was 98% or more from time zero.

FIG. 5. Arterial $Po_2$, $Pco_2$ and pH in a subject breathing 7% oxygen at 3 atmospheres. At time zero the mask gas oxygen tensions had reached 100 mm Hg. Vertical arrows indicate the times at which the mask was ventilated for 10 sec.

FIG. 6. Simultaneous arterial and alveolar oxygen tensions. Lines represent means of 2 experiments.

awareness of them should therefore be helpful in preventing serious neurological symptoms in hyperbaric chambers. We did not observe any convulsions. Substernal distress, headache, dizziness and nausea are subjective symptoms too variable to be useful diagnostically. On the other hand, the loss of peripheral vision, which we observed in 2 subjects who breathed hyperbaric oxygen for 3 hours, could be used as a sign of the onset of toxicity because it develops gradually. It has previously been described as occurring during the fourth hour of oxygen breathing(6). The data reported here show no evidence of impaired pulmonary function as evidenced by measurements of arterial and alveolar oxygen tensions. The A-a $O_2$ difference did not increase during 3 hours of breathing oxygen at 3 atmospheres. Our techniques would tend to overestimate the A-a difference since we did not correct the arterial oxygen tensions for a possible membrane factor and sampled "alveolar" gas in a mask which had a large dead space. The fact that our measured A-a differences were nonetheless of the order of 160 mm Hg strongly suggests that A-a differences in normal men breathing oxygen at 3 atmospheres are unchanged.

*Summary.* Arterial blood gas tensions, pulse and blood pressure were monitored repeatedly in 7 normal young men while they breathed 99% oxygen at 3 atmospheres in a hyperbaric chamber for periods of up to 3 hours. There was evidence that 6 of these subjects hyperventilated during the exposure. Arterial $Pco_2$ began to fall during the first 5 minutes of exposure and continued to decline to 35 mm Hg during the first 90 minutes. It tended to remain constant during the rest of the exposure. Arterial $Po_2$ rose to 2000 mm Hg during the first 5 minutes of exposure and remained at this level. The pulse rate fell by 25% and remained at this level for at least 2 hours when it began to increase. Blood

pressure was constant for the first 2 hours of exposure and began to rise at the same time as the pulse. Loss of peripheral vision as well as subjective signs of oxygen intoxication (dizziness, nausea, etc.) began to appear during the third hour of exposure but no convulsions were produced.

We should like to thank the volunteers who made this study possible as well as our colleagues from the Joint Cardiorespiratory Service of the Royal Victoria Hospital who encouraged us and helped us with the arterial blood sampling.

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Received February 18, 1966. P.S.E.B.M., 1966, v122.

## Effect of Pyrophosphate on Dissolution of Hydroxyapatite and Its Possible Importance in Calcium Homeostasis.* (31123)

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In previous studies we found that pyrophosphate was present both in plasma(1) and urine(2), in concentrations of 2-3 $\mu$M and 10-100 $\mu$M respectively. Pyrophosphate inhibited not only calcium phosphate precipitation from metastable solutions *in vitro*(3) but also inhibited calcification in tissue culture (4) and *in vivo*(5). These observations suggested that pyrophosphate might be one of the physiological regulators of calcification (6). During investigations of its possible mechanism of action, pyrophosphate was shown to have a high affinity for hydroxyapatite crystals; apatite crystals remained in equilibrium with physiological concentrations of pyrophosphate (2-3 $\mu$M) only after binding large amounts of the compound(7). These studies suggest that at least some of the pyrophosphate known to be present in bone(8,9) is situated on crystal surfaces. The possible effects of pyrophosphate on the behavior of hydroxyapatite crystals seemed therefore to be of potential interest in relation to calcium homeostasis.

In a previous paper we showed that hydroxyapatite treated with pyrophosphate was no longer able to induce precipitation of calcium phosphate even from highly supersaturated solutions(7). Preliminary observations suggested that this treated apatite also showed a somewhat different behavior during dissolution. In the present paper this effect has been investigated in more detail.

*Methods.* Hydroxyapatite was obtained from the Victor Chemical Co., USA. The crystals were shown to have a molar Ca/P ratio of 1.64. They exhibited an X-ray diffraction pattern characteristic of hydroxyapatite; no other pattern developed after heating at 900°C for 15 hours. Furthermore heating at 500°C for 15 hours, a procedure known to cause pyrophosphate formation from calcium-deficient apatites(10), converted only 0.43% of the P into pyrophosphate. The length of the crystals in electron micrographs was about 1000 Å. These results show that the crystals used were composed essentially of a non-calcium-deficient hydroxyapatite.

* This work has been supported by the Schweizerischer Nationalfonds zur Förderung der wissenschaftlichen Forschung; USPHS grant AM 07266-02 of Nat. Inst. of Arthritis and Metab. Dis.; and the Sandoz Stiftung zur Förderung der medizinisch-biologischen Wissenschaften.