The Lungs and Causes of Death in the Nocturnal Oxygen Therapy Trial*


Autopsy findings and a morphometric study of the lungs were compared in 18 subjects receiving nocturnal oxygen and 15 receiving continuous oxygen in the National Heart, Lung, and Blood Institute Nocturnal Oxygen Therapy Trial (about half of those who died). The emphysema score, average interalveolar wall distance, central airway lesions, peripheral airway lesions, and the ratio of weights of left ventricle plus septum to right ventricle were similar in the two groups. The causes of death in the two groups were also similar. This evidence supports the hypothesis that the improved prognosis observed with continuous oxygen therapy nocturnal oxygen therapy in patients with severe chronic airflow obstruction and hypoxemia was due to treatment. There was a trend for there to be more interstitial fibrosis and type 2 alveolar epithelial cell hyperplasia in those treated with nocturnal oxygen; in the hands of one observer, the type 2 cell hyperplasia was significant.

Various treatment regimens have been employed over the years in an attempt to improve the prognosis of patients with chronic obstructive lung disease. Long-term oxygen administration is expensive, and since hypoxemia is most severe during sleep, a trial was performed comparing the efficiency of nocturnal oxygen against continuous oxygen. The results demonstrated a significantly lower mortality in the group receiving continuous oxygen. The reason for this was unclear, for only two of the clinical parameters assessed—namely, hematocrit and pulmonary vascular resistance—showed time-related decreases which, although statistically significant, were small. It has been suggested the differences may have been indirect and due to associated diseases.

There are three main reasons for wishing to report the autopsy findings on patients from this study. First, it is possible that the lesions in the lung causing airflow obstruction may have been inadvertently different in the two trial groups. Although the groups were physiologically identical, it is possible, for example, that one group might have had more severe emphysema or more severe peripheral airways disease than the other. These variations, rather than the differing treatment, may have been responsible for the different outcome. Second, the difference in outcome may have resulted from associated disease processes and different causes of death. Finally, lesions have been found in patients treated with long-term oxygen, and it is possible that lesions resulting from oxygen therapy may have been more frequent in those receiving continuous oxygen.

Material and Methods

The protocol for the clinical trial has been reported elsewhere. Two hundred three patients with hypoxic chronic obstructive lung disease were recruited at six treatment centers and, after recording baseline data, were randomly allocated to receive either continuous oxygen or nocturnal oxygen. Demographic background factors and detailed physiologic measurements were identical in both study groups. The patients were followed up for an average of 19.3 months. During the time of the trial, a total of 64 patients died, 41 in the nocturnal and 23 in the continuous oxygen therapy group. Autopsy data were available from 33 of these (18 nocturnal oxygen and 15 continuous therapy).

The lungs and hearts of the patients who died in the United States were transported to Denver in refrigerated containers. Cases from the Winnipeg center were examined there. The heart was dissected, and the ratio of the weight of the left ventricle and septum to the weight of the right ventricle was calculated as described by Fulton. Usually only one lung, and nearly always the left lung, was available, and this was inflated at a constant transpulmonary pressure of 25 cm in formalin for at least 24 hours, and the inflated lung volume was then measured by water displacement. The lungs were then cut sagittally into slices. The mid sagittal slice was used to prepare a Gough-Wentworth paper-mounted whole-lung section. Six blocks of tissue of known size (3.75 cm2) were taken randomly from the lateral slice and transverse blocks were taken of main, upper, and lower lobe bronchi. These blocks were processed to paraffin, cut at 5-μ thickness, and stained with hematoxylin-eosin and elastic/Van Gieson stains. The mucous gland to wall ratio, or Reid index, was measured by a described modification as was the mucous gland/bronchial wall proportion and bronchial muscle/bronchial wall proportion. A modification was that the measurements were made by projecting the images onto a digitizing tablet with an attached microcomputer which performed the appropriate calculations. In the case of the volume proportion of glands and bronchial muscle, the areas of gland, bronchial muscle, and bronchial wall were measured as opposed to point counting. The severity of emphysema was assessed by the panel grading method from the Gough-Wentworth sections. The number and volume proportion of conducting airways smaller than 2 mm in diameter were measured. The former

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were expressed per cm², and correction was made for shrinkage from the fixed to processed tissue. The mean interalveolar wall distance (Lm) was measured and corrected for shrinkage. The panel grading system for assessing lesions in small airways was modified to obtain a total score for inflammation, fibrosis, and muscle only, rather than the eight variables described by the original authors. The inflammation score of the peripheral airways was also analyzed separately. The histologic sections of the lung were used to assess concomitant disease, notably pneumonia and thromboemboli. In addition, an assessment was made whether there were any changes which could directly be related to oxygen therapy in either group. In an attempt to answer this question, the lung sections were assessed blindly by two observers (W.T. and J.J.). Three indices of possible oxygen toxicity were chosen: hyaline membrane formation, interstitial fibrosis, and type 2 pneumocyte hyperplasia. These were independently graded on a scale of 0 to 5 by the two observers using the following guidelines:

0 = Not present in any section
1 = Minimal or questionable change in one to two fields on fewer than half the slides
2 = Mild focal change on more than half the slides
3 = Definite changes in several fields in more than half the slides
4 = Well-defined changes involving several fields in most of the slides
5 = Diffuse change in all slides

Complete autopsy records were available on 30 patients. These were reviewed and a cause of death assigned to each case. All assessments were made without knowledge of the duration of oxygen therapy group, ie, nocturnal or continuous.

The morphometric measurements were compared using Student's t test. The data concerning oxygen toxicity were compared using the Mann Whitney test for ordinal data. The differences in oxygen toxicity between the two treatment groups were assessed, as were the differences between the two observers. Probability values less than 0.05 were considered significant.

RESULTS

Review of the cause of death from the autopsy records show only minor differences between the two groups. The findings are presented in Table 1. Most deaths were directly related to chronic airflow obstruction. Both patients in the series with carcinoma of the lung received nocturnal oxygen. Other causes of death include one ruptured berry aneurysm, one suggestive thal pneumonia, and one superior mesenteric artery thrombosis with infarcted bowel.

The data from the morphometric studies on the lung are presented in Table 2. The means of the variables in the two groups are closely similar. The largest difference is in Lm which is larger in the continuous oxygen group, but the difference does not reach significant levels (p>.05).

Examination of the lungs for possible oxygen toxicity revealed some expected interobserver variation, but no significant difference between the two observers in ordinal ranking of the four assessments, ie, one observer (J.J.) ranked higher than the other (Fig 1), but the cases were ranked similarly. No case showed hyaline membrane formation. The degree of fibrosis and type 2 cell metaplasia are shown in Figure 1. There was a trend toward slightly more fibrosis and type 2 cell hyperplasia in the cases receiving nocturnal oxygen and the latter feature reached a significant difference (p<.05) in the hands of one observer (J.J.).

DISCUSSION

Analysis of the findings at autopsy in the cases examined in this trial shows no significant differences in cause of death or severity and nature of pulmonary disease between the two groups of patients. It should be noted that of necessity we were able to describe the pathologic findings in only the subjects who died. It may be that the survivors had less severe morphologic changes. We suspect that, even if this is the case, the pathology in the survivors of the nocturnal oxygen regimen would be the same as those in the continuous oxygen regimen. The lack of clinical differences in the entire baseline group suggests similar morphologic findings, particularly since the fatal cases from the two

Table 1—Cause of Death From Autopsy Data in 30 Cases

<table>
<thead>
<tr>
<th></th>
<th>Nocturnal O₂ (15 cases)</th>
<th>Continuous O₂ (15 cases)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic airflow limitation/respiratory insufficiency</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>Cor pulmonale</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Carcinoma of lung</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Arteriosclerotic heart disease</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Other</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>

Table 2—Pulmonary and Cardiac Findings in Continuous Oxygen Treatment vs Nocturnal Treatment (Mean ± SEM)*

<table>
<thead>
<tr>
<th>Group</th>
<th>Emphysema Score</th>
<th>Volume Proportion Muscle %</th>
<th>Volume Proportion Mucous Gland %</th>
<th>Reid Index</th>
<th>Lm, mm</th>
<th>Airways/ Airways cm², %</th>
<th>Inflammation</th>
<th>Small Airway Score</th>
<th>LV + Sept/ RV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nocturnal</td>
<td>63</td>
<td>± 4</td>
<td>± 0.3</td>
<td>0.51</td>
<td>0.437</td>
<td>0.95</td>
<td>0.59</td>
<td>31</td>
<td>44</td>
</tr>
<tr>
<td>Continuous</td>
<td>58</td>
<td>± 7</td>
<td>± 0.3</td>
<td>0.45</td>
<td>0.578</td>
<td>0.81</td>
<td>0.78</td>
<td>30</td>
<td>40</td>
</tr>
<tr>
<td>Oxygen</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</table>

*Volume proportion of muscle and mucous gland refer to central airways. The Reid index is a measure of bronchial mucous gland size. Lm is the average interalveolar wall distance. Airways refers to conducting airways less than 2 mm in internal diameter. LV + septum/RV is the ratio of weight of left ventricle plus septum to weight of right ventricle. Small airway score: a subjective assessment of inflammation, fibrosis, and muscle in airways less than 2 mm in diameter, 100 is the maximum score.

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groups had essentially similar pathology. Also, the patterns of cause of death are similar to the clinically determined ones in a larger clinical trial.  

The question has been raised whether the better survival of the group given continuous oxygen was due to amelioration of the pulmonary vascular disease or its complications or due to associated other disease. It appears that the improved survival can be attributed to the therapy rather than to associated disease, but the mechanism is still uncertain. Pulmonary vascular resistance decreased in the continuous oxygen group. This was not reflected in an increase in the ratio of the weight of the left ventricle plus septum to the weight of the right ventricle. We are presently engaged in a comprehensive morphometric study of the pulmonary vasculature, correlating pulmonary circulatory studies to morphologic changes in the vessels and a comparison of the vasculature of the two groups will be reported separately.

Lesions possibly due to oxygen toxicity have been reported in subjects with long-term continuous oxygen therapy. Our search for possible oxygen effects showed that, as might be expected, many of these patients had varying degrees of pulmonary fibrosis and type 2 cell hyperplasia, and nearly all of the type 2 cell hyperplasia occurred near the areas of scarring. There was no convincing evidence that the fibrosis was due to oxygen therapy; in most instances the scarring looked old and was often heavily pigmented. Type 2 cell hyperplasia was significantly greater in those treated with nocturnal oxygen in the hands of one observer. We have no convincing explanation for this observation and interpret it as a random statistical event. Matched control lungs from patients dying from chronic airflow obstruction who did not receive oxygen therapy were not available for comparison, so that we cannot con-  

clude with certainty that the lesions we observed in both treatment groups were not due to the oxygen regimen. In any event, they were trivial and not worse in patients given continuous oxygen. The possibility must be entertained that the lesions found were not due to oxygen toxicity, and that since they were more frequent in the group with the higher mortality, they were responsible for the higher mortality. This seems unlikely, since (Fig 1) the average severity was grade 1. This was defined as minimal questionable change in one to two fields in fewer than half the slides. It seems highly unlikely that lesions of this severity would have any clinical or physiologic significance.

We concluded that the improved mortality in the subjects given continuous oxygen was due to treatment and not to associated disease.

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