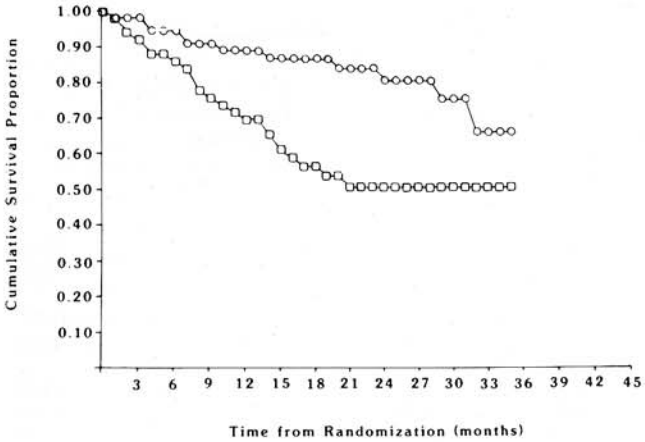

Figure 3. Survival of patients with arterial Pco_2 over 43 mm Hg. Ordinate is fraction of patients surviving; abscissa is time from randomization or duration of treatment. Open circles represent continuous O_2 therapy patients; squares represent nocturnal O_2 therapy patients. Of these patients, 35 nocturnal O_2 therapy patients and 50 continuous O_2 therapy patients were followed for 12 months, and 13 patients on nocturnal and 25 on continuous O_2 therapy were followed for 24 months.

tinuous O_2 therapy than in those on nocturnal O_2 therapy: This was not significant at 6 months ($P = 0.06$) but was significant at both 12 months ($P = 0.005$) and 18 months ($P = 0.008$). At 18 months hematocrit values showed, on the average, a fall of 2.0% from baseline in 36 nocturnal O_2 therapy patients and had decreased an average of 9.2% in 40 patients on continuous O_2 therapy. Pulmonary vascular resistance was measured in follow-up only at 6 months; at that time 49 nocturnal O_2 therapy patients showed a mean increase of 6.5% while 52 continuous O_2 therapy patients showed a mean decrease of 11.1% ($P = 0.04$).

When data for all patients were combined and baseline and follow-up data compared, significant changes in hematocrit and pulmonary vascular resistance were observed. Hematocrit values fell from a mean at baseline of 47.5% to a mean of 44.3% at 6 months. Pulmonary vascular resistance fell from a mean of 322 dyne/s • cm^5 at baseline to a mean of 281 dyne/s • cm^5 at 6 months. No significant change occurred in arterial blood gas levels, lung volumes or FEV_1, maximum work attained, mean pulmonary artery pressure, or cardiac index. With the exception of the Minnesota Multiphasic Personality Inventory, all the measures of neuropsychological function and quality of life listed in Table 2 improved significantly when all patients were considered.

Discussion

The patients studied were probably representative of patients in general with hypoxemic chronic obstructive lung disease. The study centers attempted to recruit every patient who fulfilled the entry criteria and presented no reason for exclusion (Table 1). Over 1000 patients were screened for the study; a large fraction of these were not eligible for the study chiefly because of other disease and failure to demonstrate persistent hypoxemia. Very few patients did not enter the study because they were thought "too sick" to endure 3 weeks' observation without oxygen. The only biases that operated in patient selection were that the patient live near a study center, that he or she have no serious extrapulmonary disease, and that he or she not previously have been treated with long-term oxygen therapy. Thus, except that they were largely urban dwellers and did not have major disease of other organ systems, these patients probably were representative of the type of person with obstructive disease currently thought to merit long-term low-flow oxygen therapy. As indicated in Table 2 the patients were randomized successfully. At baseline, there was no significant difference between nocturnal O_2 and continuous O_2 therapy groups in any of the variables listed, although in some neuropsychological test results there were trends favoring the continuous O_2 therapy group. The effectiveness of the prescribed dose of O_2 in relieving hypoxemia was established and repeatedly checked. Therapy other than that involving O_2 was the same in both groups and therefore could not have biased the results. Finally, as indicated in Figure 1, patients complied well with their prescribed treatment regimens; few continuous O_2 therapy patients used O_2 for 13 hours or less, and few nocturnal O_2 therapy patients used it for 19 hours or more. This record of compliance is unusually good (22) and probably occurred both because the patients were followed very closely and because they found it easy to believe that oxygen was beneficial to them. In any event, this clinical trial appeared to fulfill several important criteria: The patients were representative of the general clinical population addressed by the trial, the treatment groups were similar at the beginning of the trial, the treatment was shown to achieve its short-term goal, and each group generally followed its assigned treatment plan.

We believe that the trial gave a clear-cut answer in terms of the variable of ultimate clinical importance: mortality. Mortality in the nocturnal O_2 therapy group was nearly twice that in the continuous O_2 therapy group. The analysis of treatment-dependent differences in overall mortality was the first statistic derived from the trial data because it was considered the most important. Therefore it cannot be argued that the difference in overall mortality was a chance result of many tests being applied to the data. The probability was truly 1% that the difference in mortality between the nocturnal O_2 and the continuous O_2 therapy groups was due to chance. Had the trial been prolonged, an even more impressive statistic might have emerged; this would have reflected an even greater differential mortality that would have been ethically unacceptable. Had the trial been scheduled to last longer, the Advisory Board would have terminated it at the time that it did stop because of the mortality difference reported here.

In analyzing mortality, we analyzed all deaths. Nonrespiratory factors contributed to the deaths of some patients: Two committed suicide, one had leukemia, four had carcinoma of the lung, and one had a cerebrovascular accident. These deaths were randomly distributed between the nocturnal O_2 and the continuous O_2 therapy groups. When these patients were eliminated from consideration, survival in the continuous O_2 therapy group