Table 1. Entry and Exclusion Criteria

Entry criteria
Clinical diagnosis of chronic obstructive lung disease
Hypoxemia
$Pa_{O_2} \leq 55$ mm Hg
$Pa_{O_2} \leq 59$ plus one of the following:
Edema
Hematocrit $\geq 55\%$
P pulmonale on ECG: 3 mm in leads II, III, aVf
Lung function*
$FEV_1/FVC < 70\%$ after inhaled bronchodilator
TLC $\geq 80\%$ predicted
Age > 35
Exclusion criteria
Previous O_2 therapy: 12 h/d for 30 days during previous 2 months
Other disease that might be expected to influence mortality, morbidity, compliance with therapy, or ability to give informed consent

* FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity; TLC = total lung capacity.

rately for each investigative center. Treatment assignments were preset in blocks of four with an equal number of patients receiving nocturnal O_2 therapy and continuous O_2 therapy in each block. The order of treatment assignment was randomly computer-generated within each block of four.

Baseline studies included a complete history and physical examination, blood count, urinalysis, measurements of blood urea nitrogen and electrolytes, ECG, and chest radiograph. Lung function was assessed by measuring forced expiratory volume in 1 second (FEV_1) and forced vital capacity (FVC) spirometrically and functional residual capacity (FRC) with a plethysmograph. Arterial blood was obtained while the patient, breathing room air, rested semirecumbent and was analyzed for P_{O_2}, P_{CO_2}, and pH with appropriate electrodes. Exercise performance was studied with bicycle ergometry, using a progressive multi-stage technique. Right heart catheterization was done with measurements of pulmonary artery and wedge pressures and of cardiac output. Oxygen saturation during sleep was measured with an ear oximeter while the patient breathed air and O_2 on separate nights. Neuropsychological function was assessed by study of neuropsychological history and administration of a modified Halstead-Reitan battery (13) of tests. These tests were evaluated collectively, in terms of the Russell-Neuringer average impairment index (14), and a clinical rating scale of 1 to 6 with 6 representing maximal impairment (15). This rating was made by two neuropsychologists without knowledge of the treatment assignment of the patient. The patient's quality of life was assessed by the administration of the Minnesota Multiphasic Personality Inventory (16), the Sickness Impact Profile (17), and the Profile of Mood States (18).

After 6 months of nocturnal or continuous O_2 therapy, all baseline tests except sleep studies were repeated. Thereafter, at 6-month intervals, all baseline studies were again repeated except sleep studies, right heart catheterization, and neuropsychological testing.

After randomization, patients were instructed in the use of their oxygen equipment and discharged for follow-up as outpatients. Oxygen was administered by nasal prongs at a measured flow rate of 1 to 4 L/min. Each patient received the lowest flow in whole litres per minute that demonstrably increased resting, semirecumbent arterial P_{O_2} at least 6 mm Hg and maintained a resting arterial P_{O_2} of 60 to 80 mm Hg. This dose was increased by 1 L/min for periods of exercise and sleep. Oxygen delivery systems varied; oxygen concentrators, liquid oxygen systems, and compressed gas were all used. Compliance with therapy was checked in two ways. The patient and a family member were required to keep written records of oxygen use, and oxygen reservoirs or concentrators were fitted with timers that recorded the duration of gas flow. Because only stationary systems had such timers, oxygen use was recorded accurately in nocturnal O_2 therapy patients but underestimated in some continuous O_2 therapy patients who, in addition to a stationary system, used a portable system such as liquid oxygen walkers or small tanks of compressed gas.

Besides oxygen, all patients were treated with oral theophylline and inhaled beta-2 agonists. Diuretics and antibiotics were used as clinically indicated. Use of other drugs, such as steroids, cardiac glycosides, sedatives, tranquilizers, antidepressants and oral beta agonists, was discouraged. Therapeutic phlebotomies were not done.

All patients were followed closely to assure compliance and to assess changes in clinical state. For the first 6 months of the study, they were visited weekly in the home by a nurse practitioner, and were seen each month in outpatient clinic. After the first 6 months, they were visited at home at least once a month and were seen in the outpatient clinic at least every 3 months. At 1-month intervals during the first 6 months and at 3-month intervals thereafter, samples of arterial blood were obtained while the patient breathed his prescribed dose of oxygen and the dose adjusted if arterial P_{O_2} was not 60 to 80 mm Hg. Unscheduled clinic or emergency room visits were recorded. When a patient became ill enough to be hospitalized, the assigned treatment regimen was suspended but was resumed as soon as possible thereafter. Oxygen dose was reassessed after each hospitalization. If a patient died, an attempt was made to obtain a postmortem examination.

All observations were made under specified conditions at predetermined time intervals and recorded on standardized data forms to assure uniform collection of data by all participants. Immediately after each recorded event, copies of the completed data forms were mailed directly to a designated Data Center for editing, analysis, and storage. All the data on the study forms were subjected to an initial clerical review and were then keypunched and verified. All keypunched information was subjected to an extensive computer edit. Errors detected in this editing process were sent to the clinics for correction. Measurements based on analogue recordings, notably records of cardiac catheterization and sleep studies, were verified by the submission of a random sample amounting to 10% of the original records to single readers. All neuropsychologic data were reviewed by experts who checked them for accuracy and consistency. An Advisory Board including clinicians, epidemiologists, and other experts periodically reviewed confidential interim data on the progress of the trial. In particular, follow-up measurements and other outcome criteria were examined so that the trial could be terminated promptly if a clinically significant difference between treatments emerged. In fact, the scheduled end of the trial coincided with the development of a difference in mortality that would have necessitated termination of the trial.

Percentage of events in the nocturnal and the continuous O_2 therapy groups as well as life tables calculated according to Kaplan and Meier (19) are reported. Survivorship of all patients as of 26 May 1980, regardless of the extent of their participation, was ascertained by individual follow-up observation.

For comparison of survival in the nocturnal O_2 therapy and the continuous O_2 therapy groups, the Cox actuarial procedure (20) was applied. This statistical procedure, which is based on a proportional hazard model, takes into account the ranking of the times of follow-up and death in the two treatment groups.

Mortality data were monitored at regular intervals throughout the trial to detect treatment differences as soon as possible. Also, many other end points were evaluated in the final data analysis. Because of this, if nocturnal O_2 and continuous O_2 therapy regimens were alike in every respect, by chance alone 5% of the secondary outcome variables would show a difference significant at the 5% level (21). It is clear that, because multiple variables were evaluated and key variables analyzed during the trial, one should be cautious in assessments of statistical significance.

Results

The 203 patients who were recruited were selected