Ambulatory Oxygen Therapy, Exercise, and Survival with Advanced Chronic Obstructive Pulmonary Disease (The Nocturnal Oxygen Therapy Trial Revisited)

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[Respir Care 2000;45(2):204–211] *Key words: nocturnal oxygen therapy, long-term oxygen therapy, chronic obstructive pulmonary disease, oxygen transport, ambulation, tissue oxygenation, exercise.*

Introduction

In the 1950s, Alvan Barach became a champion of ambulatory oxygen.[1] He developed a small cylinder for compressed gas for ambulatory oxygen, illustrated in Figure 1. Figure 2 is a cartoon designed by Barach. This illustration encourages patients to get going and to walk as they pursue the adventures of life. At about the same time, Cotes reported on his observations in ambulatory oxygen.[2] "The increased exercise ability when the patient is breathing oxygen is probably due to a reduction toward the normal levels of ventilatory requirements for exercise, as a result of the relief of anoxia." It was Cotes's conclusion that "Portable oxygen should be regarded as an integral part of domiciliary oxygen therapy."[3] At the time of that writing, he had been using oxygen successfully in 4 patients at home. Figure 3 shows how he transfilled a small high-pressure cylinder from a larger tank. Figure 4 shows two lightweight, high-pressure cylinders used by Cotes in his studies.

In the early Denver study, cited in the "Historical Highlights of Long-Term Oxygen Therapy," (Respir Care 2000; 45[1]:29–36) the most striking observation was a dramatic improvement in exercise tolerance during the oxygen administration month followed by the control month in two patients (Fig. 5).[4] It could be argued, however, that this exponential improvement in exercise tolerance during the month those patients received oxygen was simply a continuation of the results of exercise training during the control month while breathing air. However, the slope of the improvement is much steeper in the oxygen month.

Pierce and Miller showed reduced recovery time with oxygen-supported exercise, compared with oxygen breathing air.[5] Liker et al were the first to conduct a controlled double-blind trial comparing portable liquid oxygen with liquid air.[6] In their study all patients reported feeling better while carrying the portable device. Three of 9 patients showed a clear-cut increase in the distance walked while breathing oxygen, compared with air. This was a very difficult study to conduct, but it was important because it gave evidence that oxygen offered more than placebo value. Additional controlled exercise studies were conducted by Bradley et al[7] and by Leggett and Flenley,[8] among others. Bradley's group showed that walk endurance was significantly increased by oxygen, although the maximum work rate could not be equally improved.

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Fig. 1. The late Alvan Barach modeling a small high-pressure oxygen cylinder capable of being transfilled from a large compressed gas L or K cylinder.

Fig. 2. Cartoon diagram by Dr Barach emphasizing the importance of walking with ambulatory oxygen.

The major purpose of this report on ambulatory oxygen is to offer a new analysis of the Nocturnal Oxygen Therapy Trial (NOTT) data in order to explore why continuous oxygen therapy (COT) was superior to nocturnal oxygen therapy (NOT). We aimed to determine if survival was related to the exercise capacities of the patients at the time of randomization to oxygen or if it was a function of the duration of oxygen administration.

Re-examination of the Nocturnal Oxygen Therapy Trial

In brief review, the NOTT study collected extensive data from a well-defined population of patients with advanced chronic obstructive pulmonary disease (COPD), who were randomly assigned to receive either NOT for approximately 12 hours per day from a stationary source or ambulatory oxygen (ie, COT that was intended to be used as close to 24 hours per day as possible). In the NOTT, extensive outcome data were obtained that can answer important questions about oxygen, exercise, survival, and hospitalization requirements in this well-defined population.

The details of the original NOTT study have been reported elsewhere.[9] Patients with chronic stable hypoxemia with partial pressure of oxygen (P_{O_2}) of $\leq$ 55 mm Hg who had no significant co-morbidities and were willing to participate in an exercise-oriented rehabilitation program utilizing oxygen were randomized to receive either NOT from a stationary oxygen system or COT from an ambulatory system.[9,10] The randomization process resulted in patients who were well-matched by age, gender, and indices of disease severity.[9] After the NOTT report, the magnetic data tapes were placed in the public domain in hopes that further analyses would be made by other investigators. This goal was not achieved at first because of the complexities of the data methods originally used, which were state-of-the-art computer technology at the time of the study.[11,12]

Recently, one of us (PLB), using newer software, was able to convert the original data into a personal computer format. The original NOTT data set was obtained from the National Heart, Lung, and Blood Institute in its original format and converted into an Access (Microsoft Corporation, Redmond, Washington) database. From this database, information was output to Excel (Microsoft Corporation, Redmond, Washington) for matching and analysis.

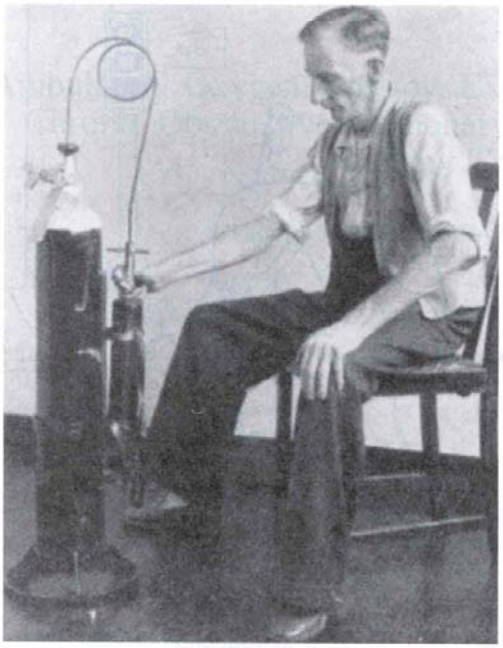

Fig. 3. JE Cotes transfilling oxygen system. (From Reference 2.)

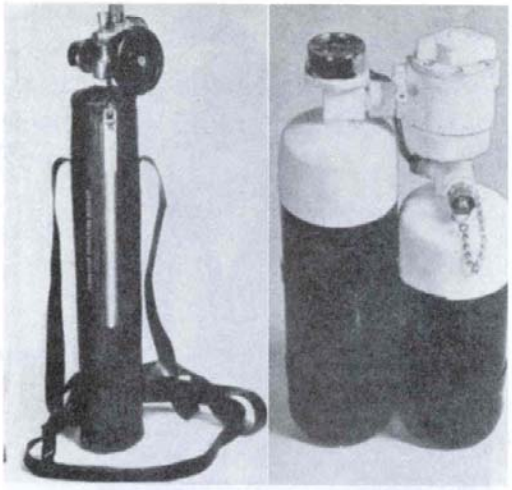

Fig. 4. Two small high-pressure cylinders used by JE Cotes. (From Reference 2.)

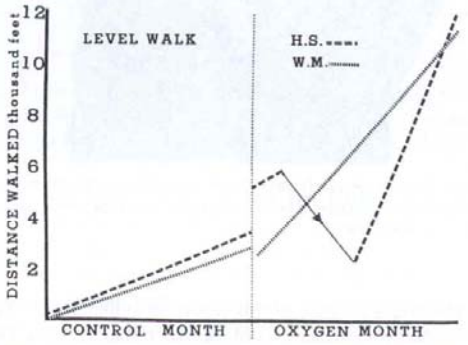

Fig. 5. Improvement in exercise tolerance in two patients trained at level walk. Note slow change during control month and marked rapid rise in tolerance during oxygen month. "H.S." and "W.M." are patients' initials. Temporary decrease in H.S.'s exercise tolerance during the oxygen month was due to an episode of acute bronchitis. (From Reference 4.)

Walking Information

In the NOTT, each candidate for the study was given a comprehensive pulmonary rehabilitation program, with exercise performed on a daily basis for 3 weeks prior to randomization to NOT or COT. Each patient was urged to walk as much as possible each day during the 3-week stabilization period, and each was given a pedometer to monitor the distance walked each day. This distance was recorded by a research nurse or technician. This 3-week

Table 1. Matching Data for Baseline Walking Comparison.*

Characteristic	Low Walk NOT	Low Walk COT	High Walk NOT	High Walk COT
n	22	18	22	18
Age, median, years	67.6	66.5	67.6	66.5
P_{O_2}, mm Hg	52.3	49.9	51.6	51.6
P_{CO_2}, mm Hg	45.7	42.6	42.4	43.2
pH	7.40	7.40	7.42	7.40
Heart rate, min^{-1}	92.6	95.2	85.9	95.8
Pulmonary artery mean pressure, mm Hg	31.6	29.1	26.9	30.1
Cardiac index, $L/min \cdot m^2$	2.76	2.88	2.62	3.04
Pulmonary vascular resistance, $dyn \cdot s \cdot cm^{-5}$	381	363	383	379
FEV_1, % of predicted pre-bronchodialator	25%	28%	25%	28%
FVC, % of predicted pre-bronchodialator	48%	51%	50%	49%

*Cardiac and blood gas data taken at rest with supplemental oxygen. All values are mean unless noted.

NOT = nocturnal oxygen therapy; COT = continuous oxygen therapy; FEV_1 = forced expiratory volume in the first second; FVC = forced vital capacity.

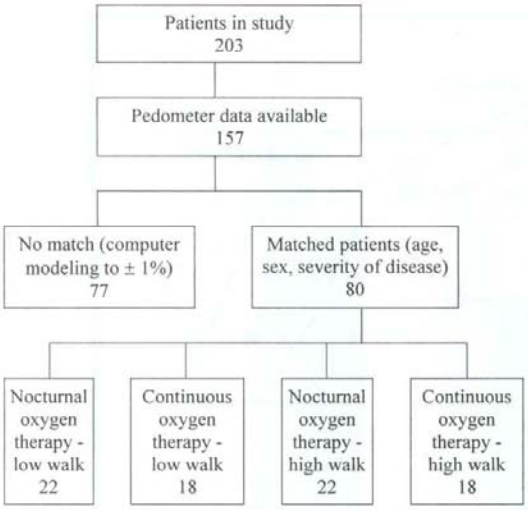

Fig. 6. Re-examination of the Nocturnal Oxygen Therapy Trial by pretreatment ambulation status. Origins of the 80 matched patients.

period was intended to bring each patient to a functional optimum before randomization to NOT or COT. The average number of feet that each patient walked per day was calculated during the third week of the stabilization period. We call this factor "walking level." Pedometer data for the 3-week stabilization and optimization period was available for 157 of the 203 total patients. We had maximum oxygen consumption measurements for 106 of the 203 total patients enrolled in the NOTT. In our matched group of 80 subjects we have maximum oxygen consumption measurements for 18 subjects with a low walking level (39 mL/min), and 24 subjects with a high walking level (59 mL/min) ($p = 0.007$). Thus, the walking level can be taken as a surrogate indicator of the maximum oxygen consumption measurement in this analysis.

We divided the patients into a low walking and a high walking group by separating at the median walking distance achieved at the end of 3 weeks. Figure 6 presents the origins of the 80 matched patients. The initial division of the patients by walking level at the median (3,590 ft/d) yielded groups that were not well matched by age. The low walking group was approximately 5 years older than the high walking group. To overcome this weakness, each low walking patient was manually matched with a high walking patient of similar age, treatment group (COT vs NOT), and percent of predicted forced expiratory volume in the first second. The resulting groups were 40 patients each in the low and high walking groups. These 80 patients were then further divided into COT and NOT groups. Table 1 shows the results of this matching, and this shows good matching by all parameters listed.

Data Analysis

The methods of Kaplan and Meier[13] were used to produce the survival function, using the product-limit estimate model. Statistical significance was tested using the method described by Cox.[14] Hospitalization data were analyzed by analysis of variance.

Results

Figure 7 presents the survival of patients with low and high exercise capability who received low (NOT) versus high (COT) oxygen. Differences in survival between the low walkers on low oxygen and high walkers on high oxygen is statistically significant ($p = 0.01$). The difference is also significant between low walkers on low oxygen and low walkers on high oxygen ($p = 0.01$).

Figure 8 presents the hospitalization data in terms of the number of admissions per year and the average length of stay per admission for the 4 matched groups. Hospital utilization was less in the high oxygen group and least in the high oxygen group with "high" exercise capability ($p = 0.05$). Using analysis of variance, a statistically significant difference was found, with a shorter length of stay in the high walking subjects who received high oxygen ($p = 0.02$).

Discussion

The first long-term oxygen studies showed a reduction in pulmonary pressures and erythrocytosis in 6 patients in each of two studies with chronic stable hypoxemia associated with advanced COPD.[4,15] Somewhat similar studies of continuous oxygen from a stationary source also showed improvement in pulmonary artery pressure, with shorter duration of oxygen therapy, including as low as 15 hours per day.[16,17] These early observations formed the basis for both the British Medical Research Council and the NOTT randomized controlled clinical trials.

The British Medical Research Council study showed a survival benefit from oxygen given for approximately 15 hours per day, including during sleep, compared with air.[18] The NOTT study, which used ambulatory COT for as many hours per day as possible (median 19.4 h, mean 17.8 h/d), compared with NOT from a stationary source (mean 11.8 h/d), showed a better survival with more continuous oxygen.[9] Figure 9 shows a comparison of these survival curves.

Improved survival in the NOTT study was related to reversibility of pulmonary hypertension.[19] Similar conclusions have been drawn by other investigators.[20–22] It is difficult to understand, however, how a modest reduction in mean pulmonary artery pressure (only 3–5 mm Hg), which causes only a slight decrease in the afterload of the

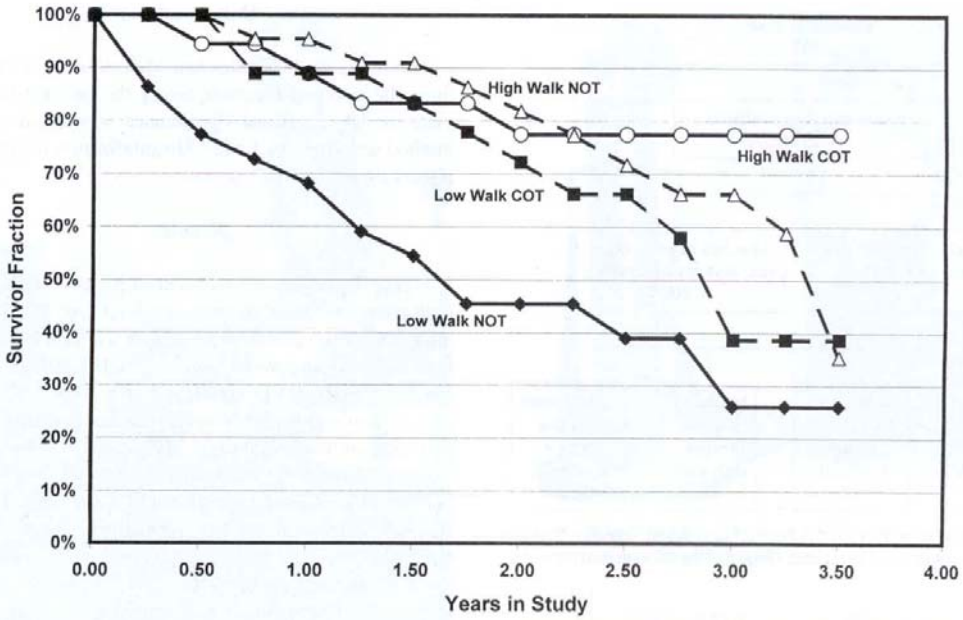

Fig. 7. Survivorship vs walking level and oxygen therapy. Comparison of survivorship in high walk, high oxygen patients compared with low walk, low oxygen patients shows highly statistically significant differences. Low walk, high oxygen survival is better than low walk, low oxygen at 2.5 years, but not at 3.5 years. These differences are statistically significant ($p = 0.01$).

right ventricle, could be the sole reason for the improved survival. In one study, improved survival was related to both a reduction in pulmonary pressure and an increase in maximum oxygen consumption.[20] In some patients who had a reduction in pulmonary artery pressure, there was an increase of left ventricular ejection fraction, which may be a reflection of improved global cardiac function because of relief of hypoxemia.[20]

Extensive exercise studies of right ventricular function during exercise in COPD have shown that an increase in exercise tolerance is related to an increase in right ventricular function and increased oxygen consumption.[23,24] Increased exercise capacity in hypoxemic COPD often results from oxygen administration and is related to an improvement in right ventricular function.[23–25] Increased right ventricular function and oxygen consumption may occur in spite of increases in pulmonary artery pressure and pulmonary vascular resistance.[23–25] The elevated pulmonary pressure and resistance are most likely due to fixed vascular changes in the pulmonary vascular bed, which are not reversible, even with long-term oxygen therapy (LTOT).[26] One study found a relationship between mixed venous oxygen tension and survival in patients who were candidates for LTOT.[27] The 5-year survival was better in patients with the highest mixed venous P_{O_2} and higher coefficient of oxygen extraction.[27] This study suggested that measures designed to increase cardiac output would be appropriate to improve tissue oxygen delivery.[27,28]

In other studies, patients who exhibited little or no ability to increase their cardiac output and systemic oxygen transport did not have increased exercise capacity.[23–25] These observations led to the conceptualization of the "right ventricular hypothesis."[29] The right ventricular hypothesis is based on the concept that limitation of right ventricular function limits systemic tissue organ transport. Before oxygen is given, ventricular function and oxygen transport may be limited by poor oxygenation of the myocardium. After oxygen is administered, right ventricular function can still be limited by structural damage of the right ventricle or by elevated right ventricular afterload from fixed pulmonary vascular changes. In any event, failure to improve right ventricular systolic function may limit tissue oxygen transport. By improving oxygen to the right ventricular myocardium, and by reducing right ventricular afterload, right ventricular function may improve. This, in turn, results in improved global cardiac function, increased tissue oxygen transport, and increased tissue energy production.

It is likely that tissue metabolic phenomena are responsible for improved survival. In the British Medical Research Council study, in men who received oxygen versus

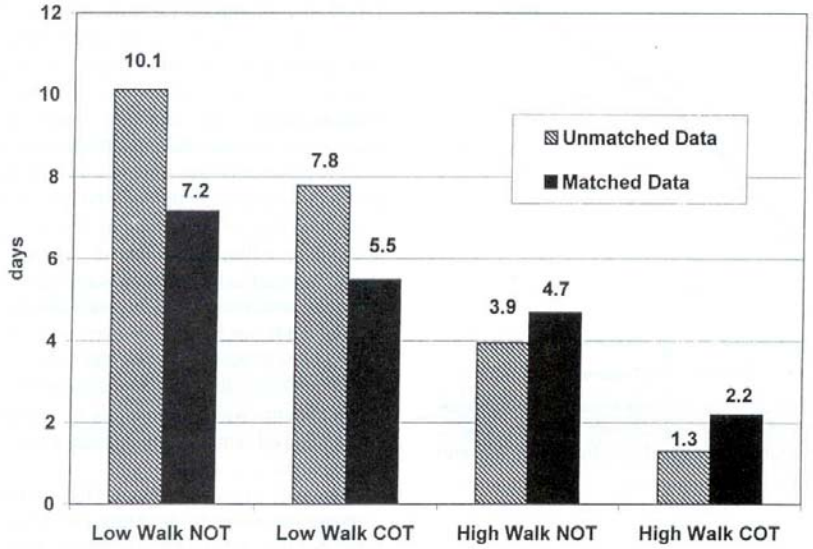

Fig. 8. Hospital days per year in study. The lowest length of stay in admissions per year was in the high walk, high oxygen patients. ($p = 0.05$ and 0.01 respectively). NOT = nocturnal oxygen therapy. COT = continuous oxygen therapy.

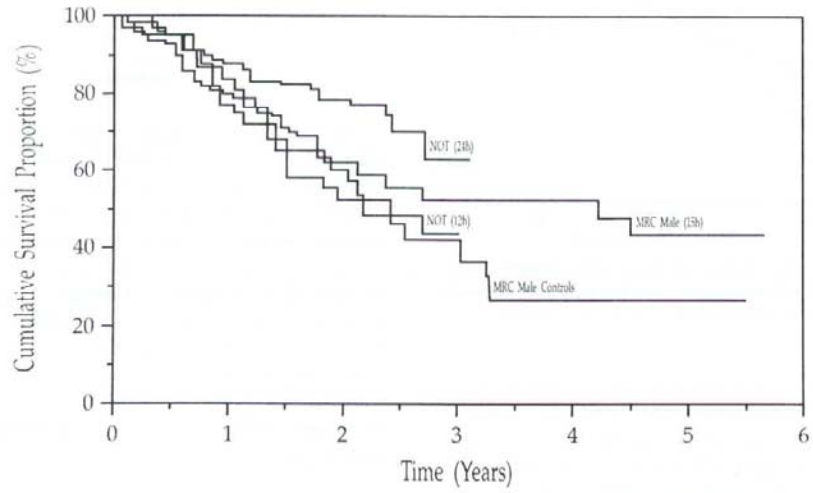

Fig. 9. Comparison of survival curves of Nocturnal Oxygen Therapy Trial (NOTT) and British Medical Research Council (MRC) study. (From Cooper CB. Long-term oxygen therapy. In: Casaburi R, Petty TL, editors. Principles and practice of pulmonary rehabilitation. Philadelphia: WB Saunders; 1993: p 184, with permission.)

men who did not receive oxygen, improved survival did not become apparent until after 500 days.[18] In the NOTT study, improved survival did not become statistically significant until 18 months (see Fig. 9).[9] These data suggest that the survival benefit from oxygen was a function of restorative metabolic changes in multiple organs, which occurred over months of LTOT.

The restorative value of oxygen in brain function has been previously reported.[30] Figure 10 shows an improvement in performance IQ, which was similar in both NOT

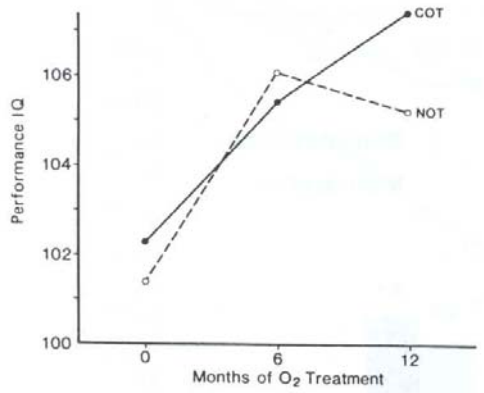

Fig. 10. Performance IQ from the Wechsler Adult Intelligence Scale in relation to duration of continuous (COT) versus nocturnal (NOT) oxygen therapy in COPD patients. (From Reference 30, with permission.)

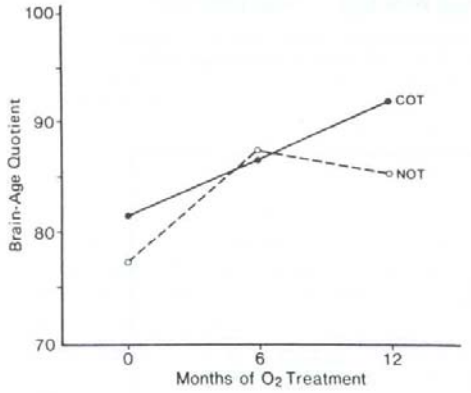

Fig. 11. Change in "fluid intelligence" (brain age quotient) in relation to continuous (COT) versus nocturnal (NOT) oxygen treatment in COPD patients. (From Reference 30, with permission.)

and COT. However, in COT there was further improvement over the subsequent 6 months. Similarly, Figure 11 shows improvement in brain age quotient, with improvement in both NOT and COT after 6 months, but further improvement after 12 months with COT.[30] An improvement in brain function could reasonably be expected to require increased energy production. Such an increase in energy production would require increased systemic oxygen delivery. This has been demonstrated in patients who can increase their exercise tolerance with supplemental oxygen.[22–24] We believe that increased exercise tolerance and improved survival are a result of increased systemic oxygen delivery during oxygen administration.

A restoration of arterial blood oxygenation while breathing air has been reported following several months of LTOT.[31] This improvement in oxygen transfer across the lungs is believed to be due to improved ventilation-perfusion matching as a result of improved oxygenation, which is known to reduce pulmonary arteriolar constriction and bronchospasm.[32] The long-term impact of LTOT on heart, brain, lung, and skeletal muscle function may also be due to a sustained increase in tissue oxygen transport and improved energy production of multiple organ systems.

A weakness of our study is that it is a retrospective analysis of a limited number of patients. But the NOTT study involved extremely well-characterized patients with exercise physiology and hospitalization outcomes. The present study suggests that improved tissue oxygen transport occurs in patients with relatively better exercise capacity who also receive more continuous ambulatory oxygen. Patients with lower levels of exercise capacity had better survival with oxygen delivered for longer periods of time.

This study suggests that new clinical trials are needed to compare outcomes from ambulatory oxygen for as many hours per day as possible, compared with stationary oxygen for an equivalent length of time. Such studies could answer the critical question about survival in relation to an ambulatory or stationary oxygen delivery source, and address the possibility of reducing hospitalizations with continuous ambulatory LTOT.

Summary

The NOTT study showed improved survival in COT patients who received LTOT for longer periods (mean 17.7 h/d, median 19.4 h/d) from an ambulatory oxygen system, compared with the survival of NOT patients who received oxygen for a mean of 11.8 h/d from a stationary system. The differences in survival could have been due to the method or the duration of oxygen therapy, or both. An increase in cardiac output and increased oxygenation of the arterial blood (oxygen content) results in increased tissue oxygen transport. In addition, COT was associated with better survival and reduced hospitalizations, compared with NOT patients who were unable to increase their walking level.

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Discussion

Kacmarek: I just wanted to ask you to comment on the restorative effects that you were discussing. You indicated that if a patient is on oxygen therapy because he or she is hypoxemic at rest, and he or she recovers from that a year or two down the road so that resting P_{O_2} is in the 60s, you would continue oxygen therapy. How about a patient who is discharged (after an acute exacerbation) with a P_{O_2} that necessitates oxygen therapy, but after a month or two they've recovered? Is that a patient who should have oxygen discontinued?

Petty: That's a very good question, and we addressed it during the oxygen consensus conferences. Certainly, with that unstable patient who has just come out of an exacerbation (often a pneumonia or just an exacerbation of COPD), we want them to go on home oxygen so they can get out of the hospital fast. We're not going to commit him or her to life-long oxygen, though, because he or she may not be a candidate in terms of being in a stable, steady state. I'm only recommending continued oxygen for patients who have a long-term, demonstrable need after a good stabilization period and then improved their ventilation-perfusion matching but don't change their overall basic spirometry. Those are the ones who shouldn't be taken off oxygen. And, Walter, you might want to elaborate on that because this was your concept.