

Rapid Communication

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OXYGEN BREATHING AND VENTILATION

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We investigated the ventilatory response to normobaric poikilocapnic hyperoxia in healthy subjects. The study was carried out in 26 subjects of the mean age 26 ± 0.9 (SE) years, who breathed pure oxygen through a two-way valve for 10 min. The subjects were in the sitting position with a mouthpiece and nose clip attached. Ventilatory flow was recorded using a pneumotachograph and minute ventilation was calculated from the tidal and frequency components. The SaO_2 and alveolar CO_2 tension were continuously monitored. Ten of the same subjects constituted a control group in which room air was substituted for oxygen and the tests repeated in the same way at another occasion. We found that oxygen breathing caused a transient 8.4% decline in ventilation, whose nadir was 1 min after the introduction of oxygen. Thereafter, ventilation increased significantly above the baseline value and showed a further rising tendency toward the end of the test. We conclude that acute oxygen treatment is unlikely to have a major inhibitory effect on the carotid body-dependent ventilatory drive in normal subjects. The determinants of the hyperoxic ventilatory stimulation remain to be established in further studies.

Key words: hyperoxia, oxygen, respiratory pattern, ventilation, ventilatory drive

INTRODUCTION

Oxygen, since its discovery by Priestly in 1774, has remained one of the most widespread therapeutic agents available. Oxygen is used in numerous clinical settings, ranging from life support in critically ill patients, for example in cases of major trauma or acute coronary syndromes, to the pathological states underlain by acute or chronic hypoxia, such as adult respiratory distress syndrome or chronic obstructive pulmonary disease. Oxygen supplementation improves survival,

exercise capability, and the quality of life. The downside of oxygen use is that oxygen is feared to diminish respiratory drive, especially that emanating from the carotid body chemoreceptors, which in the longer run could exacerbate rather than mitigate hypoxia. In the patients who receive their drive to breathe largely from the hypoxia-stimulated carotid body, relief of hypoxia abolishes the drive, causing hypoventilation and a rise in the arterial CO₂ tension (PaCO₂). In this group of patients hyperoxia might be a potential danger. The fear of hypoventilation likely stands behind the introduction of numerous clinical paradigms of the oxygen concentration, the oxygen flow rate, and the duration of supplementation.

Several studies on the ventilatory response to normobaric hyperoxia have been carried out in the past and the results are equivocal. In humans, with brief exposures of up to 1 min of hyperoxia, there occurs an immediate and transient hypoventilation (1, 2, 3). With more prolonged exposures lasting from 5 to 20 min, no change or a mild hyperventilation is observed (1, 3, 4). Similarly, in intact cats, exposure to 10 min of hyperoxia results in no change in ventilation compared with air breathing (5). However, in carotid body-deafferented cats in the same study, such exposure results in enhanced ventilation, as if respiration has been relieved from an inherently mitigating effect of the carotid body. Opposing effects on ventilation of breathing pure oxygen in conscious, intact versus chemodenervated, cats have also been found when the time of O₂ delivery was extended to up 1 h (6). In anesthetized intact cats, transient hypoventilation was noted with magnitude depending on the anesthesia level (6). These findings suggest that the immediate oxygen-induced attenuation of the carotid body effect is offset by a stimulatory action of oxygen exerted at other structures in awake animals, which seems not to hold for man, as outlined above. Recently, Becker et al. (7) have shown an oxygen concentration-dependent increase in ventilation in humans during a 30 min period of breathing O₂-enriched mixtures while maintaining isocapnia. In that study, stimulation of ventilation was mild while subjects breathed 30% O₂, but ventilation more than doubled with 75% O₂. However, in clinical settings the alveolar PCO₂ tension (P_ACO₂) is not kept constant during oxygen supplementation.

In view of the controversies surrounding the issue of respiratory drive inhibition by oxygen we decided to reexamine the effects on ventilation of acute exposure to oxygen in healthy subjects.

MATERIAL AND METHODS

Study population

Twenty six healthy volunteers (F/M - 14/12) aged 17 to 44 years (mean 26 ±0.9 SE years) participated in this study. None of them smoked and none took any medication that could influence the respiratory pattern, in particular any hormonal or psychotropic drugs. The females were studied in the first half of their menstrual cycle to avoid any interference due to varied hormonal levels. All

subjects were familiar with the study protocol and gave informed consent. The Ethics Committee for Human Research of the Polish Academy of Sciences Medical Research Center approved the study.

Study design

The study investigated the effects on ventilation and breathing pattern of a 10 min period of normobaric hyperoxia consisting of breathing pure oxygen. Additionally, 10 of the 26 subjects breathed room air on another occasion, which constituted a basic control. These control tests were performed at least 10 days apart from the oxygen ones. Subjects were seated in a chair with a mouthpiece and nose clip in place. They rebreathed from a low-pressure reservoir containing about 100 L of 100% O₂ through a low-resistance two-way Hans Rudolph valve. The valve was connected to a pneumotachographic head equipped with a built-in aerodynamic element (MES, Cracow, Poland) to record respiratory flow breath-by-breath. Minute ventilation (V_E) was calculated from the integral of the flow signal and breathing rate. Expired gas was sampled continuously at the mouth with an infrared capnograph (Spegas Industries, Ltd. Jerusalem, Israel) and analyzed for the alveolar CO₂ concentration, from which the P_ACO₂ was calculated. The P_ACO₂ was allowed to run free. Arterial oxygen saturation (SaO₂) was measured with a finger oximeter.

Data analysis

All data were presented as means \pm SE. V_E was expressed in the absolute terms as L/min and the contribution to hyperoxic response of tidal volume (V_T) and breath frequency (f) was assessed from their percentage changes from the baseline values. The means of V_T , f , and V_E were calculated as means of three respiratory cycles. The measurements were taken every minute for both oxygen and room air tests in each subject and then averaged for the group. Changes of V_E with the time of hyperoxic and room air treatments were evaluated statistically with one-way analysis of variance each. Differences between the hyperoxic and room air experiments were analyzed using an unpaired t-test. The significance level was set at $P < 0.05$.

RESULTS

The mean baseline SaO₂ for the oxygen breathing group was $97.7 \pm 0.2\%$ and increased to 100% on oxygen breathing ($P < 0.001$). The respective values for the air breathing group were $97.3 \pm 0.3\%$ and $97.3 \pm 0.4\%$, which was an inappreciable difference. The time course of the ventilatory response to hyperoxia is demonstrated in *Fig. 1A*, where the mean values of V_E are calculated for both hyperoxic and room air experiments. The ventilatory response to hyperoxia showed a biphasic pattern, consisting of early inhibition followed by stimulation that became apparent by the 3rd min. V_E dropped to 9.10 ± 0.67 L/min in the 1st min of hyperoxic exposure from the baseline value of 9.93 ± 1.07 L/min. This was a modest 8.4% decrease, which did not assume statistical significance due to a large scatter of the data. The decrease in V_E was due mostly to a decrease in f whereas V_T remained fairly stable (*Table 1*). After the 1st min decline, V_E started rising, the rise exceeded the baseline level and showed a trend for a further increase in the last minutes of the test. As opposed to the 1st min decline, the hyperoxic V_E increase

Table 1. Contribution of tidal volume (V_T) and frequency (f) to ventilatory response to hyperoxia and room air.

Test Minutes	Hyperoxia		Room Air	
	V_T	f	V_T	f
1	98 ±6.83	93 ±5.7	105 ±6.6	99 ±7.4
2	104 ±7.28	95 ±5.7	100 ±11.7	102 ±7.9
3	108 ±6.45	100 ±6.4	97 ±11.9	99 ±7.8
4	105 ±6.29	100 ±6.3	97 ±13.4	100 ±7.9
5	106 ±5.87	99 ±4.9	97 ±10.5	101 ±6.9
6	108 ±6.82	100 ±5.8	93 ±9.6	100 ±7.8
7	110 ±7.61	103 ±5.9	94 ±12.1	101 ±8.2
8	106 ±7.04	106 ±5.5	97 ±10.2	99 ±6.8
9	106 ±7.31	107 ±5.9	98 ±10.9	99 ±8.3

Data are presented as the means ±SE of percentage changes from control.

was backed by the tidal component (*Table 1*). The 1st min V_E on room air did not differ appreciably from baseline and showed only fluctuations about it thereafter.

Since the interval between the 3rd and 9th min of the test showed a basically stable level of V_E for both hyperoxic and room air trials, we pooled these data for each gas condition, neglecting the time factor, which is graphically shown in *Fig. 1A* by way of the dashed-line rectangular. The 3-9th min data, taken as one entity, were then compared with the similar period on room air and with the 1st min V_E values, as shown in *Fig. 1B*. The mean, pooled 3-9th min V_E amounted to 10.81 ±0.21 L/min on hyperoxia and to 9.45 ±0.26 L/min on air ($P<0.001$). The analysis shows that the 3-9th min hyperoxic ventilation was not only higher than the corresponding time points of room air but also higher than the 1st min of both hyperoxic ($P<0.007$) and room air ($P<0.001$) ventilation. These results underscore the overall stimulatory effect of hyperoxic breathing on ventilation, which sets in after a transient introductory decline. Such a decline was absent during room air breathing.

The $P_A\text{CO}_2$ was running free during the experiments. For the hyperoxic test, the mean baseline $P_A\text{CO}_2$ value was 4.27 ±0.07 kPa and it decreased to 4.09 ±0.03 kPa in the 3-9th min period. The respective values for the room air test were 4.01 ±0.09 kPa and 4.05 ±0.04 kPa. These changes in the $P_A\text{CO}_2$ level were mild and did not differ significantly.

DISCUSSION

This study demonstrates that short-term pure oxygen breathing led to a prompt decrease in minute ventilation whose nadir took place one minute after the

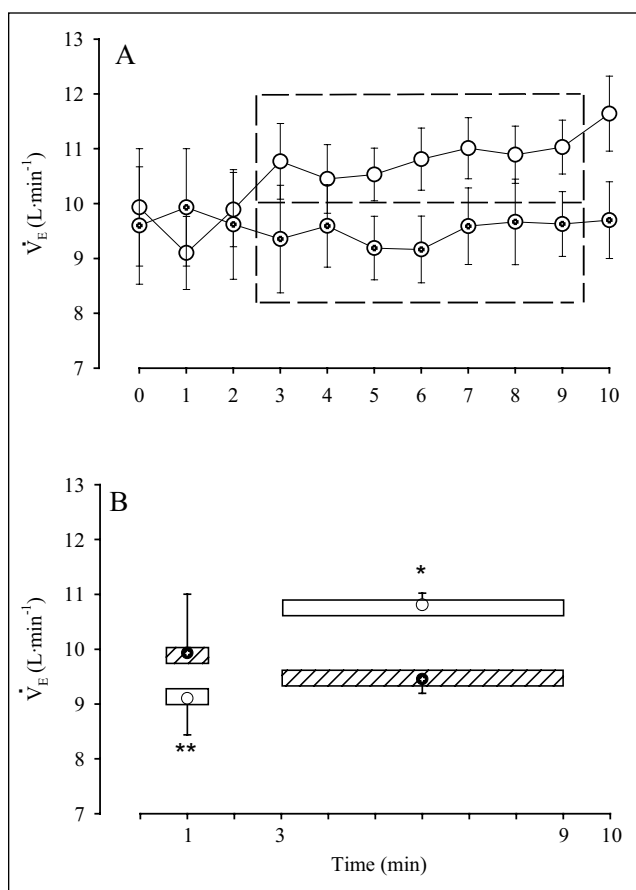


Fig. 1. A - the time course of minute ventilation during hyperoxic (open circles) and room air (target circles) exposure tests. Symbols are the group means (\pm SE). The dashed-line rectangular, encompassing data points of the 3-9th min, depicts the pooled values, subjected to further analysis as shown in B (see text for details). *Hyperoxic 3-9th \dot{V}_E significantly higher than both room air data pools (hatched symbol bars) ($P < 0.001$); **Hyperoxic 1st min \dot{V}_E significantly lower than the remaining, pooled hyperoxic data points (long open symbol bar) ($P < 0.007$).

introduction of oxygen into the inspiratory line. Thereafter, ventilation not only recovered but also increased above the baseline level, showing a further stimulatory trend in the 10 min test time. These findings suggest that there is no major, sustained curtailment of respiratory drive in response to acute exposure to oxygen in normal humans. An 8.4% drop in ventilation observed in the 1st min of oxygen breathing corresponds, in all likelihood, to the inhibitory effect stemming from the attenuated carotid body function by oxygen. This suggestion is supported by the dominant role of breath frequency in decreasing ventilation at this stage, which is in accordance with the role of the carotid body regarding regulation of respiratory timing in conscious humans (8) or cats (6).

A drop in ventilation is determined to increase $PaCO_2$ that, via a chemoreflex, fosters a rebound of the ventilation. The transient decline in ventilation we observed could have been somehow accentuated, had we kept the PCO_2 constant. However, the following hyperoxic enhancement of ventilation, which is mitigated by decreasing $PaCO_2$, would also have been accentuated. We chose not to regulate

the PCO_2 in this study, since it is not routinely done in clinical settings of oxygen treatment. A moderate magnitude of ventilatory decrease, much smaller than the known nearly total, sustained inhibition of carotid body chemoreceptor afferent discharge by oxygen (9), suggests that there are carotid body-independent compensatory mechanisms that uphold ventilation at a safe level or drive it above baseline with continued exposure to hyperoxia. There are several plausible explanations for the hyperoxia-induced ventilatory enhancement.

Oxygen might evoke toxic effects at the lung level, leading to the activation of irritant and other airway receptors, which through the vagal afferents could stimulate ventilation (10). However, none of the subjects studied reported any symptoms, such as cough or airway irritation, which suggests that this afferentation did not play a key role in the ventilatory enhancement observed.

The hyperoxic stimulation of ventilation might be due to a reduction of cerebral blood flow, which leads to an increase in PCO_2 in the brain and cerebrospinal spaces. A 15% decrease in cerebral blood flow has been demonstrated by Lambertsen et al. (11) in subjects breathing 100% O_2 for 1 h. The stimulatory effect would be mediated by the central chemoreceptors that respond to the CO_2 retention. Others have shown, however, that the cerebral blood flow remains fairly stable for up to 10 min of hyperoxia (12), the time period used in the present study.

Yet another mechanism that could participate in the hyperoxic enhancement of ventilation is the Haldane effect. Normally, 30% of CO_2 eliminated in the lungs comes from the carbamino sources carried with the venous blood hemoglobin. Oxygenated hemoglobin has a lower transport capacity for CO_2 than does the non-oxygenated one due both to a less reduced state of carbamino bonds and a decreased buffering capacity (13). While breathing pure oxygen, mixed venous O_2 saturation may increase as much as 10% from the ~70% present during normal air breathing. This decreases the content of CO_2 carried in the form of the carbamino load and consequently also the CO_2 elimination at the lung capillaries, which, in turn, causes an increase in brain tissue PCO_2 that would stimulate respiration via the central chemoreceptors. The Haldane effect has a fleeting character in healthy subjects, since the increased PCO_2 is promptly lowered by higher ventilation due to the CO_2 -induced stimulation of central chemoreceptors (11). The effect might be more of a factor in the hyperoxic ventilatory stimulation when the PCO_2 is kept constant. In such an instance, Becker et al. (14) found that 30 min of normobaric hyperoxia consisting of 50% O_2 in N_2 resulted in the stimulation of minute ventilation by 60%. On the other hand, these authors reported that the SaO_2 increase flattened out 5 min in hyperoxia, yet minute ventilation continued to increase over the time of the hyperoxic exposure, which suggests other than the Haldane, as yet unidentified, mechanisms behind the hyperoxic hyperventilation. These mechanisms might also have to do with the elaboration of signaling molecules in the carotid chemoreceptor cells in response to change in PaO_2 (15). The limited data available make it difficult to discern the

exact determinants of the effect of hyperoxia on ventilation, which should be clarified in alternative study designs.

In summary, the study failed to show a sustained, inhibitory effect on ventilation of acute exposure to oxygen in normal subjects, which could be judged as being of a major clinical relevance. Although the study did not determine the mechanisms of hyperoxia-induced ventilatory enhancement, we believe we have shown that acute oxygen does not constitute a detriment to respiratory drive which could substantiate the fear of oxygen use in clinical settings that might come to occur in such subjects.

Acknowledgments: This study was supported by the statutory budget of the Polish Academy of Sciences Medical Research Center. We are thankful to Dr. Leszek Czerwosz for his advise on the way of statistical analysis of the data. We are indebted to the ladies from Warsaw-Mokotów University of the Third Age who kindly volunteered, as subjects, for the study. Our thanks also go to Professors Leszek Radwan and Janusz Kowalski of the Department of Physiopathology of the National Tuberculosis and Lung Diseases Research Institute in Warsaw for their comments during the study.

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Received: April 23, 2003

Accepted: February 3, 2004

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