Acute Effects of Oxygen Treatment Upon Information Processing In Hypoxemic COPD Patients*

Dawn K. Wilson, M.A.; Robert M. Kaplan, Ph.D.; Richard M. Timms, M.D., F.C.C.P.; and Arthur Dawson, M.D.
Acute Effects of Oxygen Treatment Upon Information Processing in Hypoxemic COPD Patients*

Dawn K. Wilson, M.A.; Robert M. Kaplan, Ph.D.; Richard M. Timms, M.D., F. C. C. P.; and Arthur Dawson, M.D.

The present study investigated the effects of oxygen therapy upon human information processing for hypoxemic COPD patients. Each of ten patients was admitted to a general clinical research center for a two-day period. In a randomly counter-balanced factorial design, patients breathed either room air or enriched oxygen for either six hours or 20 minutes prior to testing. The tests evaluated speed of information processing, ability to detect correct sequence of tones, and serial memory. In addition, patients were evaluated on critical flicker fusion and story recall. The results suggested that acute oxygen therapy does not reverse information processing deficits observed in hypoxemic COPD patients.

Several studies have demonstrated that patients with chronic obstructive pulmonary disease (COPD) have impairments in perceptual and motor abilities. For example, Grant et al. found that 42 percent of 203 hypoxemic COPD patients had moderate-to-severe neuropsychologic impairments suggestive of cerebral dysfunction, as compared with only 14 percent of 74 matched control subjects. Whether these impairments are permanent or reversible has not yet been determined.

Studies that have evaluated hyperoxygenation procedures to correct central nervous system (CNS) impairments have produced inconsistent results. Jacobs and colleagues examined 13 elderly men with organic brain syndrome who were given 30 intermittent exposures to 100 percent oxygen at 2.5 atmospheres of pressure. Five patients breathing a low-oxygen mixture (10 percent oxygen, 90 percent nitrogen) served as the control group. Those receiving enriched oxygen performed better on psychologic tasks than did control subjects. The controls improved their performances once they were switched to the hyperoxygenation condition. In a second study, Jacobs and colleagues evaluated the effects of oxygen treatment after patients had been off therapy for 24 hours, 72 hours, seven days, or ten days. They found that enhancement of psychological performance lasted longer than would be expected as a result of increased PaO₂ levels. Performance on several standardized tasks declined as the duration of time after treatment increased.

In contrast to the positive results reported by Jacobs and colleagues, several investigators have failed to demonstrate acute benefits of hyperbaric oxygen treatment. For example, Goldfarb et al. were unable to replicate the findings with a group of ten organic mental syndrome patients. Thompson et al. similarly failed to find any benefit of hyperbaric oxygen treatment for patients with cerebrovascular disease. Other data corroborate these findings.

Research investigating the long-term effects of normobaric oxygen treatments on information processing has revealed some additional support for the CNS benefits of oxygen therapy. Krop and colleagues examined ten hypoxemic COPD patients (PaO₂ < 55 mm Hg) in comparison to 12 COPD patients whose PaO₂ levels were greater than 55 mm Hg. Continuous oxygen therapy was administered at 2 L per minute by nasal cannula to the ten hypoxemic patients for four weeks. A series of neuropsychologic and psychological tests were administered before and after the treatment phase was implemented. Hypoxemic COPD patients showed significant improvements from pretest to posttest on eight of ten neuropsychologic tests. Control patients, who were not initially impaired, did not improve significantly. In addition, resting oxygen tension (PaO₂) levels were immediately enhanced as a result of oxygen treatment for hypoxemic patients (no measure of PaO₂ was taken for control subjects during this period). Another study by Brezinova and colleagues examined EEGs in 14 COPD patients who were administered oxygen treatments. While eight patients received long-term (normobaric) oxygen therapy, four patients were maintained on regular room air. Patients on long-term oxygen treatment showed significantly faster EEG waves than did control patients. The frequency of the EEG wave was also positively correlated with arterial oxygen saturation. However, the relationship between fast EEG waves and cognitive function is uncertain.

Another study by Heaton et al. demonstrated small positive effects of long-term oxygen therapy. The
Nocturnal Oxygen Therapy Trial (NOTT) investigators randomly assigned hypoxemic COPD patients to either continuous oxygen therapy or nocturnal oxygen therapy. One hundred fifty patients were followed for six months and 37 were tested one year after treatment. Fifty-three healthy normal subjects were individually matched with 55 randomly selected COPD patients and followed for six months. A neuropsychologic test battery was administered before and after six months of supplemental oxygen treatment. The results indicated that the treatment COPD patients had made significant gains in comparison to controls on several of the subscales (eg, trial making test, finger-tapping test of motor speed, and hand dynamometer test of grip strength). In addition, clinical ratings by a clinician blind to treatment condition demonstrated that COPD patients improved over control subjects on verbal language, abstraction, and flexibility of thinking, and simple sensory and motor abilities. Yet, the authors emphasized that these improvements were relatively subtle and did not constitute reversal of neuropsychologic impairments. However, at a 12-month follow-up the 20 continuous oxygen patients had significantly improved in comparison to 17 nocturnal oxygen patients. While these studies suggest that long-term normobaric oxygen therapy may improve cognitive performance, it is difficult to separate the benefits from other health effects observed in the NOTT trial. In addition, it is still not clear whether the acute effects of oxygen therapy can impact on neuropsychologic functioning.

Studies showing a significant benefit for COPD patients have used oxygen therapy for at least one month or considerably longer. The incremental benefit of continuous over nocturnal therapy does not appear unless patients are followed for one year. There are several methodologic problems common to the reports appearing in the literature. One difficulty is that there has been a dependence on scales such as the Wechsler memory scale and portions of the Bender motor Gestalt test. Although these tests are commonly used, some of the subscales are influenced by the patient's familiarity with words and concepts. Recent research in human information processing and neuroscience has produced tasks that are independent of verbal ability and assess specific components of human information processing. Some of these tasks were employed in the present research. A second problem with most of the reported studies is that the mental tasks are subject to practice effects. Thus, improvement can be expected over baseline as a result of practice alone. Some studies have conducted baseline testing while patients are breathing room air and follow-up testing while patients experienced supplemental oxygen. Thus, treatment and practice effects are confounded. In order to avoid these problems, it is necessary to use a counterbalanced design so that practice effects can be systematically controlled. Finally, many of the existing studies use control groups of unknown comparability to the treatment group. In nearly all published papers (except the NOTT study) these control groups are very small and consist of only a few patients. An alternative approach to this problem is to use a within-subjects experimental design in which each subject serves as his or her own control.

In this paper, we report an evaluation of the effects of acute oxygen therapy on information processing in hypoxemic COPD patients. The effects of oxygen therapy were assessed using tests of human information processing and a counterbalanced design to control for practice effects. In addition, we studied the effects of duration of treatment—using 20-minute and six-hour exposure periods. Both the patient and the experimenter were blind to the experimental treatment.

**Method**

**Subjects**

Ten hypoxemic COPD patients were recruited for participation in the study. Each patient had been clinically diagnosed with COPD by standard American Thoracic Society criteria. They ranged in age from 48 to 79 years (M = 66.30; SD = 8.33). Criteria for acceptance into the study included a resting room air PaO2 level of less than 55 mm Hg. All patients had a current prescription for oxygen therapy.

**Setting**

Each patient was admitted to the General Clinical Research Center at the Scripps Clinic and Research Foundation in La Jolla, CA. They were maintained in the unit for two days and one night. Upon entry to the unit, a Hewlett-Packard ear oximeter was used to determine SaO2. The patient was exposed to treatment from 9:00 AM to 3:00 PM. Then, the test battery was given while the patient continued to breathe the assigned gas mixture. The patient was then exposed to another gas for a 20-minute period and the testing was conducted a second time. The procedure for the second day was the same. Patients were allowed to use their oxygen therapy during the night between the two days of the experiment. During each day of testing, a regular lunch was served except beverages containing caffeine were not allowed.

**Experimental Conditions**

A 2 × 2 factorial design was used to generate four experimental conditions for each subject. The first factor was gas mixture. For two of the four testing sessions, the patient breathed enriched oxygen at a minimum of 2 L per minute flow rate or an adequate flow rate to achieve a 90 percent or greater arterial saturation. For the other two testing sessions, he/she breathed room air. A second variable was duration. For two of the four sessions, the current gas mixture had been used for six hours prior to testing and for two of the four sessions, it had been used for 20 minutes. At the beginning of the first day, the GCRC nurse assigned the patient to a counterbalanced experimental sequence based on a predetermined random schedule. The six-hour treatment was always given first each day and the 20-minute exposure was always the opposite gas mixture as was used for the six-hour exposure. Thus, for example, if a patient was randomly assigned to oxygen treatment on the first day, he/she would receive oxygen treatment for six hours followed by testing, room air for 20 minutes, and a second testing. On the second day,
he/she would receive room air for six hours, testing, oxygen therapy for 20 minutes, and a second testing.

Both the patient and the experimenter were blind to gas mixture. The attending nurse took ear oximeter readings once every hour during both days. However, she was instructed not to reveal the readings to either the patient or the experimenter.

**Test Battery**

The repetition test (Rep Test) consists of a series of trials in which two complex tones are presented sequentially. Tone 1 has a fundamental frequency of 100 Hz and tone 2 has a frequency of 305 Hz. The interval between the tones, known as the interstimulus interval (ISI), was systematically varied. Half of the trials were conducted with short ISIs (M = 55 ms, with variation across trials), while the other half of the trials had long ISIs (constant at 428 ms). The Rep Test yields ten different scores. The first test was detection, which determines whether the subject can distinguish between the two complex tones. Each tone was associated with one of two panels that were mounted on a response box. The experimenter demonstrated three trials for each tone and then had the subject perform three trials. Next, the association test was used to determine whether the subject could associate the correct tone with the correct panel on the response box. During this test, tone 1 and tone 2 are presented individually in a random order. Thirdly, a sequencing test was used to train the subjects to respond to two stimuli presented in succession. For example, if tone 1 was presented twice, the bottom panel was to be pressed twice. The sequence tone 2, tone 1, was indicated by pressing the top panel and then the bottom panel, and so on. Half of the trials used long ISIs while the other half used short ISIs. The short and long ISIs were scored separately. These first three tests described are known as “perceptual tests” and only involve one or two tone patterns. In addition, several “serial memory” tests were used. The same two tones are used during these tests, but they differ in the number of tone patterns that are to be identified. Three serial memory tests with three, four, and five tones were used, and each test contained a short and long ISI sequence.

The validity of the Rep Test is described in an overview by Tallal. The task yields different scores for aspects of auditory information processing. In particular, it is capable of separating sensory function from associative memory, sequencing, and serial memory. Specific components of the test have been shown to be affected by lesions in brain sites known to control these functions.

After completion of the Rep Test, each subject was administered the critical flicker fusion test (CFT). This test is a measure of visual perception that requires each subject to judge characteristics of two different visual stimuli (a flickering light source and a fused light source). The subjects’ CFT scores were the mean scores for three trials ascending (flicker to fusion) and three trials descending (fusion to flicker). Mean CFT scores were expressed in hertz units. An integration aspect of visual information processing merges one image into the next to create a smooth visual perception. The threshold for this integration function has been shown to be related to perceptual/sensory functioning.

Lastly, subjects were given the story recall duration of exposure for fact questions (F 1 = 14.02, p < 0.001). Subjects had higher SaO₂ levels while breathing oxygen than while breathing room air. Thus, the manipulation for gas mixture was effective in changing oxygen saturation levels. The duration effect and the interaction were nonsignificant.

The results from the Rep Test were analyzed using a four-factor within-subject analysis of variance (ANOVA). The design for the analysis was 2 × 2 × 4 × 2. The factors were for gas mixture (room air vs O₂), duration (20 minutes vs six hours), problem complexity (sequencing, serial memory 3, serial memory 4, serial memory 5), and interstimulus interval (short vs long). Overall, there was no significant effect for gas mixture or duration on performance scores. The mean performance in each of these conditions is summarized in Figure 1. The bottom portion shows performance for long ISIs. As the figure shows, performance was near perfect for all groups with long ISIs. This suggests that sensory function and short-term memory were well intact for all subjects under all conditions.

The top portion of Figure 1 shows performance with short interstimulus intervals. Two features of the figure are important. First, errors in performance gradually increased as problems became more difficult. Second, there was little difference between short and long ISIs for easy problems (see comparison of the top and bottom portions of Figure 1). However, as problems grew more difficult, the effect of the ISI increased.

The results of the analysis of variance demonstrated a strong main effect for problem complexity (F 3/27 = 21.90, p < 0.001). In addition, there was a main effect for ISI (F 1/9 = 18.78, p < 0.001), and there was a significant effect for the interaction of problem difficulty and ISI (F 3/27 = 16.73, p < 0.001).

A 2 × 2 (gas mixture × duration) within-subject analysis of variance was used to analyze the results of the critical flicker fusion tests. The experimental effects for the critical flicker fusion tests were statistically nonsignificant. A second 2 × 2 within-subject analysis of variance of the critical flicker fusion tests was statistically nonsignificant. A second 2 × 2 within-subject analysis of variance of the critical flicker fusion tests was statistically nonsignificant. A second 2 × 2 within-subject analysis of variance of the critical flicker fusion tests was statistically nonsignificant.

**Discussion**

Previous studies on the effects of hypoxemia upon human information processing have produced inconsistent results. Evidence is accumulating to suggest that long-term hypoxemia is associated with impaired...
Acute Effects of Oxygen upon Information Processing (Wilson et al)

242

group results is of some interest. Krop and colleagues found a significant benefit of oxygen treatment after one month of therapy, while it took a much longer time for a similar outcome to emerge in the NOTT trial. One explanation for this difference is that all NOTT patients were tested on room air, while the Krop patients remained on their treatment oxygen or room air for testing. Heaton and co-workers suggest that two different mechanisms may account for the benefits of oxygen upon brain function. First, there is a short-term effect upon the activity of hypoxic neurons, and second, there may be a longer-term change in the synthesis of macromolecules that may be required for the formation of neurotransmitters or to meet other CNS metabolic requirements. Our data suggest that the first mechanism cannot affect improved cognitive function on its own. Optimal improvement may require the activation of the first (acute) mechanism only after the second mechanism has been activated.

One explanation for the negative results reported herein is that statistical power was low due to the small sample size. Although this remains a possibility, the sample size in the present study is comparable to that in the original Jacobs investigation. However, we gained additional statistical power through replicated measurements in the factorial repeated measures design. Evidence of the statistical power is provided by the ability to detect the expected differences attributable to ISI and to problem difficulty. In addition, the information processing tasks used in the present study are believed to be more sensitive than those used in earlier investigations. Lastly, while studies on the acute effects of hyperbaric oxygen therapy upon information processing have produced contradictory results, the data for the present study are consistent with those of Raskin et al which included the largest sample to date and a control group comparison.

In summary, small sample size may limit the generalizability of our findings. However, we find little evidence that acute information processing deficits in COPD patients can be reversed by six-hour or 20-minute oxygen therapy.

Conclusions

Cerebral changes in hypoxemic COPD have emerged as a complex puzzle. Considerable evidence suggests that hypoxemic COPD may result in CNS effects that are reflected in memory and abstraction deficits. Long-term oxygen therapy may retard these effects or may produce mild improvements. The acute effects of oxygen therapy are less clearly established. Although some evidence from other (non-COPD) patients with CNS problems indicates benefits, our data corroborate other reports failing to demonstrate cognitive improvements following acute oxygen therapy. If there are acute benefits, we suggest that they
accrue only after an extended period of chronic treatment.

REFERENCES
7 Raskin A, Gershon S, Crook TH, Sathananthan G, Ferris S. The effects of hyperbaric and normobaric oxygen on cognitive impair-
ment in the elderly. Arch Gen Psychiatr 1978; 35:50-56