

# A Novel Device for Measuring Long-Term Oxygen Therapy Adherence: A Preliminary Validation

Sun-Kai V Lin PhD, Samuel T Kuna MD, and Daniel K Bogen MD PhD

**INTRODUCTION:** Current methods for measuring patient adherence to long-term oxygen therapy fail to measure the actual amount of time the patient is inhaling oxygen and the pattern of oxygen use within the day. We have developed a novel oxygen-adherence monitor to address these limitations, and this report introduces the monitor and provides preliminary data validating its use. **METHODS:** This battery-powered monitor attaches to the oxygen source and detects respiratory-related pressure fluctuations transmitted through the nasal cannula. The monitor takes a measurement over a 25-second period, at 4-min intervals. It detects and stores data on 4 different states that describe the patient's actual use of the oxygen source and nasal cannula: source-off/cannula-off, source-off/cannula-on, source-on/cannula-off, and source-on/cannula-on. We studied the monitor's performance with 10 patients with chronic obstructive pulmonary disease, during a directly-observed sequence of using and not using supplemental oxygen via nasal cannula, while sitting and walking. **RESULTS:** The monitor correctly detected 122 out of 129 measurements among all participants, yielding a 95% detection accuracy. **CONCLUSION:** A monitor that objectively measures oxygen inhalation, rather than oxygen expenditure, may help improve the management of patients on long-term oxygen therapy. *Key words: adherence, compliance, monitor, long-term oxygen therapy.* [Respir Care 2006;51(3):266–271. © 2006 Daedalus Enterprises]

## Introduction

Long-term oxygen therapy (LTOT) is a well-established treatment for patients with severe hypoxemia due to cardiopulmonary diseases.<sup>1,2</sup> In hypoxemic patients with chronic obstructive pulmonary disease (COPD), LTOT (> 15 h/d) can improve survival and quality of life, and can reduce the number of hospitalizations.<sup>3,4</sup> COPD is the fourth leading cause of death in the United States and is the only leading cause of death for which the mortality rate is currently increasing, so the need for oxygen therapy will not diminish in the years ahead.<sup>5,6</sup> Unfortunately, the benefits

of oxygen therapy are not realized without a price. In the United States, approximately 800,000 patients receive LTOT annually, representing approximately 30% (\$1.3 billion United States) of total Medicare expenditures for durable medical equipment.<sup>5</sup>

Studies based on current methods for assessing adherence to LTOT indicate that many patients do not adhere to the treating physician's prescribed LTOT regimen, resulting in inadequate treatment and wasted reimbursement dollars.<sup>7–9</sup> Currently, clinical researchers assess LTOT adherence by calculating the average daily use, by (1) recording the hour-meter reading of the oxygen concentrator, (2) counting the patient's use of oxygen cylinders, or (3) weighing the liquid oxygen reservoir. The concentrator's hour-meter reading can give average equipment "power-on" time per day. The number of cylinders used or the change in weight of the liquid oxygen reservoir can yield the average amount of oxygen expended per day.<sup>10</sup> However, these measures of patient adherence fail to discern whether the patient is actually inhaling the oxygen, as opposed to merely having the oxygen source turned on, and, further, fail to provide information regarding the timing of oxygen use within the day. Given these limitations, it is likely that

---

Sun-Kai V Lin PhD and Daniel K Bogen MD PhD are affiliated with the Department of Bioengineering, University of Pennsylvania, Philadelphia, Pennsylvania. Samuel T Kuna MD is affiliated with the Pulmonary, Allergy, and Critical Care Division, Department of Medicine, and with the Center for Sleep and Respiratory Neurobiology, University of Pennsylvania, Philadelphia, Pennsylvania, and with the Philadelphia Veterans Affairs Medical Center, Philadelphia, Pennsylvania.

Correspondence: Sun-Kai V Lin PhD, Department of Bioengineering, University of Pennsylvania, 120 Hayden Hall, 3320 Smith Walk, Philadelphia PA 19104. E-mail: sunkai.lin@gmail.com.

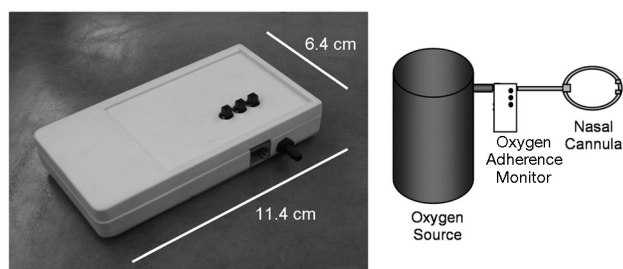


Fig. 1. Left: Functioning prototype of the oxygen-adherence monitor. Right: Schematic showing circuit placement of oxygen-adherence monitor.

previous studies that used these methods overestimated actual adherence.

We have developed a novel oxygen-adherence monitor that addresses the above limitations, and, we believe, for the first time objectively documents when a patient is actually receiving oxygen treatment. Our monitor attaches to the oxygen source and detects respiratory-related pressure fluctuations transmitted through the nasal cannula. The monitor is designed to detect when the oxygen source is turned on and when the patient is actually wearing the nasal cannula and receiving the treatment. The purpose of this report is to introduce our monitor and provide some preliminary data that validates its use in patients with COPD, while sitting and walking.

## Methods

### Description of Monitor Device

The monitor works by sensing pressure in the oxygen-delivery tubing that runs from the oxygen source to the nasal cannula. It is attached via a T-shaped connector to the oxygen-supply tubing, between the oxygen source and the nasal cannula (Fig. 1). The connector is placed close to the oxygen source, so the monitor can be secured to the source. When the oxygen supply is turned on, the monitor senses the elevated pressure in the tubing; otherwise, the pressure is at the ambient atmospheric pressure. When the patient has the cannula prongs in the nares, respiratory-related pressure fluctuations are superimposed on the supply pressure, indicating that the patient is wearing the nasal cannula. Thus, 4 different states can be detected to describe use of the oxygen source and cannula: (1) source-off/cannula-off, (2) source-off/cannula-on, (3) source-on/cannula-off, and (4) source-on/cannula-on.

The monitor consists of a pneumatic filtering system and an electronic detection system (Fig. 2). Two pressure signals can be extracted from the oxygen-delivery tubing: breathing-pressure fluctuations and the oxygen-source pressure. These 2 pressure signals are then analyzed in the

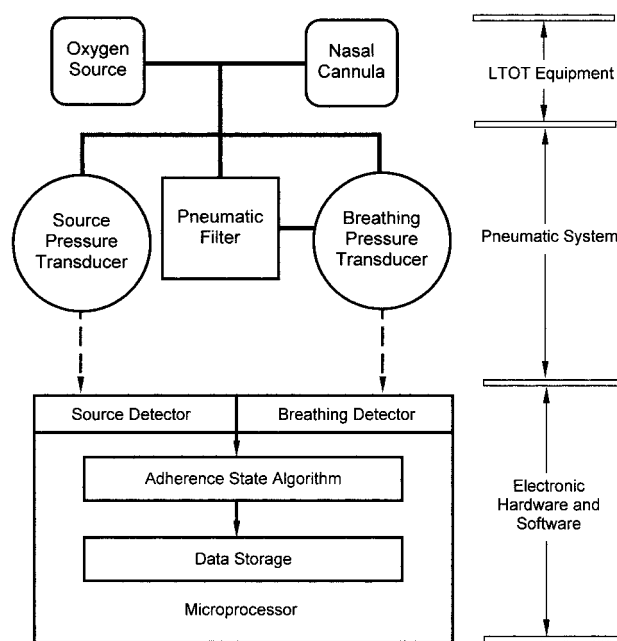


Fig. 2. Function diagram of the oxygen-adherence monitor. The output of the adherence-state algorithm is the on/off status of the oxygen source and cannula use.

electronics of the monitor to detect (1) whether the oxygen supply is on, and (2) whether the patient is breathing oxygen through the cannula.

The purpose of the pneumatic filtering system is to isolate the breathing-pressure fluctuations from the oxygen-supply pressure. Superimposed on the supply pressure are the small pressure fluctuations in the nares, generated by the patient's respiration (ie, unfiltered pressure). The supply pressure is extracted by passing the unfiltered pressure through a low-pass pneumatic filter, eliminating frequencies  $> 0.1$  Hz. Since the typical quiet breathing rate in a healthy adult ranges from 12–16 breaths/min, or 0.2–0.27 Hz, we selected a cutoff frequency of 0.1 Hz (6 breaths/min). Subtracting the supply pressure from the unfiltered pressure through a differential pressure transducer isolates the breathing-pressure fluctuations.

The electronic system consists of 2 pressure transducers, a microprocessor (which samples the data coming from the pressure transducers), a memory storage chip, and a serial port (which allows cable connection for downloading data to a computer). The microprocessor is programmed to identify the 4 different on/off states, record the exact time and date when each state occurred, and tabulate the total time spent in each state. The different states are measured over a 25-second period, at 4-min intervals. For each state identified, the state and its associated timing information is stored as a single event in a memory storage chip, which is capable of storing up to 32,768 events. Periodic (as opposed to continuous) mea-

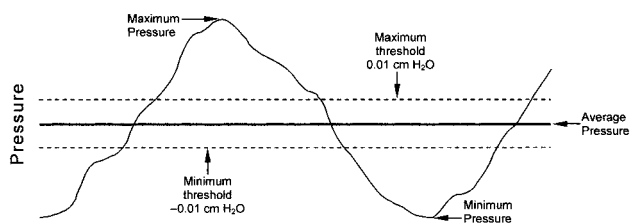


Fig. 3. Schematic of pressure versus time for a single breath, demonstrating the threshold placements. Average = (maximum pressure - minimum pressure)/2.

surement extends battery life. The monitor can theoretically collect data for approximately 8 months, using 2 AA batteries. For the purpose of this study, the downloaded data were displayed in text format, showing the time and date for each identified state.

To determine whether the oxygen source is turned on or off, the pressure in the tubing generated by the oxygen source is compared to a source threshold pressure. The purpose of this threshold is to determine whether the pressure in the oxygen-supply tubing is above atmospheric. The source threshold pressure was set to 1.1 cm H<sub>2</sub>O, so the source-on state was identified when tubing pressure was  $\geq 1.1$  cm H<sub>2</sub>O. The source-off state was identified when tubing pressure was  $< 1.1$  cm H<sub>2</sub>O. The source threshold pressure of 1.1 cm H<sub>2</sub>O was a level capable of detecting even a low oxygen flow. When the flow from an E-size oxygen cylinder (with the standard approximately 2-m length of tubing) was set at 0.5 L/min, the measured pressure in the tube was 4 cm H<sub>2</sub>O.

To determine whether the cannula prongs are in the nares, the breathing-pressure fluctuation amplitude is compared to a set of breathing-pressure fluctuation thresholds. An upper threshold is used for expiration and a lower threshold for inspiration. The thresholds are placed equidistant from a baseline, which is the average of the maximum and minimum values of the nasal pressure signal (Fig. 3). A full breath is defined as a pressure-decrease during inspiration, to below the lower threshold, followed by a pressure-increase during expiration, to above the upper threshold, or vice versa. To avoid false positives due to transient signals, the definition of "inspiration" (or "expiration") requires that the incoming nasal-pressure signal stays below (or above) the threshold for at least 500 ms. Signals that cross the threshold but do not last  $\geq 500$  ms are considered transient noise and disregarded. Breathing is detected when 2 or more full breaths occur over the 25-second sampling period. During bench testing, a value of approximately 0.01 cm H<sub>2</sub>O (about 5% of the pressure-fluctuation of a shallow breath) between the 2 thresholds proved to be an effective detection criterion for breathing. Figure 4 shows typical pressure signals detected by the oxygen-adherence monitor in a healthy adult male during

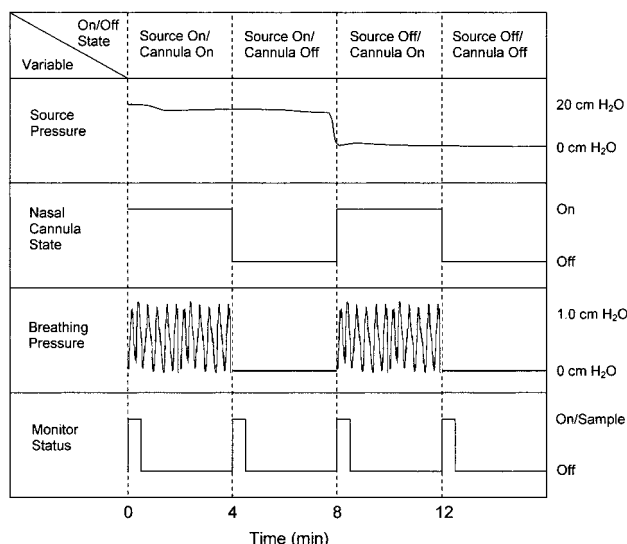


Fig. 4. Example waveforms of pressure signals in the oxygen-delivery tubing during all 4 on/off states. Source Pressure: a direct, unamplified measurement of the pressure in the oxygen-delivery tubing to determine whether the oxygen source is on or off ( $\geq 1.1$  cm H<sub>2</sub>O indicates oxygen source on). Nasal Cannula State: measurement (via direct observation by one of the researchers) of whether the nasal cannula prongs are in the nares. Breathing Pressure: an amplified breathing signal obtained by the microprocessor. Monitor Status: shows when the monitor turns on and samples the incoming breathing-pressure signal. The monitor turns off after sampling, to conserve battery power.

quiet breathing with an oxygen cylinder. Flow was set at 2 L/min, and an approximately 2-m length of tubing was used. There are a total of 4 consecutive measurements, each representing one of the 4 states. The monitor does not record the actual waveforms, but stores the state by monitoring each waveform to determine which of the 4 conditions is present.

### Validation Protocol

We directly observed a timed sequence of the subjects using and not using supplemental oxygen via nasal cannula, while sitting and walking. The study subjects were 10 patients (9 men) with COPD: mean  $\pm$  SD age  $63 \pm 13$  y, mean  $\pm$  SD height  $175.7 \pm 6.6$  cm, mean  $\pm$  SD weight  $88 \pm 18$  kg. COPD was defined by spirometry values: ratio of forced expiratory volume in the first second to forced vital capacity (FEV<sub>1</sub>/FVC)  $< 70\%$  and FEV<sub>1</sub>  $< 80\%$  of predicted, without a substantial response to bronchodilator administration. The mean  $\pm$  SD percent-of-predicted FEV<sub>1</sub> and FEV<sub>1</sub>/FVC values for all the patients were  $33.7 \pm 18.9\%$  and  $45.5 \pm 20.2\%$ , respectively.

The protocol was a modified version of a standard clinical evaluation used to assess a patient's LTOT requirements (Table 1). During the evaluation, 3 different conditions

## OXYGEN-ADHERENCE MONITOR

Table 1. Modified LTOT Evaluation Protocol Using an Oxygen Cylinder Source

| Event      | Duration (min) | Nasal Cannula (on/off) | Oxygen Source (on/off) |
|------------|----------------|------------------------|------------------------|
| 1. Sitting | 12             | off                    | off                    |
| 2. Sitting | 12             | off                    | on                     |
| 3. 6-MWT*  | 6              | off                    | on                     |
| 4. Sitting | 12             | on                     | on                     |
| 5. 6-MWT*  | 6              | on                     | on                     |

LTOT = long-term oxygen therapy

\*6-min walk test, per American Thoracic Society guidelines<sup>11</sup>

were assessed: (1) source-on/cannula-on, (2) source-on/cannula-off, (3) source-off/cannula-off.

Patients were administered oxygen at 2–3 L/min via nasal cannula with an approximately 2-m length of tubing connected to an E-size oxygen cylinder, which was placed in a hand-drawn cylinder cart. The monitor was attached to the cylinder. Testing lasted approximately 48 min. The protocol was precisely timed so that the transitions between the different conditions would not occur when the monitor was making a measurement.

As our standard we used direct observation of the patient by one author (SKVL), who kept a written log of the time and oxygen-use state of each transition. He scored all the records in order to eliminate inter-observer variability. The monitor's electronic recordings were not displayed during the tests, but instead were downloaded after patient testing.

Patients were monitored with pulse oximetry throughout the protocol, and oxygen saturation remained above 87%. During the walking condition<sup>11</sup> when the nasal cannula was not being worn, patients already receiving LTOT were provided with an alternative oxygen source to prevent exercise-induced oxygen desaturation. The study was approved by the institutional review board of the University of Pennsylvania. All participants gave written, informed consent.

### Analysis

The data from the oxygen-adherence monitor, collected at 4-min intervals over the entire study period, were downloaded, in text format, for analysis. Each measurement was compared to SKVL's written log.

The overall detection accuracy of the monitor was assessed by computing the percentage of measurements that were correct, relative to the written log. The monitor's sensitivity and specificity were assessed. Sensitivity was defined as the proportion of measurements directly observed as cannula-on that the monitor detected as cannula-

Table 2. Sensitivity and Specificity of the Monitor

|                   |             | Direct Observation by Researcher      |  |
|-------------------|-------------|---------------------------------------|--|
|                   |             | Cannula On                            | Cannula Off                            |
| Monitor Detection | Cannula On  | 42                                    | 0                                      |
|                   | Cannula Off | 7                                     | 80                                     |
|                   |             | ↓                                     | ↓                                      |
|                   |             | Sensitivity =<br>42/(42 + 7)<br>= 86% | Specificity =<br>80/(0 + 80)<br>= 100% |

on. A sensitive monitor would rarely indicate that the patient was not wearing the cannula when the cannula was actually being worn. Specificity was defined as the proportion of measurements directly observed as cannula-off that the monitor detected as cannula-off. A specific monitor would rarely indicate that the patient was wearing the cannula when the cannula was actually not being worn.

### Results

The monitor performed 12–13 measurements with each participant. One participant could not fully complete the 6-min walk while wearing the cannula, resulting in one less measurement. Over all the participants, the monitor correctly detected 122 of 129 measurements, achieving an overall detection accuracy of 95%. The sensitivity and specificity were 86% and 100%, respectively (Table 2).

All the incorrect measurements occurred with 4 male patients (designated patients A, B, C, and D) while they were wearing the cannula. Four incorrect measurements occurred while these patients were sitting: a single time each with patients A and B, and twice with patient C. The remaining 3 incorrect measurements occurred while patients were walking: a single time with patient D and twice with patient C. Four of the 7 errors occurred with patient C, who had a very distinct pattern of pursed-lip mouth breathing, both while sitting and walking.

### Discussion

We have developed a novel monitor to objectively document patient adherence to LTOT. To our knowledge, our monitor is the first to objectively document when the patient is actually receiving oxygen treatment. The monitor senses the respiratory-related pressure fluctuations transmitted from the nares through the nasal cannula tubing. The monitor also senses the elevated pressure in the oxygen-supply tubing when the oxygen source is turned on, thus capturing the actual amount of time that the oxygen is turned on/off and when the patient is breathing/not breath-



ing oxygen. Current methods used to measure LTOT adherence measure only the average daily amount of oxygen expended. Unlike our monitor, these other methods do not provide information on oxygen use patterns within the day or whether the patient is actually breathing the oxygen. Our monitor is capable of detecting 4 different states; however, this study assessed the accuracy of only 3 on/off states: source-on/cannula-on, source-on/cannula-off, and source-off/cannula-off. The source-off/cannula-on state was not tested, but was included in the adherence-state algorithm, because it might provide useful information in future investigations of adherence patterns.

One prior attempt at improving LTOT-adherence monitoring was reported by Phillips et al.<sup>12</sup> Their device was based on measuring the amount of time the patient wore the nasal cannula. The device employed plastic electrodes connected to a battery-operated timing device that sensed when the cannula was in contact with the skin. This device was tested in patients receiving LTOT from an oxygen concentrator over a 1-week period. Based on the concentrator's power-on time, mean oxygen use per day was 18.2 hours, compared to a mean of 12.7 hours per day based on their device. The results indicated that oxygen concentrator power-on time overestimates LTOT adherence.

The device of Phillips et al.<sup>12</sup> has several limitations: the sensing electrodes are quite large, they cover a substantial area of the face, they must be attached to the nasal cannula, and the recorder is in close proximity to the patient. These obtrusive aspects may cause patients to alter their LTOT adherence. In addition, though the device senses whether the cannula is on the face, it does not actually measure if the patient is breathing the oxygen. And the device measures only mean daily hours of use; it does not assess daily oxygen-use patterns. Our oxygen-adherence monitor addresses these limitations: (1) it is attached to the oxygen source, and nothing other than the standard nasal cannula is attached to the patient, (2) it detects whether the patient is breathing the oxygen, and (3) it records the time of each event, thus providing the oxygen-use pattern within each day.

Other currently employed LTOT-adherence monitoring methods depend on the fixed oxygen source: the number of oxygen cylinders used, the change in weight of the liquid oxygen reservoir, or the oxygen concentrator power-on time. Our monitor has the potential advantage of being able to measure adherence regardless of the oxygen source. The standardization of oxygen adherence measurement across different oxygen source options would allow more accurate comparison of patient adherence across different modes of delivery.

One aspect of our monitor that was not tested in this study was its accuracy with intermittent-demand oxygen-conserving devices. These devices produce pressure spikes during inhalation, when the oxygen is delivered to the

patient. The effect of these spikes on the pneumatic system of our monitor (ie, settling time of the filter) has not been systematically tested and needs to be further assessed.

In this study, high detection accuracy (95%) was achieved because of the low breathing threshold setting (ie, 5% of a shallow breath). At such a low threshold, the monitor may be susceptible to noise or transient signals that could result in false positives; nonetheless, the employed breath-detection algorithm correctly detected when the patient was not wearing the cannula, either while sitting or walking (100% specificity). When the patient was wearing the cannula, however, the monitor was incorrect in 7 of the 49 measurements, either while sitting or walking (86% sensitivity). Because the breathing threshold setting was set extremely low, these errors were most likely due to exceptionally small nasal-pressure signals that went undetected by the monitor during the measurement period. A small nasal pressure signal could occur because of predominant mouth breathing, since mouth breathing, especially when associated with closure of the nasopharynx, is associated with lower nasal pressure.<sup>13</sup> This phenomenon may explain why 4 of the 7 total errors occurred in the patient who had a very distinct pattern of pursed-lip mouth breathing.

The detection accuracy, sensitivity, and specificity of the monitor were validated in this study by taking every measurement into consideration. Although 100% sensitivity was not obtained, 100% accuracy may not be necessary for long-term adherence measurements. Most patients are prescribed either continuous or nocturnal LTOT, so occasional false detections over a period of months would not be important for adherence-monitoring or therapy. For long-term adherence monitoring, the accuracy of the monitor may be enhanced by using consistent detections over several consecutive measurements to determine whether the oxygen source and nasal cannula are on or off. However, this type of analysis could not be applied to the current data because of the relatively small number of measurements obtained from each subject. Additional studies are needed to further validate the monitor over longer time periods, under less controlled conditions.

The potential importance of our monitor's capabilities is demonstrated by recent experience with patient adherence to continuous positive airway pressure (CPAP, administered via nose mask, during sleep) treatment among patients with obstructive sleep apnea.<sup>14,15</sup> Similar to our oxygen-adherence monitor, some CPAP machines provide precise information about patient adherence to treatment, by recording when the circuit is pressurized (ie, when the machine is turned on and the patient is wearing the mask). Research using these CPAP adherence data illustrates the rich amount of information that could result from the use of our LTOT adherence monitor and its potential to influence the management of patients on oxygen therapy. For

example, recent studies found that long-term adherence to CPAP can be predicted in the first few days of treatment,<sup>16,17</sup> and that patient education and support at the initiation of CPAP treatment improves adherence.<sup>18</sup> These important findings from the CPAP adherence monitor have improved the management of patients using CPAP. Although the nature of CPAP therapy and LTOT are dissimilar, these examples from CPAP therapy show that objective monitoring of LTOT adherence may lead to effective adherence-promotion interventions.

### Conclusions

We have developed a novel oxygen-adherence monitor that can objectively measure oxygen inhalation, rather than oxygen expenditure, in patients with COPD, while sitting and walking. The monitor's overall detection accuracy was 95%. Further studies are required to confirm these promising results. The future studies will evaluate the monitor during activities of daily living, during sleep, and over extended periods. We believe the clinical application of this monitor will provide valuable new insights on the adherence patterns, predictors of adherence, and interventions to improve adherence to LTOT.

### ACKNOWLEDGMENTS

Jerome Beverly, Sharif Branham, and Tracy Seeger provided technical assistance.

### REFERENCES

- Report of the Medical Research Council Working Party. Long term domiciliary oxygen therapy in chronic hypoxic cor pulmonale complicating chronic bronchitis and emphysema. *Lancet* 1981;1(8222): 681-686.
- Nocturnal Oxygen Therapy Trial Group. Continuous or nocturnal oxygen therapy in hypoxemic chronic obstructive lung disease: a clinical trial. *Ann Intern Med* 1980;93(3):391-398.
- Criner GJ. Effects of long-term oxygen therapy on mortality and morbidity. *Respir Care* 2000;45(1):105-118.
- Pierson DJ. Pathophysiology and clinical effects of chronic hypoxia. *Respir Care* 2000;45(1):39-51; discussion 51-53.
- Dunne PJ. The demographics and economics of long-term oxygen therapy. *Respir Care* 2000;45(2):223-228; discussion 228-230.
- Pauwels RA, Buist AS, Calverley PMA, Jenkins CR, Hurd SS; GOLD Scientific Committee. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. NHLBI/WHO Global Initiative for Chronic Obstructive Lung Disease (GOLD) Workshop summary. *Am J Respir Crit Care Med* 2001;163(5):1256-1276.
- Walshaw MJ, Lim R, Evans CC, Hind CR. Factors influencing the compliance of patients using oxygen concentrators for long-term home oxygen therapy. *Respir Med* 1990;84(4):331-333.
- Granados A, Escarrabill J, Borrás JM, Rodríguez-Roisin R. The importance of process variables analysis in the assessment of long-term oxygen therapy by concentrator. *Respir Med* 1997;91(2):89-93.
- Howard P, Waterhouse JC, Billings CG. Compliance with long-term oxygen therapy by concentrator. *Eur Respir J* 1992;5(1):128-129.
- Avdeev SN, Aisanov ZR, Chuchalin AG. Compliance as a critical issue in long-term oxygen therapy. *Monaldi Arch Chest Dis* 1999; 54(1):61-66.
- ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories. ATS statement: guidelines for the six-minute walk test. *Am J Respir Crit Care Med* 2002;166(1):111-117.
- Phillips GD, Harrison NK, Cummin AR, Ward J, Shenoy VS, Newey V, et al. New method for measuring compliance with long term oxygen treatment. *BMJ* 1994;308(6943):1544-1545.
- Thurnheer R, Xiex X, Bloch KE. Accuracy of nasal cannula pressure recordings for assessment of ventilation during sleep. *Am J Respir Crit Care Med* 2001;164(10 Pt 1):1914-1919.
- Kribbs NB, Pack AI, Kline LR, Smith PL, Schwartz AR, Schubert NM, et al. Objective measurement of patterns of nasal CPAP use by patients with obstructive sleep apnea. *Am Rev Respir Dis* 1993; 147(4):887-895.
- Reeves-Hoche MK, Meck R, Zwillich CW. Nasal CPAP: an objective evaluation of patient compliance. *Am J Respir Crit Care Med* 1994;149(1):149-154.
- Weaver TE, Kribbs NB, Pack AI, Kline LR, Chugh DK, Maislin G, et al. Night-to-night variability in CPAP use over first three months of treatment. *Sleep* 1997;20(4):278-283.
- McArdle N, Devereux G, Heidamejad H, Engleman HM, Mackay TW, Douglas NJ. Long-term use of CPAP therapy for sleep apnea/hypopnea syndrome. *Am J Respir Crit Care Med* 1999;159(4 Pt 1):1108-1114.
- Hoy CJ, Vennelle M, Kingshott RN, Engleman HM, Douglas NJ. Can intensive support improve continuous positive airway pressure use in patients with the sleep apnea/hypopnea syndrome? *Am J Respir Crit Care Med* 1999;159(4 Pt 1):1096-1100.