Introduction and Aim of the Work

Introduction:

Episodes of significant O2 desaturation and hypoxaemia may occur during sleep in patients with chronic obstructive pulmonary disease (COPD). These episodes can be adequately treated with long term supplemental O2 ***(Vos et al., 1995).***

It has been suggested that even transient elevations of pulmonary artery pressure consequent to nocturnal O2 desaturation may lead to development of core pulmonale ***(Levi-valenci et al., 1992).*** However, recent evidence casts doubt on this hypothesis ***(Chaouat et al., 1997).***

Certainly patients with COPD who experience, nocturnal fall in O2 saturation have poorer quality of sleep compared to healthy controls and their quality of life relates to the severity of hypoxaemia ***(Okabadej et al., 1996).***

In addition, mortality in COPD patient is greater at night when compared with age matched controls and nocturnal death is particularly common in COPD patient who are hypoxaemic and hypercapnic. Furthermore, in hypoxaemic patient with COPD nocturnal death is more common in those breathing air than in those receiving supplementary O2 ***(McNicholas, 1984).***

Obstructive airway disease (OAD) has been estimated to affect 14-16 millions in the United States causing substantial morbidity and mortality ***(National Heart Lung & Blood Institute, 2002).***

Sleep apnea hypopnea (SAH) is also prevalent in community ***(Ronaldy et al., 1999)*** by chance alone some persons would be expected to have both conditions, previously termed an (overlap syndrome) ***(Flentey, 1985). Guilleminault et al., (1980)*** have suggested that the prevalence of obstructive airway disease (OAD) in patient with SAH exceeds the prevalence of OAD in the general population, conversely an unexpected high prevalence of SAH has also been reported in patient with OAD. A putative association between OAD and SAH could be due to the rate of tobacco smoking some but not all, studies have suggested that tobacco use is a risk factor for both entities ***(Hoffsteinv et al., 2002).***

In addition, OAD has been associated with nocturnal hypxaemia, poor sleep quality and insufficient or disrupted sleep ***(McKeon et al., 1988).*** The sleep related physiological disturbances may be associated with abnormal ventilatory control and upper airway instability during sleep ***(Spengler et al., 2000).***

A number of studies have suggested that the presence of OAD and SAH leads to greater blood gas & pulmonary haemodynamic disturbations than found in individuals with OAD or SAH alone ***(Weitzenbtum, 1998).*** Thereby increasing risk of cor pulmonale on the basis of these studies as well as data suggesting a specific association between OAD and SAH some authors have suggested that a diagnostic evaluation for SAH should be conducted in all OAD patients ***(Chaouat et al., 1995).***

The Aim of this work is to:

1) Determine the rate of occurrence of nocturnal O2 desaturators (NOD) in COPD patient with or without sleep apnea hypopnea syndrome (OSAHS).
2) Determine the predictors of OSAHS and NOD in COPD patients.

Sleep and Breathing Pattern

Physiology of Sleep and Breathing:

Sleep is a behavioral state characterized by inactivity and reduced responsiveness to external stimuli. Neurophysiologic monitoring results in a classification (in humans) into two distinct broad states termed non-rapid eye movement (NREM) sleep and rapid eye movement (REM) sleep. States are distinguished by recording electroencephalogram (EEG), electrooculogram, and electromyogram of the chin muscles. The combination of these measures and the cardiopulmonary monitoring of airflow, respiratory effort, O_2 saturation, and heart rate, along with identification of body position, comprise polysomnography ***(Chesson et al., 1997).***

By polysomnography, NREM sleep is further classified into four stages, which correlate with the difficulty in producing an arousal. Stage I is light sleep, slightly beyond drowsiness, whereas stage IV represents deep sleep. The EEG shows decreased frequency and increased amplitude as sleep progresses from stage I to stage IV. REM sleep is the stage when most dreaming occurs, and there occurs presynaptic inhibition of antigravity muscles. There is, however, activation of the cortex, the EEG being fast mixed frequencies with low amplitude (resembling awake EEG). Thus, REM sleep is described as paradoxical sleep: active central nervous system and paralysis of skeletal muscle. REM sleep occurs in

cycles every 90 to 110 minutes, and the longer bouts of REM sleep occur more toward the end of a nocturnal sleep period ***(Han and Strohi, 2000).***

Autonomic regulation during sleep:

Ventilatory behavior refers to the elements of tidal volume and frequency that contribute to minute ventilation. Phases of inspiration and expiration are thought of as having a neural and mechanical element ***(Richter and Spyer, 2001).*** Ventilatory rate and rhythm are organized at a neural level by interactions between groups of neurons located in the medulla: a dorsal group located in the vicinity of the nucleus tractus solitarius and a ventral group consisting of neurons in the nucleus retroambigualis and paraambigualis, the nucleus retrofacialis, and the nucleus ambigualis. Efferent activity of the nerves that supply upper airway muscles is adjusted by nucleus ambigualis activity, and activity to the chest-wall muscles by dorsal medullary nuclei. The activity of these rnedullary groups of respiratory neurons can be altered by descending pathways from pontine and suprapontine areas and can be affected by the sleep/wake cycle, in particular the waxing and waning of the median raphe, or reticular activating system ***(Ramirez and Richer, 1996).***

The medulla helps coordinate the activation of the chest wall and upper airway muscle groups in both time and amplitude ***(Van Lunteren and Strohi, 1986)*** The electric activity of upper airway muscles precedes the onset of activation of the diaphragm and is entrained to the respiratory rhythm. Phasic amplitude increases and decreases in the activity of many upper airway muscles are altered by the same chemical stimuli (CO_2 and hypoxia) that affect diaphragm and intercostal muscle activity. Uncoupling or mismatches in upper airway and chest wall muscle activation can occur as a result of local reflexes and of changes in medullary outflow. The effects of such mismatch on ventilation will depend in part on the mechanical properties of the lungs/chest wall or the upper airway ***(Suratt, 1988).***

Breathing rate and depth are the result of a feedback control system in which the brainstem (controller) organizes neuromuscular output to the respiratory muscles of the upper airway and chest wall. Muscle action generates tidal volume through the mechanical actions of the chest wall and lungs (the controlled system). Sensors monitor the success/failure of controlled system outputs of ventilation and gas exchange; these are the peripheral (carotid body) and central (medullary) chemoreceptors, and mechanoreceptors distributed along the upper and lower airways, joints, lungs, and skeletal muscles ***(Badr and Strohi, 2004).***

There are putative set points for this system based on, a need for homeostatic control of pH and O_2 delivery. These set points are altered in sleep at various points in this system. One example of the operation of a set point is the apneic threshold, also defined as that level of arterial (or central) CO_2 below which there is no threshold for activation of inspiration. Certainly, brain centers other than the medulla and pons contribute to breathing rate and depth and can override to a certain extent brainstem mechanisms for breathing. However, during sleep these "higher" centers appear to have less influence on and be actively inhibiting respiration, unless engaged in an arousal response from sleep, something that can happen not only with respiratory abnormalities but also with a variety of external stimuli and intrinsic mechanisms ***(Badr and Strohi, 2004).***

Changes in Ventilatory Behavior with Sleep

Sleep is accompanied by a reduction in movements and a passive appearance of a sleeping subject. There is a reduction in metabolic rate and, therefore, a reduced need to breathe. In addition, there is a loss of a wakefulness stimulus. Thus, breathing during sleep becomes generally more responsive to chemoreceptor and mechanoreceptor stimuli, and less responsive to higher centers. Consequences of sleep onset include reduced tidal volume, changes in lung mechanics, reduced activity of upper airway dilators, and reduced upper airway caliber ***(Dempsey and Skatrad, 2001).***

Sleep alters postural muscle tone and autonomic outflow, resulting in alterations in chest-wall, lung, and upper airway mechanics. Furthermore, in NREM sleep, the ratio of rib cage to abdominal displacement is greater than that during wakefulness, whereas in REM sleep, it is less. These changes in movement may affect the distribution of ventilation in the lungs, increasing ventilation-perfusion mismatching, and so contribute to hypoxia necessitating changes in respiratory output and possibly initiating an unstable breathing pattern ***(Strohi et al., 1986).***

*** Upper Airway Caliber and Compliance:**

Reduced motor output during sleep is associated with reduced tidal volume, alveolar hypoventilation, and elevated $PaCO_2$: Upper airway dilating muscle activity is reduced during NREM sleep, especially in those muscles with tonic activity (independent of the phase of respiration), such as the tensor palatini muscle, which is reduced at sleep onset ***(Mezzanotte, 1996).*** Upper airway caliber is reduced during sleep, likely owing to decreased upper airway dilating muscle activity ***(Rowley et al., 1998 and Rowley et al., 2001).*** The mechanical corollary of reduced caliber is increased upper airway resistanc ***(Henke et al., 1991).*** In addition, pharyngeal compliance increases during NREM sleep relative to wakefulness ***(Rowley et al., 1998),*** so that the normal negative

pressures produced by the chest wall muscles during inspiration tend to further stress the patency of the upper airway. The degree of upper airway rigidity can depend on the bony and cartilaginous structures supporting the airway, on the soft tissue features of the upper airway, and on the level of activity in upper airway muscles. If upper airway caliber or compliance is compromised, inspiratory flow limitation develops secondary to negative intrathoracic pressure, manifesting by a plateau in flow despite continued development of negative pressure ***(Henke et al., 1991). .***

In REM sleep, despite muscle atonia, pharyngeal compliance is not increased ***(Rowley et al., 1998).*** In fact, the retropalatal airway is less compliant during REM sleep relative to NREM. This finding indicates the significance of non-neuromuscular factors in maintaining upper airway patency during sleep. REM sleep is a special case because peripheral atonia is accompanied by augmented inspiratory medullary neuronal activity and because the REM sleep EEG shares many features of the awake EEG ***(Rowley et al., 1998).***

Changes in ventilation during NREM sleep:

During NREM sleep, ventilation declines. It becomes regular in stages 3 and 4 sleep. In stages I and 2 of NREM sleep, however, ventilation is more likely to be variable and, in certain persons, periodic breathing with cycles of waxing and waning in ventilation occur ***(Pack et al., 1998).***

One of the important principles of the effect of sleep on respiratory control is that sleep differentially affects the activity of the muscles of the respiratory pump and the dilator muscles of the upper airway, with changes in the latter being more profound. There are exceptions to this rule: in particular the activity of some laryngeal muscles is profoundly suppressed during sleep, whereas that of others is not. Overall, however, one major reason for the reduction in ventilation in NREM sleep is an increase in resistance secondary to a decrease in activity of the dilator muscles of the upper airway, especially in the pharyngeal region. However, no change occurs in the transdiaphragmatic pressure difference during inspiration, a measure of diaphragmatic function. As a consequence of this decrease in ventilation in NREM sleep, PaCO2, rises, typically from its normal value of 40mmHg to (45 – 46) mmHg. The magnitude of this increase in PaCO2 is a function of the responsiveness of the system to CO2 during wakefulness: subjects with low ventilatory responses to CO2 have larger increases in Paco2 than do subjects with high responses. Parallel to this increase in PaCO2, the PaO2 falls to (3 – 10) mmHg and oxygen saturation decrease by < 2% during sleep ***(Stevens, 2004).*** In normal persons, who are operating on the flat part of the oxygen saturation curve, the Pao2 does not fall to a level where significant desaturations occur. However, m persons with low Pao2 during wakefu1ness, who operate closer to the “knee” of the oxygen

saturation curve, this fail in PaO2 during sleep may lead to a significant hypoxemia. For example, patients with chronic obstructive pulmonary disease may require supplemental oxygen during sleep but not during wakefulness. In concentration to the change in the apnea threshold to PaCO2, the slope of the response to PCO2, decreases during sleep. Such a decrease may result either from a decrease in central CO2 sensitivity (e.g., due to state-dependent changes in the activity or membrane properties of CO2-sensitive neurons in the brain stem) or from the reduced activity at the respiratory motor output (e.g., due to the sleep-related withdrawal of the excitatory effect of the wakefulness stimulus on respiratory motor neurons or their pre-motor cells). Although a reduction in excitability at motor neuronal levels does occur, the evidence for state-dependent changes in central CO2 sensitivity is much less compelling. Overall, however, the progressive declines in the ventilatory response to CO2 are smaller in stages 1 and 2 than in stages 3 and 4 NREM sleep. They must contribute to the hypoventilation that occurs during sleep by making the system less able to compensate for the increase m upper-airway resistance ***(Pack et al., 1998).***

Another major change that occurs during NREM sleep is an increase in the CO2 apnea threshold (the PaCO2 at which there is insufficient chemical drive and ventilation ceases). During wakefulness, PaCO2 can be reduced by assisted ventilation to values as low as 20 mmHg and rhythmic ventilation will be maintained; thus, the CO2 apnea threshold during wakefulness is extremely low. In contrast, during NREM sleep, the Paco2 need be reduced only to values close to the normal awake PaCO2 (38 to 40 mmHg) and ventilation will cease. Thus, the normal increase in PaCO2 that occurs during NREM sleep is often necessary to maintain rhythmic ventilation. This NREM sleep-related

increase in apnea threshold has pro-found implications. In situations where ventilation is stimulated-for example, by hypoxia-PaCO2 may be reduced below the apnea threshold typical for normoxic conditions, creating a state of increased vulnerability to central apneas. It is likely that unexplained central apnea during sleep occurs in association with hypocapnia. If this is the mechanism for these apneas, increase in the PaCO2 should abolish them. Instances have been reported of persons with central apnea in whom apnea was relieved when they breathed air enriched with low concentrations of CO2 ***(Pack et al., 1998).***

*** Changes in ventilation during REM sleep:**

Associated with the flurries in activity, such as eye movements, there are phasic changes in ventilation: increases in ventilation occur from increases in respiratory rate, and reductions in ventilation accompany slowing of the respiratory rate. Despite this profound breath-to-breath variability in normal persons during REM sleep, the average ventilation changes very little compared to wakefulness. The phasic changes in ventilatory output affect the rib cage more than the abdomen; hence, when compartmental ventilation is measured, rib cage ventilation decreases more ***(Pack et al., 1998).***

Sleep-Disordered Breathing

Definition:
Sleep-disordered breathing is present when there are recurrent episodes of cessation of respiration (apnea) or decrements in airflow (hypoponeas) during sleep ***(Schwab et al., 1998).***

Subjects without clinical problems may exhibit obstructive or central apneas at sleep onset or during periods of REM sleep ***(Young et al., 1993).*** Apneic episodes are usually less than 15 seconds -in duration and are not repetitive. Occasionally, longer periods of apnea lasting 30 seconds or more are seen in normal subjects, particularly during REM sleep. These episodes may not be accompanied by arousal or sleep-state changes ***(Block et al., 1997).***

In healthy young subjects, some studies have shown that more boys than girls have frequent apneas during sleep, but others report little sex difference in the occurrence of apneas. After the sixth decade, however, respiratory disturbances during sleep seem to increase in number and occur with equal frequency in men and women. Patients with a clinically -important sleep apnea may be distinguished from normal by the existence of repetitive apneas greater than 10 seconds in duration during stages I and II and REM sleep and by improvement in daytime symptoms and general performance with treatment of SDB ***(Redline and Strohl, 1998).***

In U.S. communities, 9% to 12% of women and 27% to 35% of men may have an apnea-hypopnea index greater than normal; however, many people with an apnea-hypopnea greater than five have no symptoms or apparent illness. If the definition of illness is the presence of daytime sleepiness or cardiovascular complications such as hypertension, the estimates are that 2% to 4% of those in the community having

symptomatic SDB. These studies also suggest that these subjects have higher accident rates and substantial disability ***(Partinen, 1995).***

Snoring is believed to be a predisposing feature in the development of disease ***(Dalmasso et al., 1996).*** Snoring increases with age, so that approximately 45% of men and 30% of women age 65 years are said to snore. Hypertension is two to three times and diabetes is 1.5 times more likely among persons who snore, even after age and obesity arc taken into account ***(Al-Delaimy et al., 2002).***

Genetic of sleep disordered breathing (SDB):

Sleep disordered breathing (SDB) has been shown to exhibit familial clustering, and -if snoring is considered as a variant of SDB, the familial incidence of snoring and sleep apnea is quite striking. There is some evidence from cephalometric measurements that the arrangement of the jaw to the head and neck is inherited ***(Guilleminault et al., 1995 and Kulnis et al., 2000).*** Conceivably, individuals with a certain structural framework would be predisposed to snoring and/or apneas. It is also known that there are familial traits in hypercapnic and hypoxic sensitivity; these could relate to the tendency to breathe periodically during sleep. It is not known if there is a familial trait involving the respiratory coordination of muscles of the chest wall and upper airway. In addition, obesity and alcoholism (factors associated with SDB) can be family traits and, to the extent that these factors are causally related to apneas, are bases for familial clustering of sleep apnea ***(Badr and Strohi, 2004).***

There is increasing evidence that sleep apnea has a genetic component ***(Redline et al., 1992).*** Symptoms relating to apnea are present with two to six times greater frequency in family members of affected patients than in a control population. Sleep apneic activity itself is present more often in first-degree relatives of patients than in age-, sex-, and socioeconomic-matched control families. These family studies also suggest that the frequency of sleep apnea is underestimated in tile community and that the symptomatic sequelae of multiple apneas are

quite variable. The experience in directly measuring for genetic factors in SDB is limited. Taking a candidate gene approach, there was observed an increased prevalence (twofold) in a polymorphism for apolipoprotein E, which is also associated with cardiovascular disease and Alzheimer disease ***(Kadotani et al., 2001).*** This has not been confirmed in other studies, perhaps because the observation may occur as a function of age or of the ascertained population. From human studies of families with one (or more) affected members (the Cleveland Family Study), there is statistical evidence for an oligogenic transmission explaining some 27% of the variation in apnea-hypopnea index expression in the community. In whites, analysis of an age-adjusted (log-transformed) apnea-hypopnea index suggests recessive mendelian inheritance with separate distributions for each sex, accounting for 21% to 27% of the variance, with an additional 8% to 9% of the variation owing to other familial factors, either environmental or polygenic. Similarly, transmission patterns in the African-American sample were consistent with mendelian inheritance, accounting for 25% of the total variation with an additional 8% due to other familial effects. Consideration of body mass index (BMI) in the analytic model showed different results according to each race. Adjustment for BMI in whites significantly reduced the major gene effect; however, in African Americans, there remained an effect accounting for 19% of the total variation with an additional 8% of the variance owing to other familial effects. These results provide support for an underlying genetic basis for obstructive sleep apnea independent of the contribution of BMI to the disease in African Americans. The analyses in whites suggested that a major gene for obstructive sleep apnea might be closely related to genes for or effects of obesity ***(Badr and Strohi, 2004).***

Types of sleep-related breathing disorders:

The sleep-related breathing disorders have been categorized in various ways. The most basic schema divides them into obstructive or central apneic events. An American Academy of Sleep Medicine (AASM) Task Force Report published in 1999 defined four separate syndromes associated with abnormal respiratory events during sleep among adults, namely, obstructive sleep apnea-hypopnea syndrome (OSAHS), central sleep apnea-hypopnea syndrome, Cheyne-Stokes breathing syndrome, and sleep hypoventilation syndrome. In this classification, the upper airway resistance syndrome was not regarded as a distinct syndrome; instead, respiratory event-related arousals (RERAs) were considered part of the syndrome of OSAHS ***(American Academy of Sleep Medicine, 1999).***

1) Obstructive sleep apnea-hypopnea syndrome:

Obstructive sleep apnea can either coexist with three other syndrome (obesity hypoventilion syndrome, central sleep apnea and upper airway resistance syndrome or occur independently ***(Pack et al., 1998).*** Obstructive sleep apnea should be regarded as a continuum a spectrum of diseases from snoring to the obesity-hypoventilation syndrome ***(Schwab et al., 1998).***

Snoring:

Snoring should not be considered normal; it is often the first manifestation of SDB.

Upper-airway resistance syndrome:

Upper-airway resistance syndrome can cause symptoms similar to those of obstructive sleep apnea. This syndrome is characterized by repeated arousals secondary to increased upper-airway resistance (or crescendo snoring). At the end of the episode of crescendo snoring, arousal occurs with an abrupt decrease in upper-airway resistance, so that snoring disappears, albeit temporarily. In the upper-airway resistance syndrome, there are no apneas or significant decreases in oxyhemoglobin saturation. It is proposed that the arousals in the upper-airway resistance syndrome, analogous to arousals from apneas or hypopneas, result in sleep fragmentation and daytime sleepiness. The incidence and prevalence of the upper-airway resistance syndrome are unknown ***(Schwab et al., 1998).***

Obstructive sleep apnea hypopnea syndrome (OSAHS):

OSAHS is characterized by repetitive reduction or cessation of airflow during sleep caused by partial or complete upper airway occlusion in the presence of respiratory efforts. Mixed apnea, period of apnea caused by an absence of respiratory efforts precedes upper airway obstruction, is included in this syndrome. these events are typically accompanied by oxygen desaturation arousals, and sleep disruption ***(Philips et al., 1998).***

Apnea is characterized by a cessation of airflow for 10 seconds or longer. Although there is most universal consensus regarding the definition of apnea in adults, presence of hypopnea continues to be identified using various criteria, including (1) a 50% reduction in airflow accompanied by a 4% fall in oxygen saturation (SaO_2) or an arousal, (2) a 50% reduction in airflow accompanied by a fall in SaO_2, or (3) an reduction in airflow with or without oxygen desaturation or arousal ***(Philips et al., 1998).***

The criteria used for scoring hypopneas influence the diagnosis of OSAHS and the rating of its severity. Different scoring criteria for hypopneas may result in varying apnea-hypopnea indices. Interpretation of polyomnographic records ideally should include a description of the scoring method used to derive hypopneas. The sum of apneas and hypopneas divided by the total sleep time is commonly referred to as the apnea-hypopnea index. The respiratory disturbance index (RDI) is the sum of apneas, hypopneas, and RERAs divided by the total sleep time ***(Manser et al., 2001).***

Estimates of the severity of sleep-disordered breathing depend on the approach to measuring RDI. ***Redline et al. (2000)*** examined the relationships among RDIs defined by different definitions of apneas and hypopneas in 5046 participants in the Sleep Heart Health Study who

underwent overnight unattended 12-channel polysomnography. The correlation between RDIs based on various definitions ranged from 0.99 to 0.68, and the magnitude of the median RDI varied from 29.3 when it was based on events identified on the basis of flow or volume amplitude criteria alone to 2 for an RDI that required a 4% oxygen desaturation with events ***(Redline et al., 2000).***

It is generally not necessary to distinguish apnea from hypopneas in routine clinical care, and often the two respiratory events are scored and reported together. The diagnostic criteria for apneas and hypopneas recommended by the AASM Task Force include a reduction (> 50%) in the amplitude of breathing from baseline during sleep associated with either an oxygen desaturation (>3%) or an arousal plus an event duration of at least 10 seconds. RERAs, which do not fulfill the criteria for either apnea or hypopnea, consist of increasing respiratory efforts that last 10 seconds or longer and culminate in an arousal or a progressive more esophageal pressure preceding a change in esophageal pressure to a less negative level ***(AASM, 1999).***

The reference standard for measuring an obstructive apnea-hypopnea is a reduction in total oronasal airflow detected by a pneumotachometer placed in a well-fitted facemask. Other methods used to identify obstructive apnea-hypopneas include measurement of nasal pressure, respiratory inductance plethysmography (RIP), piezo sensors, strain gauges, thoracic impedance, thermal sensors, and expired carbon dioxide (CO_2). Whereas measurement techniques that identify apneas also are able to detect hypopneas, methods that measure hypopneas may not necessarily be adequate in identifying apneic events. The reference standard for identifying a RERA is the measurement of esophageal

pressure. RERAs also can be detected using measurements of nasal pressure and surface diaphragmatic electromyography ***(AASM, 1999).*** The demonstration of five or more obstructive apneas-hypopneas or RERAs per hour of sleep during an overnight study, plus excessive daytime sleepiness (that is not caused by other factors) or two or more of the following manifestations, including choking or gasping during sleep, recurrent awakenings from sleep, unrefreshing sleep, daytime fatigue, impaired concentration, establishes the diagnosis of OSAHS ***(AASM, 1999).***

2) Central sleep apnea-hypopnea syndrome:

This syndrome is characterized by repeptitive episodes of sleep-related apnea unaccompanied by upper airway obstruction. Each respiratory event consists of reduced airflow, 10 seconds or longer in duration, associated with a reduction in esophageal pressure excursions from baseline levels and often with oxygen desaturation and arousals. The diagnostic criteria for central sleep apnea-hypopnea syndrome consist of (1) excessive daytime sleepiness or frequent arousals / awakenings, and (2) at least five central apnea-hypopneas per hour of sleep during an overnight study, and (3) awake arterial carbon dioxide tension ($PaCO_2$) of less than 45 mmHg. Esophageal pressure monitoring is the reference standard measurement of central apnea-hypopneas. Other methods, such as RIP, surface diaphragmatic electromyography, thermal sensors, expired CO_2, piezo sensors and strain gauges, are relatively insensitive in identifying these events ***(AASM, 1999).***

3) Cheyne-Stokes breathing syndrome:

In this syndrome, cyclical waxing and waning of respiration develops, with central apnea or hypopnea alternating with hyperpnea. Transient arousals that occur at the crest of hyperpnea may lead to sleep fragmentation and excessive somnolence. The reference standards of measuring airflow and respiratory effort are pneumotachometry and esophageal pressure monitoring, respectively. Other techniques for detecting Cheyne-Stokes breathing include RIP, surface diaphragmatic electromyography, oronasal airflow monitoring, and oximetry. Cheyne-Stokes breathing syndrome is diagnosed based on the following criteria: (1) presence of congestive heart failure or cerebral neurologic disorders,

(2) three or more consecutive cycles of respiratory irregularity characterized by crescendo-decrescendo amplitude of breathing lasting at least 10 consecutive minutes, and (3) five or more central apnea-hypopneas per hour of sleep ***(AASM, 1999).***

4) Obesity hypoventilation syndrome:

Persons with obesity hypoventilation syndrome may have oxygen desaturation and hypercapnia during sleep unrelated to distinct periods of apnea-hypopnea. Periods of hypoventilation are more frequent and severe during rapid eye movement sleep than in non-rapid eye movement sleep. $PaCO_2$ monitoring is the reference standard measurement for identifying obesity hypoventilation. Continuous oximetry (demonstrating a decline in SaO_2 without accompanying respiratory events), transcutaneous carbon dioxide ($PtcCO_2$) monitoring, calibrated RIP (showing reduced tidal volume and minute ventilation), and end-tidal carbon dioxide ($PtcCO_2$) measurements also have been used to monitor sleep hypoventilation. The diagnosis of obesity hypoventilation syndrome is based on the presence of morbid obesity cor pulmonale, pulmonary hypertension, excessive somnolence not secondary to other factors, erythrocytosis or awake $PaCO_2$ of more than 45 mm Hg, and an increase in $PaCO_2$ during sleep by more than 10 mm Hg compared with levels during wakefulness or sleep-related oxygen desaturation not caused by apnea-hypopnea ***(AASM, 1999).***

Syndromes criteria and severity classification of SDB:

Sleep disordered breathing (SDB) is characterized by transient upper airway resistance, repetitive reduction or cessation of airflow caused by partial or complete occlusion of the upper airway during sleep, associated with fragmentation of sleep, arousals, bradytachycardia, and more or less oxygen desaturation, despite the presence of increasing respiratory effort. Apnea in adults is defined as the cessation of airflow for greater than or equal to 10 seconds. Various criteria have been utilized to define hypopnea, including (1) greater than 50% reduction in the amplitude of

breathing from baseline during sleep, or (2) less than 50% reduction in the amplitude of breathing during sleep associated with either greater than 3% oxygen desaturation or an arousal, or (3) greater than 30% reduction in the amplitude of breathing during sleep or 30% reduction in the nasal cannula-pressure transducer curve associated with oxygen desaturation greater than or equal to 4%, and (4) event duration greater than or equal to 10 seconds ***(Guilleminault and Chowdhuris, 2000).***

Respiratory event-related arousals consist of limitation of flow greater than or equal to 10 seconds and terminating in an arousal associated with snoring. Introduction of the nasal cannula-pressure transducer system and esophageal pressure (Pes) monitoring has led to recognition of various patterns of increased respiratory effort that disrupt sleep but are not apneas or hypopneas, such as Pes crescendo (a progressive increase in Pes) and sustained continuous effort (a persistent increase in Pes without any crescendo, over several epochs). These events terminate in Pes reversal (an abrupt drop in Pes) that occurs independently of the electroencephalogram pattern, which may be an alpha electroencephalogram arousal, a burst of delta activity, or no visually seen change in electroencephalogram pattern ***(Guilleminault and Chowdhuris, 2000).***

Although the authors believe that UARS clearly represents a syndrome distinct from OSA, in evaluating SDB the American Academy of Sleep Medicine Task Force in 1999 included UARS in the OSAHS and defined it as the demonstration of five or more obstructive apneas-hypopneas or respiratory event-related arousals per hour of sleep. This deficiency means that minutes of increased respiratory effort with unstable sleep are currently not tabulated in many clinical polysomnograms, and real impairment of subjects is underestimated, particularly in UARS subjects. OSA can be classified based on the apneas plus hypopneas per hour of sleep index (AHI) or respiratory

disturbance index ([RDI] apneas plus hypopneas plus respiratory event-related arousals per hour of sleep) into mild (5 < AHI or RDI < 15); moderate (15 < AHI or RDI < 30); or severe (AHI or RDI > 30) ***(Redline et al., 2000).***

OSA can also be classified by ***Gottlieb (1999)*** based on AHI into mild (5 – 19), moderate AHI (19 – 39) and severe AHI (≥ 40).

Predictors of sleep apnea hypopnea syndrome:

Berlin Questionnaire:

The Berlin Questionnaire was an outcome of the Conference on Sleep in Primary Care, which involved 120 U.S. and German pulmonary and primary care physicians and was held in April 1996 in Berlin, Germany. The conference also proposed a plan for risk grouping to simplify recognition of sleep apnea; this strategy was shown to be useful in sleep clinic and community surveys. Predetermination of high risk and lower risk for sleep apnea was based on responses in three symptom categories. In category 1, high risk was defined as persistent symptoms (>3 to 4 times/wk) in two or more questions about their snoring. In category 2, high risk was defined as persistent (>3 to 4 times/wk) waketime sleepiness, drowsy driving, or both. In category 3, high risk was defined as a history of high blood pressure or a body mass index more than 30 kg/m^2. To be considered at high risk for sleep apnea, a patient had to qualify for at least two symptom categories. Those who denied having persistent symptoms or who qualified for only one symptom category were placed in the lower risk group (Netzer et al., 1999).

1- Berlin Questionnaire:

1- Has your weight changed?

Increased/ Decreased/ No change

2-a Do you snore?

Yes/ No/ Do not know

2-b Snoring loudness

Loud as breathing/ Loud as talking/ Louder than talking/Very loud

2-c Snoring frequency

Almost every day/ 3-4 times per week/ 1-2 times per week/ 1-2 times per month/ Never or almost never

2-d Does your snoring bother other people?

Yes/ No

2-e How often have your breathing pauses been noticed?

Almost every day/ 3-4 times per week/ 1-2 times per week/ 1-2 times per month/ Never or almost never

3-a Are you tired after day time sleepiness?

Almost every day/ 3-4 times per week/ 1-2 times per week/ 1-2 times per month/ Never or almost never

3-b Are you tired during wake time?

Almost every day/ 3-4 times per week/ 1-2 times per week/ 1-2 times per month/ Never or almost never

3-c Have you ever fallen asleep while driving?

Yes/ No

4- Do you have high blood pressure?

Yes/ Not Do not know

(Netzer et al., 1999)

2- The Epworth Sleepiness Scale:

The Epworth Sleepiness Scale is one of the most widely used subjective methods to assess sleepiness. It is a short questionnaire that includes a list of 8 social circumstances with the likelihood that the

person will fall asleep, rated on a 4-point scale. Patients rate the likelihood of dozing on a 0 to 3 scale: 0 = "would never doze," 1 = "slight chance of dozing," 2= "moderate chance of dozing," and 3 "high chance of dozing." The scale assesses probability of sleeping rather than specific feelings or symptoms of sleepiness. It usually has been shown to correlate with other objective measures of sleepiness such as the multiple sleep latency test (MSLT), although the correlation is typically weak. The maximum score is 24, and scores greater than 12 are thought to signify excessive daytime sleepiness. Normal subjects usually score less than 10 ***(Stevens, 2004).***

Epworth Sleepiness Scale (Johns, 1991):

1. Sitting and reading
2. Watching TV
3. Sitting inactive in a public place (e.g.. theater or a meeting)
4. As a passenger in a car for an hour without a break
5. Lying down to rest in the afternoon when the circumstances permit
6. Sitting and talking to someone
7. Sitting quietly after a lunch without alcohol
8. In a car, while stopped for a minute in traffic

3- The Stanford Sleepiness Scale:

The Stanford Sleepiness Scale is another commonly used scale to assess sleepiness. It is a short questionnaire with several different responses used to describe the patient's current state of alertness rather than likelihood of dozing. The patient describes level of sleepiness on a 7-point scale according to his/her feelings and symptoms. This scale is limited in usefulness due to lack of reference values and validation of physiologic measures. On the other hand, it is probably more sensitive to

the acute effects of sleep deptivation than the Epworth Sleepiness Scale and can be used repeatedly during an experimental sleep deprivation experiment ***(Stevens, 2004).***

Stanford Sleepiness Scale:

- Feeling active and vital, alert; wide awake
- Functioning at a high level, but not at peak: able to concentrate
- Relaxed; awake; not at full alertness; responsive
- A little foggy; not at peak; let down
- Fogginess; beginning to lose interest in remaining awake; slowed down
- Sleepiness; prefer to be lying down; fighting sleep; woozy
- Almost in reverie; sleep onset soon; lost struggle to remain awake

(Glenville and Broughton, 1978)

Obstructive Sleep Apnea-Hypopnea Syndrome

Definition:

Obstructive sleep apnea (OSA) is a condition characterized by repetitive obstruction of the upper airway often resulting in oxygen desaturation and arousals from sleep. The daytime manifestations include excessive sleepiness, poor concentration, and fatigue, all of which contribute to low productivity and high risk for accidents. OSA also has far-reaching negative cardiovascular impact ***(Bassiri and Cruilleminatt, 2000).*** Many types of abnormal breathing during sleep have been described that are related to, but not accurately described as, apneas. The AASM task force defined obstructive sleep apnea-hypopnea syndrome (OSAHS) as recurrent episodes of partial (hypopnea) or complete (apnea) upper airway obstruction despite ongoing respiratory effort during sleep. This usually results in oxygen desaturation and may lead to gradual increase in $PaCO_2$. The events are often terminated by arousals that are detected and scored by EEG criteria. Episodes with an initial absence of respiratory effort followed by gradually increasing effort against an occluded airway are referred to as mixed apneas and are considered a part of OSAHS. Excessive daytime sleepiness is related to sleep disruption (recurrent arousals caused by apneas and hypopneas) and possibly also to recurrent hypoxemia ***(AASM, 1999).***

The same AASM task force defines an obstructive apnea-hypopnea event as (1) a clear decrease (> 50%) from baseline in the amplitude of a valid measure of breathing during sleep; (2) a clear amplitude reduction of a validated measure of breathing during sleep that does not reach the previous criterion but is associated with either an oxygen desaturation of greater than 3% or an arousal; and (3) the event lasts 10 seconds or

longer. Hypopnea has been further defined by the Sleep Heart Health Study as an abnormal respiratory event lasting at least 10 seconds with at least a 30% reduction in thoracoabdominal movement or airflow as compared with baseline, and with at least a 4% oxygen desaturation. Respiratory effort-related arousals are characterized by increasing respiratory effort leading to an arousal from sleep, but do not meet the criteria for an apnea or hypopnea. Respiratory effort-related arousals are associated with a pattern of progressively more negative esophageal pressure, terminated by its sudden increase and arousal. They last 10 seconds or longer and are a part of the upper airway resistance syndrome (Guilleminaulty et al., 1995). EEG arousal is an abrupt shift in EEG frequency, which may include θ, α, or frequencies greater than 16 Hz but not spindles, and lasting 3 seconds or longer ***(ASDA Atlas task force, 1992).***

Epidemiology

OSA can affect various age groups. The prevalence of adult OSA in the United States has been reported to be 4% in men and 2% in women between the ages of 30 and 60 years. The actual prevalence, however, may be higher. ***Young et al. (1997)*** estimated that among middle-aged adults, 93% of women and 82% of men with OSA have not been clinically diagnosed. The Wisconsin Sleep Cohort study evaluated the association of premenopause, perimenopause, and postmenopause with OSA in a group of 589 women. Using multivariate regression analysis adjusted for age, body habitus, smoking, and other potential confounding factors, ***(Young et al., 2003)*** calculated the odds ratios (95% CI) for apnea-hypopnea index (AHI) greater than five events per hour of sleep to be 1.2 (range 0.7 – 2.2) with perimenopause and 2.6 (range 1.4 – 4.8) with postmenopause. These results suggest that the menopausal transition is significantly associated with an increased risk of OSA independent of known confounding factors ***(Young et al., 2003).*** After menopause, women develop OSA at a rate similar to men ***(Tishler et al., 2003).*** The maximum prevalence of OSA occurs between the fifth and seventh decades. Obesity increases the risk of developing OSA, and race may be a risk factor ***(Redline et al., 1997).***

Risk factors for obstructive sleep apnea:

1) Genetic:

Substantial work has been completed identifying the genetic, environmental, and physiologic risk factors associated with OSA. Collectively, genetic studies suggest a strong familial component in OSA. The factors explaining this aggregation are likely combinations of genetic influences on the size of the upper airway (anatomy), pharyngeal mechanics and activation of upper airway dilator muscles, stability of ventilatory control, and as yet unidentified physiologic mechanisms ***(peppard,et al2000)***

2) Obesity:

The strongest risk factor for the development of OSA is obesity; several cross-sectional studies have identified the body mass index (BMI) and waist-to-hip ratio as independent risk factors for the development of apnea. The strongest incidence data for an association of apnea and obesity come from the Wisconsin Sleep Cohort, in which Peppard and colleagues demonstrated that a 10% increase in weight predicted a six-fold increase in the odds for the development of sleep-disordered breathing. Their model also predicted a 32% higher apnea-hypopnea index in obese persons than in their nonobese counterparts. In addition, a 10% decrease in weight during an 11-year follow-up led to a significant reduction in the apnea-hypopnea index, suggesting that weight loss does improve outcome in this disorder ***(Pepaard et al., 2000).***

OSA is common in morbidly obese patients, although obesity related hypoventilation syndromes are also frequently encountered in these subjects. ***Reata (2001)*** estimated that 50% of morbidly obese patients (BMI > 40) have an apnea-hypopnea index of at least 10 events per hour of sleep. Severe OSA, defined as more than 30 events of obstructed breathing per hour, was seen in 25% of this cohort. In addition, several studies have demonstrated a good correlation between the degree of obesity (BMI or upper body obesity) and the severity of OSA. However, many obese patients do not experience sleep-disordered breathing. Thus, despite evidence that obesity is a major risk factor, the

caused link between obesity and OSA remains poorly defined ***(Reata, 2001).***

3) Aging:

The prevalence of OSA increases with age. OSA affects approximately 4% of male Americans and 2% of female Americans. However, at each level of apnea severity, the prevalence of OSA is higher in older subjects ***(Young et al., 1993).***

The importance of OSA as a cause of morbidity and mortality in the elderly has been questioned. ***Lavie et al. (1995)*** reported a increased relative risk for dying of OSA (0.33) in elderly persons (older than 70 years of age) in comparison with the risk for death in a younger population with OSA. However, an increased mortality in nursing home residents and elderly, institutionalized patients with Alzheimer disease and concomitant OSA were noted. It remains unclear whether treatment of this population with continuous positive airway pressure (CPAP) substantially improves cognitive outcomes or decreases mortality ***(Lavie et al., 1995).***

4) Gender:

Despite consistent evidence that sleep apnea is more common in men than in women, the explanation for these gender-related differences in the prevalence of OSA remains unclear. However, regardless of the mechanism, men and postmenopausal women should be considered at higher risk for the development of sleep apnea ***(Lavie et al., 1995).***

5) Exogenous Influences:

Other variables, such as alcohol and nicotine intake, are modifiable clinical risk factors that influence the prevalence of sleep-disordered breathing. Large doses of ethanol were shown to increase the frequency of apnea and the duration and severity of oxygen desaturation. An increase in the apnea-hypopnea index was also observed when ethanol was given in smaller doses to normal subjects without sleep disordered breathing. Nicotine has been associated with an increased risk for sleep-

disordered breathing. As part of the Wisconsin Sleep Cohort questionnaire, subjects were asked about their smoking habits. Heavy current smoking (> 40 cigarettes per day) put subjects at the greatest risk for sleep-disordered breathing (odds ratio of 40.47 in comparison with nonsmokers). However, former smoking was not found to be a substantial risk factor for snoring or sleep-disordered breathing after control for confounders. Based on these studies, physicians should encourage smoking cessation and avoidance of ethanol during the evening hours ***(Wetter et al., 1999).***

Pathogenesis:

Narrowing or closure may occur at one or more sites in an unstable upper airway (i.e., in the velopharynx, oropharynx, or hypopharynx). Upper-airway dysfunction and the specific sites of narrowing or closure are influenced by the underlying neuromuscular tone, upper-airway muscle synchrony, and the stage of sleep ***(Mathur and Douglas, 1995).*** These events are generally most prominent during rapid-eye-movement (REM) sleep because of the hypotonia of the upper-airway muscles characteristic of this stage of sleep ***(Bonsignore et al., 1994).***

Upper-airway size is determined by soft-tissue and skeletal factors that are also the major determinants of upper-airway patency during sleep. In obese patients; increased adipose tissue in the neck may predispose the airway to narrowing. Magnetic resonance imaging has documented fatty infiltration into the pharyngeal tissue of patients with sleep apnea. Patients of normal body weight in whom sleep apnea develops may have tonsillar hypertrophy or craniofacial skeletal abnormalities that also predispose the airway to narrowing or closure during sleep. These craniofacial abnormalities may be evident on a cephalometric radiograph, although not readily apparent on physical examination ***(Mathur and Douglas, 1995).***

Genetic and environmental factors may also adversely affect airway size. Sleep apnea has been identified as common to some families. The increased incidence of sleep apnea in these families is not explained by obesity alone. Genetically determined craniofacial features or abnormalities of ventilatory control may account for this pattern of familial apnea ***(Mathur and Douglas, 1995).***

If the soft palate is exposed to recurrent vibratory trauma (snoring) and high negative inspiratory pressure, the result can be lengthening of the soft palate due to stretching and thickening caused by edema ***(Mathur and Douglas, 1995).*** It is possible that the changes in the soft palate of patients with sleep apnea may thus be a consequence of breathing against increased upper-airway resistance rather than the cause of that increased resistance ***(Mathur and Douglas, 1995).***

Clinical predictors of the severity of apnea:

History and Physical Examination Findings:

In assessing the clinical probability of sleep apnea, the physician should be aware of relevant symptoms and airway examination findings that are associated with an increased likelihood of sleep-disordered breathing. Since the description by Guilleminault and colleagues, sleep apnea has been associated with snoring, witnessed apneas, choking, restless sleep, morning headaches, excessive daytime somnolence, and occasionally impotence ***(Johns et al., 1991).***

Tools for the subjective assessment of sleep such as the Epworth Sleepiness Scale and the Stanford Sleepiness Scale, were developed as psychometric aids for quantifying subjective symptoms of sleepiness or alertness. The Epworth Scale, which is the most commonly used in-

strument, rates sleepiness behaviorally and has been validated clinically. People are asked to rate their ability to fall asleep (i.e., in a car, in church, while talking to someone, while watching television). Overall, the Epworth Scale is helpful in subjectively quantifying how sleepy a person feels during a 30-day period. However, it does not accurately predict objective sleepiness as measured by the multiple sleep latency test, nor does it accurately predict the severity of sleep apnea ***(Hoffstein and Szalai, 1993).***

Many clinical prediction rules have been developed to assess the probability of OSA based on combinations of the risk factors and clinical variables previously noted. In a study of 594 persons, the patients with OSA had more subjective complaints of snoring, nocturnal choking, excessive daytime sleepiness, and impotence than the controls without apnea. However, these subjective findings do not correlate well with the severity of sleep-disordered breathing as assessed by overnight polysomnography. Entering both subjective complaints and objective measures such as the BMI, age, and blood pressure into regression models explains more of the variance (46%, $P < .05$) in the apnea-hypopnea index than any single factor, suggesting that the clinical impression alone is not sufficient to predict the severity of apnea reliably. In a study from Oxford of 1,001 patients, the apnea-hypopnea index correlated best with neck size, BMI, age, and ethanol consumption in a regression model ***(Stradling et al., 1991).***

A report by Flewons and colleagues included both clinician prior predictions of OSA and the clinical variables previously described to develop a clinical scoring system for sleep apnea. They reported that a large neck circumference, hypertension, habitual snoring, and bed partner

reports of gasping and choking were the most significant predictors of severe apnea-hypopnea (OR = 0.34). Notably missing from the predictors of severe apnea-hypopnea were daytime sleepiness and cognitive deficits, such as an inability to concentrate, neither of which was found to correlate well with severe sleep-disordered breathing ***(Flemons et al., 1999).***

Anatomic Assessment

A number of anatomic risk factors are important in the development of sleep-disordered breathing; some of these can be assessed by physical examination, whereas others require either cephalometric techniques (i.e., lateral x-ray films) or magnetic resonance imaging. A crowded pharynx with a low-lying uvula and soft palate is a frequent finding in patients with OSA. Macroglossia and retrognathism are also common. Occasionally, large tonsils are noted. In one report, large tonsils and lateral narrowing of the pharyngeal airway were the most important physical findings that predicted sleep-disordered breathing ***(Schellenberg et al., 2000).***

A neck circumference larger than 17.2 inches (43.7 cm) in a male patient also increases the odds of OSA substantially, probably as a consequence of increased amounts of neck fat and large lateral pharyngeal fat pads. The analysis of cephalometric radiographs has been used by several groups to identify subjects at risk for OSA and to predict successful upper airway surgery. Ccphalometry is widely available, easily performed, and a less expensive way to study the upper airway than computed tomography or magnetic resonance imaging. However, specific, standardized radiographic equipment and techniques and interpretive skills are required. Collectively, these data suggest that a diagnosis of OSA should be considered in a patient who on cephalometry has enlarged tonsils, a large tongue, a narrow crowded airway, or retrognathism (defined by specific soft tissue and bony structures).

Cephalometric x-rays may thus confirm the findings but are generally not helpful as a screening tool for OSA ***(Woodson et al., 1997).***

Polysomnography and Other tests:

Overnight pulse oximetry has occasionally been used as a screening test to identify patients with sleep apnea, but it is not a substitute for polysomnography because of its inability to detect UARS and arousal but unassociated with significant desaturation ***(Lee-Choiong, 2002).*** Full-night polysomnography is routinely indicated for patients suspected of having OSA syndrome. Esophageal pressure (pes) monitoring during polysomnography recording is the reference standard in detecting respiratory effort. Pulse transit time measures the transmission time for the arterial pulse pressure wave to travel from the aortic valve to the periphery and increases during inspiratory falls in blood pressure and decreases during arousal-induced increases in blood pressure. Pulse transit time has a high sensitivity and specificity in distinguishing between central and obstructive apnea-hypopnea and may be used if Pes monitoring is not available. Polysomnography monitoring in adult OSA demonstrates greater than five obstructive apneas per hour of sleep, lasting at least 10 seconds and associated with one or more of the following: (1) frequent arousals from sleep; (2) bradytachycardia; and (3) arterial oxygen desaturation ***(Lee-Choiong, 2002).***

In some circumstances, split-night full-night polysomnography may be considered. During split-night full-night polysomnography recordings, the first half of the night is spent in diagnostic recording, with the second half of the night used for CPAP titration. In a consensus statement, formulated these guidelines: split-night studies may be considered in patients with RDI greater than 40 events per hour during the first 2 hours of a diagnostic polysomnography, of which the final portion is used to titrate CPAP. Patients with RDI between 20 and 40 per hour may undergo a split-night study based on the occurrence of obstructive respiratory events of prolonged duration or associated with severe O_2 desaturation a minimum of 3 hours of sleep is recommended for adequate titration; the split-night study requires the recording and analysis of the same parameters as a standard diagnostic full-night polysomnography; and an additional full-night CPAP titration may be required if the split-night study does not allow for abolishment of most obstructive events or if the prescribed CPAP treatment does not control clinical symptoms.

Split-night studies can potentially underestimate the severity of OSA, however, because breathing abnormalities are usually worse during REM sleep in overweight patients, and the longest REM sleep periods are in the second half of the night. In addition, CPAP titration during split-night recordings may be suboptimal because of the shorter time spent on titration ***(Loube et al., 1999).***

Limited-channel diagnostic full-night polysomnography (cardiorespiratory sleep studies) may be adequate in patients who have a high pretest probability of OSA based on validated screening algorithms. Minimum parameters recorded and measured in limited-channel full-night polysomnography are oronasal airflow, chest wall respiratory effort, electrocardiogram, and oxyhemoglobin saturation ***(Loube et al., 1999).*** These limited sleep studies, however, cannot effectively distinguish sleep from wake or determine sleep stage, are less accurate than standard full-night polysomnography in determining the number of obstructive respiratory events, and are unable to detect co-existing non-OSA sleep disorders. They cannot recognize UARS. They recognize subjects with severe problems. Multiple sleep latency testing, which consists of four to five daytime naps during which sleep latency is measured, provides an objective measure of sleepiness and propensity to sleep. OSA patients may or may not demonstrate a mean sleep latency of less than 10 minutes (normal > 10 minutes). Maintenance of Wakefulness Test is preferred by some to evaluate the propensity of subjects to stay alert ***(Loube et al., 1999).***

Comorbid Conditions Associated with Obstructive Sleep Apnea

1. Bronchial Asthma

Nocturnal worsening of symptoms and sleep disturbance are significant problems for patients with asthma. In one study, up to 40% of asthmatics experienced symptoms every night. The normal circadian variation in airway function, with the highest airflow in the late afternoon (4:00 PM) and the lowest in the early morning (4:00 AM), is exaggerated in patients with obstructive airway diseases. In patients with nocturnal asthma the forced expiratory volume in first second or peak flow can fall as much as 20% to 40% in the morning hours (morning dippers). The etiology of this variation is multifactorial and includes circadian changes in the amounts of circulating steroids and epinephrine, cholinergic tone, and possibly inflammatory mediators in the lungs. Sleep also seems to have an adverse effect on asthma, independent of other factors. The easiest way to diagnose severe nocturnal worsening of asthma is to have the patient record peak flow measurements at bedtime and on awakening ***(Martin, 1993).***

Treatment of patients with nocturnal asthma should begin with inhaled corticosteroids ***(Weersink et al., 1997).*** This medication has been shown to reduce the circadian fluctuation in airway tone. Patients with continued nocturnal symptoms despite an adequate dose of inhaled corticosteroids can then be treated with a long-acting bronchodilator. Theophylline has been proved effective despite the stimulatory effects of the medication. In dosing theophylline, the goal should be to obtain the highest levels during the time of greatest airflow obstruction (at night and early morning). Long-acting inhaled beta 2 agonists (salmeterol and formoterol) are also useful for control of symptoms in nocturnal asthma and potentially might cause less sleep disruption than theophylline. ***Selby et al. (1997),*** however, found only a slight advantage for salmeterol compared with theophylline in sleep quality (fewer arousals). The falls in morning flow rates were similar but awakenings were less frequent on salmeterol. ***Weigand et al. (1999)*** found salmeterol to be more effective

than theophylline at preventing the morning drop in flow rates. The drugs did not differ in polysomnographic findings but patients perceived better sleep with salmeterol than theophylline. If OSA is also present, nocturnal asthma may improve with effective treatment ***(Weersink et al., 1997).***

2. Chronic obstructive pulmonary disease:
Patients with COPD often have multiple sleep complaints, such as insomnia (difficulty initiating or maintaining sleep) and frequent awakenings with shortness of breath or cough. The sleep of patients with COPD is poor, with low total sleep times, and reduced amounts of slow wave and REM sleep. Airflow obstruction typically worsens in the early morning hours similar to asthmatics ***(Douglas and Flenley, 1990).*** Those with moderate to severe COPD may also exhibit significant falls in the oxygen saturation during sleep. COPD patients with an awake PaO_2 of 50 to 60 mm Hg have desaturation during sleep as even normal persons have a fall in PaO_2 of 8 to 10 mm Hg during non-REM (NREM) sleep. The most severe desaturations occur during REM sleep, where there is skeletal muscle hypotonia and periods of hypoventilation characterized by irregular breathing, reduced respiratory effort, and small tidal volumes ***(Fletcher et al., 1983).*** Of note, REM-associated nonapneic hypoventilation may result in severe hypoxemia even if the daytime PaO_2 is greater than or equal to 60 mmHg. NREM and REM sleep normally occupy about 80% and 20% of the total sleep time, respectively.
In general, patients with lower SaO_2 and higher $PaCO_2$ are more likely to have significant nocturnal desaturation; however, there is considerable individual variation ***(Hudgel et al., 1983).***

Low-flow oxygen by nasal cannula can prevent the typical, nonapneic arterial oxygen desaturation manifested by patients with COPD, without substantially increasing the nocturnal $PaCO_2$ ***(Goldstein et al., 1984).*** The benefits of chronic 24-hour oxygen therapy in patients with COPD have been well documented by the ***Nocturnal Oxygen Treatment Trial (1980)*** and other studies of patients meeting the standard criteria of a daytime PaO_2 less than 55 mm Hg breathing room air. The value of 55 mm Hg was chosen because below this point pulmonary arterial pressure starts to increase significantly secondary to hypoxic vasoconstriction. In the Nocturnal Oxygen Treatment Trial study, patients also received oxygen if the PaO_2 was 55 to 59 mm Hg and evidence of end organ damage was present (pedal edema, hematocrit > 55%, or P pulmonale on EKG). Today most physicians consider evidence of significant cor

pulmonale or neurologic dysfunction an indication for oxygen treatment in this group with borderline oxygenation. The indication for nocturnal oxygen in patients with a daytime PaO_2 greater than or equal to 60 mm Hg but with nocturnal arterial oxygen desaturation is not established ***(Chaouat et al., 2001).*** Brief periods of mild REM hypoxemia probably should not be treated. One could make a case for nocturnal oxygen if there is severe REM-associated desaturation or prolonged desaturation to less than 85% during NREM sleep. Of note, patients with the overlap syndrome (sleep apnea plus COPD) are best treated with positive airway pressure (CPAP or bilevel positive airway pressure) with the addition of supplemental oxygen if needed. Giving such patients oxygen alone may increase apnea duration, incompletely reverse desaturation, and may result in large increases in nocturnal $PaCO_2$ ***(Goldstein et al., 1984).***

Treatment of nocturnal symptoms in patients with COPD includes theophylline and long-acting beta agonists. Sustained-action theophylline improves morning pulmonary function compared with short-acting beta agonists without negatively impacting sleep. Theophylline and long-acting beta agonists have not been compared in COPD subjects. In asthma, however, some studies showed a possible slight advantage for long-acting beta agonists. Ipratropium bromide at bedtime has also been shown to be useful in COPD and the only problem with this medication is the relatively short duration of action. Many COPD patients complain of insomnia despite bronchodilator treatment. Studies have found that benzodiazepine receptor agonists are generally safe. COPD patients with hypoventilation or those with coexistent sleep apnea, however, should not be prescribed hypnotics ***(Girault et al., 1996).***

3. Hypertension

OSA is an independent risk factor for hypertension, and hypertension is a frequent comorbid condition with sleep apnea ***(Dart et al., 2003).*** About 30% of patients with systemic hypertension have sleep apnea, whereas 50% or more of patients with sleep apnea have systemic hypertension ***(Somers and Fletcher, 2002). Moller et al. (2003)*** performed 24-hour blood pressure monitoring and measured plasma levels of vasoactive hormones (renin, angiotensin II, aldosterone, atrial natriuretic peptide, brain natriuretic peptide, vasopressin, and endothelin-1) in 24 OSA patients and 18 control subjects. Compared with controls, OSA patients had significantly higher blood pressure and heart rate, and the sleep-related nocturnal blood pressure drop was reduced. Moreover, angiotensin II and aldosterone levels were significantly higher in OSA subjects compared with controls, with angiotensin II correlating

positively with daytime blood pressure recordings. Thirteen OSA patients re-examined after 14 months of CPAP therapy demonstrated reduction in blood pressure, which correlated with a decrease in both plasma renin and plasma angiotensin II concentrations ***(Moller et al., 2003).***

Hypertension associated with OSA may be generated by sympathetic overactivity triggered by intermittent hypoxemia, large negative fluctuations in intrathoracic pressure, and arousal from sleep. Several studies have demonstrated reversal of sustained daytime hypertension by effective treatment of apnea through surgery or nasal CPAP ***(Logan et al., 2003).***

4. Cardiovascular disease:

The Sleep Heart Health Study reported that OSA is associated with relative odds of 2.38 for heart failure, independent of other known risk factors ***(Javaheri, 2003).*** OSA has also been implicated in the pathogenesis of pulmonary hypertension, nocturnal cardiac ischemia, nocturnal arrhythmias, and atherosclerosis ***(Somers and Fletcher, 2002).*** OSA patients demonstrate transient fluctuations in pulmonary artery pressure and pulmonary wedge pressure coincident with apneas, which may lead to progressive increase in pulmonary artery pressure. Permanent precapillary pulmonary hypertension at rest has been observed in some OSA patients and is reported to be poorly reversible after OSA treatment. Various studies have demonstrated that OSA can precipitate nocturnal angina in patients with coronary artery disease. Myocardial ischemia associated with OSA is postulated to result from a combination of increased left ventricular afterload, sympathoadrenal stimulation, and postapneic tachycardia. In a study of 400 OSA patients conducted by ***Bassiri and Guilleminault (2000),*** cardiac arrhythmias consisting of nonsustained ventricular tachycardia (N = 8), sinus arrest lasting 2.5 to 3 seconds (N = 43), second-degree atrioventricular conduction block (N = 31), and premature ventricular contractions (N = 75) were noted in 193 (48%) of subjects. A relationship between low SaO_2 (<75%) and presence of severe arrhythmias was shown. A prospective study of 147 consecutive patients demonstrated significantly higher prevalence of nocturnal paroxysmal asystole in OSA patients and increased episodes of bradycardia and pauses that correlated with the severity of the sleep apnea. OSA has been linked to other risk markers for cardiovascular

disease, including leptin, C-reactive protein, homocysteine, and insulin-resistance syndrome. The independent role of OSA in these overweight and obese subjects is unclear ***(Phillips and Somers, 2002).***

5. Cerebro vascular disease:

The relationship between OSAS and cerebrovascular disease is bidirectional. Habitual snoring increases the risk of cerebrovascular disease with odds ratios ranging from 2.1 to 3.3 (95% CI) ***(Bassetti and Chervin, 2000).*** Sixty percent to 95% of patients with acute strokes or transient ischemic attacks has OSA ***(Dyken et al., 1996).*** One hundred fourteen male snorers, 40 to 65 years of age, with complaints of disturbed sleep underwent ultasonographic examination of both carotid arteries to evaluate intima-media thickness and the presence of plaque. The study revealed significantly higher intima-media thickness values in OSA patients compared with habitual snorers. Age and BMI were significantly associated with intima-media thickness, whereas age and BMI were most predictive for plaque. ***Kaynak et al. (2003)*** suggested that SDB may be a predisposing factor for atherosclerosis and may precipitate plaque formation. Proposed mechanisms underlying increased risk of stroke in OSA patients are multifactorial and include hypertension, reduction in cerebral blood flow, altered cerebral autoregulation, impaired endothelial function, accelerated atherogenesis, thrombosis, and paradoxic embolism ***(Yaggi and Mohsenin, 2003).***

6. Obesity-metabolic syndrome:

Approximately 60% to 90% of OSA patients are obese ***(Benumof, 2002).*** Obesity is the most common metabolic abnormality seen with sleep apnea and is predominantly central in pattern. BMI, body weight, and the sum of fat skin folds are good predictors for the degree of OSA. The percentage of body fat and BMI are good predictors of AHI greater than 10, with high sensitivity (95.5%) but low specificity (46.2%) ***(Schafer et al., 2002).*** A review of MRI scans demonstrated a significant correlation between AHI and intra-abdominal and subcutaneous abdominal fat, but no correlation was established with subcutaneous fat in the neck region or parapharyngeal fat in the airway vicinity. Leptin concentrations correlate with AHI and with biochemical markers of the metabolic syndrome (lipoproteins, glucose). ***Vgontzas et al. (2003)*** have demonstrated elevations of interleukin-6, tumor necrosis factor-alpha, leptin, and insulin levels in sleep apnea, independent of obesity. Upper body obesity is linked to increased risk of diabetes, hyperlipidemia, insulin resistance and hyperinsulinemia, hyperuricemia, hypertension, and cardiovascular or cerebrovascular disease ***(Grunstein, 2002).*** OSA has been implicated

as an independent risk factor for insulin resistance, a known_risk factor for atherogenesis, but this independence has been challenged by other data ***(Ip et al., 2002).***

7. Gastroesophageal reflux and obstructive sleep apnea:

Given the negative intrathoracic pressure during obstructive apnea and the frequent arousals from sleep, one would suspect that nocturnal GER is common in patients with OSA. ***Green et al. (2003)*** prospectively examined 331 OSA patients. Significant nighttime GER was found in 62% of subjects before OSA treatment. Patients compliant with CPAP had a 48% improvement in their nocturnal GER symptoms. There was no change in nighttime reflux symptoms if patients did not use CPAP. Furthermore, there was a strong correlation between higher CPAP pressures and improvement in nocturnal GER symptom scores. This study shows that nocturnal reflux is common in OSA patients and that nasal CPAP decreases the frequency of nocturnal GER symptoms. Of note, the fact that nocturnal GER is common in OSA patients and that CPAP reduces GER does not necessarily prove that OSA causes GER. In some studies episodes of GER were not correlated with apneic events. CPAP by increasing the pressure gradient between the thorax and the stomach may also reduce GER independent of the effects of CPAP on OSA ***(Graf et al., 1995).***

8. Sleep in endocrine disorders:

Hypothyroidism has been associated with sleep apnea. There are no large cohort studies evaluating the prevalence of sleep apnea in hypothyroid subjects. Obesity may be a significant confounding factor. ***Pelttari et al. (1994)*** examined 26 patients with hypothyroidism and 188 euthyroid control subjects finding that 50% of hypothyroid patients and 29% of control subjects had significant respiratory events ***(Winkelman et al., 1996).*** Postmenopausal women with OSA (who are at higher risk for hypothyroidism) or OSA patients without predisposing OSA risk factors, might warrant thyroid studies. There are case reports showing resolution of OSA after attaining normal thyroid function; however, it takes an extended period of time. Hypothyroid sleep apnea should be treated as usual (nasal CPAP), while the euthyroid state is being restored, and until a repeat sleep study off treatment shows the absence of OSA. Hypothyroidism has differing effects on sleep in patients without OSA, including complaints of excessive daytime sleepiness and a reduction in delta sleep percentage. Hyperthyroidism has been associated with insomnia. There are conflicting data concerning hyperthyroidism's effect on sleep architecture ***(Winkelman et al., 1996).***

Growth hormone excess resulting in acromegaly is also associated with sleep apnea. ***Grunstein et al. (1991)*** noted that 60% of unselected acromegaly patients have sleep apnea. Potential pathophysiologic mechanisms of this association include macroglossia and increased muscle mass of the upper airway. Because OSA is also noted in acromegalic patients, alterations in central ventilatory control may also play a role ***(Grunstein et al., 1991).*** Acromegalic patients without OSA may also have excessive daytime sleepiness with an increase in REM sleep ***(Astrom et al., 1991).*** There are limited data examining sleep characteristics with growth hormone deficiency. One study showed a reduction in delta sleep, although more research is needed to make any conclusions ***(Winkelman et al., 1996).***

Adrenocorticosteroid excess, as seen in Cushing's disease, is associated with sleep apnea in approximately 30% of patients. Other investigations have shown shortened REM latencies and poor sleep efficiencies, although more data are needed to draw further conclusions ***(Shipley et al., 1992).***

Studies have suggested that patients with OSA have impaired glucose tolerance, but unfortunately obesity is a major confounding factor. Some studies have suggested that OSA impairs glucose tolerance independent of the associated obesity. A large cohort study, however, did not document that SDB was an independent risk factor for diabetes. Diabetic patients did seem to have more central apnea or periodic breathing. OSA patients with smaller degrees of obesity had a more clear-cut impairment of glucose control secondary to SDB. The impaired glucose control in OSA patients that is independent of obesity is thought secondary to increased sympathetic activity. ***Harsch et al. (2004)*** found

that CPAP treatment rapidly improves insulin sensitivity in OSA patients. The improvement was greater in patients with lower body mass. Significant improvement in glucose control with long-term CPAP has yet to be demonstrated ***(Harsch et al., 2004).***

Mild to moderate chronic sleep deprivation is a chronic behavior in many industrialized societies. ***Spiegel et al. (1999)*** found sleep restriction to 4 hours of sleep at night impaired glucose tolerance, increased the evening cortisol, and increased sympathetic activation in normal subjects. The authors hypothesized that sleep debt may increase the severity of age-related chronic disorders ***(Spiegel et al., 1999).***

Chronic Obstructive Pulmonary Disease (COPD)

Definition:

Several different definitions exist for COPD. ***American Thoracic Society (1995)*** has defined COPD as "a disease state characterized by the presence of airflow limitation due to chronic bronchitis or emphysema, the airflow obstruction is generally progressive, may be accompanied by airway hyperreactivity, and may be partially reversible ***(American Thoracic Society, 1995).***

European Respiratory Society (ERS) defined COPD as "reduced maximum expiratory flow and slow forced emptying of the lungs, which is slowly progressive and mostly irreversible to present medical treatment ***(Siafakas et al., 1995).***

Global Initiative for Chronic Obstructive Lung Disease (GOLD, 2003) classified COPD as a disease state characterized by airflow limitation that is not fully reversible. The airflow limitation is usually both progressive and associated with an abnormal inflammatory response of the lungs to noxious particles or gases. For these three different definitions, however, the precise classification of airflow limitation, reversibility, and severity of disease varies. In addition, the definitions and diagnoses of chronic bronchitis, and emphysema also can vary ***(Mannino, 2002).***

Chronic Bronchitis:

Chronic bronchitis is the presence of a chronic productive cough for at least 3 months in each of at least 2 successive years, provided other causes of chronic cough have been ruled out ***(David, 2005).***

Emphysema:

Emphysema, defined in anatomical terms, is the destruction of alveolar walls and permanent enlargement of the airspaces distal to the terminal bronchioles ***(American Thoracic Society, 1995).*** The ensuing loss of lung elastic recoil and intraluminal pressure in the terminal airways causes small airways to lose their patency, especially during forced expiratory maneuvers. Clinically, the patient experiences progressive dyspnea. It is not clear how most clinicians diagnose emphysema. Imaging technology has improved dramatically in recent years and may provide new opportunities to accurately classify the presence of emphysema ***(National Emphysema Treatment Trial Research Group, 2002).***

Epidemiology of COPD:

Most of the information available on COPD prevalence, morbidity, and mortality comes from developed countries. Even in these countries, accurate epidemiologic data on COPD are difficult and expensive to collect. Prevalence and morbidity data greatly underestimate the total burden of COPD because the disease is usually not diagnosed until it is clinically apparent and moderately advanced. The prevalence of COPD is highest in countries where cigarette smoking has been, or still is, very common, whereas the prevalence is lowest in countries where smoking is less common, or total tobacco consumption per individual is low. ***(Pauwels et al., 2001).***

In the past, most studies showed that COPD prevalence and mortality were greater among men than women. More recent studies from developed countries show that the prevalence of the disease is almost equal in men and women, which probably reflects changing patterns of

tobacco smoking. Some studies have in fact suggested that women are more susceptible to the effects of tobacco smoke than men. ***(GOLD, 2003).***

Diagnosis of COPD:

Clinical Features Of COPD:

History:

Patients with COPD have usually been smoking at least 20 cigarettes per day for 20 or more years before symptoms develop. They commonly present in the fifth decade with productive cough or an acute chest illness. Dyspnea on effort usually does not occur until the sixth or seventh decade. Sputum production is insidious, initially occurring only in the morning, the daily volume rarely exceeds 60 ml. Sputum is usually mucoid but becomes purulent with an exacerbation. Acute chest illnesses characterized by increased cough, purulent sputum, wheezing, dyspnea, and occasionally fever may occur intermittently***(Wright et al., 1992).***

The history of wheezing and dyspnea may lead to an erroneous diagnosis of asthma. With disease progression, the intervals between acute exacerbations grow shorter. Late in the course of the disease, an exacerbation may give rise to hypoxemia with cyanosis, the latter accentuated by erythrocytosis. Morning headache suggests hypercapnia, hypercapnia, with more severe hypoxemia, is often present in end-stage disease. Weight loss occurs in some patients. Cor pulmonale with right heart failure and edema may develop in patients with hypoxemia and hypercapnia. Since bronchogenic carcinoma occurs with increased frequency in smokers with COPD, an episode of hemoptysis raises the possibility that carcinoma has developed. Most episodes of hemoptysis,

however, are due to mucosal erosion and not to carcinoma ***(American Thoracic Society, 1995).***

Physical Examination:

Early on examination of the chest may reveal only slowed expiration and wheezing on forced expiration. As obstruction progresses, hyperinflation becomes evident, and the anteroposterior diameter of the chest increases. The diaphragm becomes limited in its motion. Breath sounds are decreased, expiration is prolonged, and heart sounds often become distant. Coarse crackles may be heard at the lung bases. Wheezes are frequently heard, especially on forced expiration ***(Reynolds, 1991).***

Patients with end-stage COPD may adopt positions that relieve dyspnea, such as leaning forward with arms outstretched and weight supported on the palms. The accessory respiratory muscles of the neck and shoulder girdle are in full use. Expiration often takes place through pursed lips. Paradoxical indrawing of the lower interspaces is often evident. Cyanosis may be present. An enlarged, tender liver indicates heart failure, neck vein distention, especially during expiration, may be observed in the absence of heart failure, due to increased intrathoracic pressure. Asterixis may be seen with severe hypercapnia ***(American Thoracic Society, 1995).***

Diagnostic Studies:

Chest Radiography:

Because emphysema is defined in anatomical terms, radiographic images of the lungs provide the clearest evidence of its presence. In frontal and lateral chest radiographs, distention of the lungs is indicated

by a low, flat diaphragm, an increased retrosternal airspace, and a long, narrow heart shadow. Rapid tapering of the vascular shadows, accompanied by hypertransradiancy of the lungs, is a sign of emphysema, bullae, presenting as radiolucent areas larger than 1 cm in diameter and surrounded by arcuate hairline shadows, are proof of its presence. Bullae, however, reflect only locally severe disease and are not necessarily indicative of widespread emphysema. With complicating pulmonary hypertension and right ventricular hypertrophy, the hilar vascular shadows are prominent, and the heart shadow encroaches on the retrosternal space as the right ventricle enlarges anteriorly. The enlargement may become evident only on comparison with previous chest radiographs. Studies correlating lung structure and the chest radiograph show that emphysema is consistently diagnosed when the disease is severe, is not diagnosed when the disease is mild, and is diagnosed in about half the instances of moderate disease ***(Sanders, 1991).***

Computed Tomography:

Computed tomography (CT), especially high resolution CT (collimation of l-2 mm), has much greater sensitivity and specificity than standard chest radiography. It may even identify the specific anatomic type of emphysema. Because this information rarely alters therapy, CT has no place in the routine care of patients with COPD. It is, however, the main imaging tool to predict the benefit of pulmonary resection for giant bullous disease and for diagnosing complicating bronchiectasis***(Klein et al., 1992).***

Pulmonary function tests:

The role of respiratory function tests in COPD encompasses diagnosis, assessment of severity, prognosis and following the course of the disease ***(Gibson and MacNee, 1998)***.

Measurement of airflow limitation:

To help identify patients earlier in the course of the disease, spirometry should be performed for patients who have chronic cough and sputum production and a history of exposure to risk factors, even if they do not have dyspnea. Spirometry should measure the maximal volume of air forcibly exhaled from the point of maximal inhalation (FVC) and the volume of air exhaled during the first second of this maneuver (FEV_1), and the ratio of these two measurements (FEV_1/FVC) should be calculated. Patients with COPD typically show a decrease in both FEV_1 and FVC. The presence of a post bronchodilator $FEV_1 < 80\%$ of the predicted value in combination with an $FEV_1/FVC < 70\%$ confirms the presence of airflow limitation that is not fully reversible. The FEV_1/FVC on its own is a more sensitive measure of airflow limitation, and an $FEV_1/FVC < 70\%$ is considered an early sign of airflow limitation in patients whose FEV_1 remains normal (≥ 80% predicted) ***(Pauwels et al., 2001).***

In moderate to severe disease, the severity of airflow limitation is best assessed by the FEV_1 in relation to reference values ***(Quanjer et al., 1994)***. Categorization of the severity of airway obstruction is inevitably arbitrary and the levels used vary in the different guidelines for the management of COPD ***(American Thoracic Society, 1995, Siafakas et al., 1995 and British Thoracic Society, 1997).***

Grading of severity of airway obstruction in terms of forced expiratory volume in first second (FEV_1) percentage of predicted.

	Mild	**Moderate**	**Severe**
ATS	≥ 50	35-49	< 35
ERS	≥ 70	50-69	< 50
BTS	60-79	40-59	< 40

ATS: American Thoracic Society, **ERS:** European Respiratory Society, **BTS:** British Thoracic Society.

According to the recent GOLD (2004) study, COPD was classified into the following stages.

Classification of COPD according to ***GOLD, 2004***.

Stage	Characteristics
Stage 0: ***At Risk***	**Chronic cough and sputum production, lung function is still normal.**
Stage I*:** ***Mild COPD	**Mild airflow limitation (FEV1/FVC < 70% but FEV1 ≥ 80% predicted) and usually, but not always, chronic cough and sputum production.** • **At this stage, the individual may not be aware that his or her lung function is abnormal.**
Stage II: ***Moderate COPD***	**Worsening airflow limitation (50% ≤ FEV1 < 80% predicted), and usually the progression of symptoms, with shortness of breath typically developing on exertion.**
Stage III: ***Severe COPD***	**Further worsening of airflow limitation (30% ≤ FEV1 < 50% predicted), increased shortness of breath, and repeated exacerbations which have an impact on patients' quality of life.** • **Exacerbations of symptoms, which have an impact on a patient's quality of life and prognosis, are especially seen in patients with FEV1< 50% predicted.**
Stage IV: ***Very Severe COPD***	**Severe airflow limitation (FEV1 < 30% predicted) or FEV1 < 50% predicted plus chronic respiratory failure or clinical signs of right sided heart failure. Patients may have very severe (Stage IV) COPD even if the FEV1 is > 30% predicted, whenever these complications are present.** • **At this stage, quality of life is very appreciably impaired and exacerbations may be life-threatening.**

Classification based on postbronchodilator FEV_1

FEV_1: forced expiratory volume in first second, FVC: Forced vital capacity, respiratory failure: arterial partial pressure of oxygen (PaO_2) less than 8.0 kPa (60mmHg) with or without arterial partial pressure of carbon dioxide ($PaCO_2$) greater than 6.7 kPa (50 mmHg) while breathing air at sea level ***(GOLD, 2004).***

Transfer factor:

A reduction in the single-breath carbon monoxide transfer factor (TLCO), is usually present in patients with symptomatic COPD. The transfer coefficient (KCO) is the best functional indicator of the presence and severity of emphysema. Although non- specific, the measurement is of clinical value in distinguishing patients with emphysema from those

with asthma, in whom KCO is generally not reduced ***(Siafakas et al., 1995).***

Respiratory muscle function:

Maximum inspiratory and expiratory pressures (PImax and PEmax, respectively) are reduced in many patients with COPD. Whereas PI, max is impaired by hyperinflation due to shortening of the inspiratory muscles. PE, max is less influenced by respiratory mechanics ***(Siafakas et al, 1995).*** Reduction in PEmax can be attributed to muscle weakness, which is common in advanced COPD ***(Rochester and Braun, 1985).***

Measurement of respiratory pressures is indicated particularly if malnutrition or steroid myopathy is suspected, or if dyspnea or hypercapnea appear out of proportion to the reduction in FEVl ***(Gibson & MacNee, 1998).***

In patients for whom measurement of PImax and PEmax do not resolve the question being asked, transdiaphragmatic pressures and nerve stimulation tests provide more sophisticated assessment of respiratory muscle function. ***(Crapo, 2004).***

ECG Findings:

Significant ECG findings are usually seen only in cases of advanced COPD. In patients with right atrial hypertrophy, tall, (>3 mm) peaked P waves are characteristic (P pulmonale). ***(Gibson and MacNee, 1998).*** The criteria for right ventricular enlargement are met in only one-third of patients with COPD. Some patients will have an arrhythmia, which is usually an atrial arrhythmia. **(Panettieri and Fishman, 2002).**

Laboratory Studies:

Complete Blood Count (CBC) is indicated to rule out anemia as a source of dyspnea or secondary polycythemia as a cause of lethargy. Polycythaemia should be suspected when the haematocrit is > 47% in females and > 52% in males, and/or the haemoglobin is > 16 gm/dl in females and > 18 gm/dl in males ***(Gibson and MacNee, 1998).***

A WBC count may help to evaluate recurrent infections or a possible current infection. Eosinophilia may be present, which would suggest an allergic or asthmatic component. A Comprehensive Metabolic Profile (CMP) allows the physician to evaluate hepatic and renal function and thus determine whether medication doses should be modified. Baseline values of serum potassium are important in patients with cor pulmonale who may require treatment with diuretics, as electrolyte depletion contributes to muscle weakness, which in turn may exacerbate dyspnea **(Petty et al., 1980).**

Alpha 1-Antitrypsin Deficiency:

American Thoracic Society (1995) reported that screening for α 1-antitrypsin deficiency should be considered in patients with any of the following:

- Premature onset of COPD, with moderate or severe impairment by or before age 50.
- A predominance of basilar emphysema with dyspnea in a smoker.
- Development of unremitting asthma, especially in a person under age 50 (screening is indicated even in the presence of atopy).
- A family history of α 1-antitrypsin deficiency.

- Cirrhosis without apparent risk factors.

Blood Gases / Pulse Oximetry:

Oxygen saturation via pulse oximetry on room air at rest and with exercise should be performed. In the early stages of COPD, oxygen saturation levels are normal. In the later stages of the disease, oxygen levels with exercise and then with rest will decrease. Pulse oximetry can be invaluable for determining the degree and source of the patient's impairment. Continuous pulse oximetry performed while the patient walks in place to breathlessness help distinguish cardiac problems from pulmonary problems. In the patient who is limited by his respiratory capacity, the O2 saturation will fall with a mild to moderate increase in the heart rate. In the cardiac patient, the heart rate will increase toward maximum without a fall in the oxygen level ***(American Thoracic Society, 1995).***

In the office practice, many family physicians obtain an O2 saturation reading using pulse oximetry both at rest and after exercise stepping in place or walking. A resting O2 saturation level less than 88 percent, or a decrease of 5 percent or more, qualifies the patient for the use of oxygen with exercise and indicates that the lungs are the limiting factor to exercise ***(Petty et al., 1980).***

ABGs reveals hypoxaemia without hypercapina in early stages of COPD, with progression to hypercapnia in the later stages of COPD, acute exacerbation and during sleep ***(Dvaid and David, 1999).***

Sputum Examination:

In stable chronic bronchitis, sputum is mucoid, and the predominant cell is the macrophage. With an exacerbation, sputum

usually becomes purulent, with an influx of neutrophils. Gram's stain usually shows a mixture of organisms. The most frequent pathogens cultured from the sputum are *Streptococcus pneumoniae* and *HaemophiIus influenzae.* Other oropharyngeal flora, such as *Moraxella catarrhalis,* have been shown to cause exacerbations. In the outpatient setting, however, cultures or even Gram's stains are rarely necessary before instituting antimicrobial therapy ***(Reynolds, 1991).***

Chronic Obstructive Pulmonary Disease and Obstructive Sleep Apnea

Sleep has well-recognized effects on breathing, which in normal individuals have no adverse impact. These effects include a mild degree of hypoventilation with consequent hypercapnia, and a diminished responsiveness to respiratory stimuli. However, in patients with chronic lung disease, these physiologic changes during sleep may have a profound effect on gas exchange, and episodes of profound hypoxemia may develop, particularly during rapid eye movement (REM) sleep ***(Douglas et al., 1979).***

Sleep apnea represents at least 5 episodes of cessation of breathing per hour of sleep, each lasting 10 seconds or longer, whereas hypopnea signifies diminution in airflow decline in oxygen saturation, and EEG arousal. Clinically, apnea and hypopnea are subsumed under "sleep-disordered breathing" (SDB) and bundled together into "respiratory disturbance index" (RDI), or "apnea-hypopnea index" (AHI) to denote the severity of SDB. Apneas may be obstructive, central, or mixed, depending on whether or not the apnea features upper airway obstruction. sleep apnea, obstructive sleep apnea (OSA), and SDB are used interchangeably. Snoring, daytime somnolence, fatigue, and intellectual decline are symptoms of OSA; obesity is a common but not invariable association ***(Young et al., 1993).***

The 1960s and the 1970s brought recognition that sleep worsened arterial hypoxemia in COPD. Cardiac arrhythmias, nocturnal deaths, myocardial stress, electrocardiographic abnormalities, systemic and pulmonary hypertension, and erythropoietin-mediated erythrocytosis became the attributed consequences, and SDB and worsening ventilation-

perfusion mismatch from retained secretions and the unproven lateral rib-cage paradox ("Hoover sign") the proposed mechanisms. The ensuing years have shown that some of these cases represent the overlap syndrome, and the remainder, REM-sleep-related nocturnal oxyhemoglobin desaturation (NOD) ***(White et al., 1995).***

Nocturnal oxyhemoglobin desaturation occurs across all ranges of daytime hypoxemia. Those with moderate to severe daytime hypoxemia (daytime $PaO_2 \leq 55$ mm Hg) fall under the criteria for long-term oxygen therapy (LTOT). In those with only mild daytime hypoxemia (daytime PaO_2 60–70 mm Hg), some with nocturnal hypoxemia represent the overlap syndrome and will be so identified and treated. The rest represent REM-related NOD, which are referred to in this review as NOD associated with mild daytime hypoxemia (NOD-DH). Consensus is lacking as to the consequences of, and the treatment for NOD-DH. It is probably not benign because experimental studies ***(McGrath et al., 1973)*** and some clinical studies suggest it leads to pulmonary hypertension and perhaps premature mortality. However, patients with NOD-DH fall outside the current criteria for LTOT. At this time, PSG remains the only reliable method of separating overlap from NOD-DH. Applying CPAP to all patients with nocturnal hypoxemia is arbitrary and expensive; on the other hand, oxygen therapy alone could cause prolongation of apneic episodes in those with the overlap syndrome with possible adverse consequences ***(Fletcher et al., 1992).***

The Wisconsin Sleep Cohort study found SDB (defined as RDI ≥ 5/h) to be common, with an estimated prevalence of 9% in women and 24% in men ***(Young et al., 1993).*** Some reports impute a high association between COPD and OSA. Such association might reflect a

selection bias arising from using referral populations in pulmonary clinics or sleep laboratories ***(Sharma et al., 2002),*** or might be the mere superimposition of two common clinical conditions or even due to a common etiologic agent (tobacco smoke). ***Flenley (1985)*** identified this association as the "overlap syndrome" with the following features: REM sleep-associated "swinging" SaO_2 pattern and a larger-than-usual rise in PCO_2, or headache following sleep with O_2 supplementation ***(De Miguel et al., 2002).***

In other studies, overlap patients, compared with pure OSA subjects, were older, predominantly men, and showed greater small airways dysfunction (lower $FEF_{50\%}$ and $FEF_{75\%}$), higher pulmonary artery pressures at rest and on steady-state exercise, and propensity for greater hypercapnia and hypoxemia ***(Resta et al., 2000).*** Overlap patients, compared with a COPD cohort, were more obese, showed greater neck circumference, and displayed disproportionate degrees of hypoxemia and hypercapnia for the level of pulmonary function impairment. Thus, observed apneas, snoring and daytime somnolence, obesity, disproportionate hypoxemia or hypercapnia or lower-extremity edema in the COPD patient should prompt a workup for OSA. A minority of OSA patients report insomnia instead of somnolence and the use of ethanol, over-the-counter sleep aids or even prescription hypnotics (especially benzodiazepines that affect upper airway tone) to treat such insomnia might unmask their OSA or provoke its worsening. Identification of the overlap patient is important, given their greater proclivity for pulmonary hypertension and right heart failure ***(Whyte and Douglas, 1991).***

Nocturnal oxygen desaturation (NOD) has long been recognized in COPD patients, who may spend > 30% of sleep time with oxygen

saturation < 90% or > 5% of sleep time below awake SpO2, mostly during REM sleep. The degree of nocturnal O2 desaturation differs markedly among COPD patients and is often difficult to predict. Pulmonary function testing correlates poorly with nocturnal hypoxemia. Nocturnal hypoxemia is affected by co-morbidities such as heart failure and obstructive sleep apnea (OSA), which were not always excluded in studies. Patients with more chronic bronchitis ("blue bloaters") show the best correlation between awake oxygen saturation and lowest saturation, when cardiac arrhythmia are also likely to occur. The hypoxic ventilatory response during the awake state is not useful in predicting nocturnal oxygen saturation change, but moderate desaturation during exercise does have some predictive value for reduced nocturnal mean and nadir saturation ***(Mulloy and McNicholas, 1996).***

Continuous positive airway pressure (CPAP) remains the initial therapy for most patients with OSA. Its mode of action in OSA still remains a controversy. Upper airway obstruction during OSA increases the respiratory muscle load; in this context, it is notable that, in COPD patients, nasal CPAP significantly and substantially improves inspiratory muscle strength and endurance as well as functional ability ***(Mezzanotte et al., 1994).*** CPAP might also counteract the increase in auto-positive end-expiratory pressure (auto-PEEP) during REM sleep. Although the results and potential complexities of the treatment of the overlap syndrome remain largely undocumented, weight, gas exchange, and spirometry improved in all of de Miguel's subjects, but improvements in weight, $PaCO_2$, and HCO_3 were more striking in hypercapnic subjects. The improvements at 6 months' follow-up were sustained at 18 months, but not beyond ***(de Miguel et al., 2002).***

Mechanisms of Nocturnal Oxygen Desaturation in COPD:

1- Hypoventilation

Studies using noninvasive methods of quantifying respiration have shown clear evidence of hypoventilation, particularly during REM sleep, associated with periods of hypoxemia in patients with COPD, but the semiquantitative nature of these measurements makes it difficult to determine if this is the sole mechanism of oxygen desaturation, or whether other factors are involved ***(Goldstein et al., 1984).***

2- Impact of the Oxyhemoglobin Dissociation Curve:

There is a close relationship between awake PaO2 and nocturnal arterial oxygen saturation (SaO2) levels, and it has been proposed that nocturnal oxygen desaturation in patients with COPD is largely the consequence of the combined effects of physiologic hypoventilation during sleep and the fact that hypoxemic patients show a proportionately greater fall in SaO2 with hypoventilation than normoxemic, because of the effects of the oxyhemoglobin dissociation curve. However, PaO2 has also been shown to fall more during sleep in major desaturators as compared with minor desaturators, which indicates that other factors must also play a part in nocturnal oxygen desaturation in patients with COPD ***(Mulloy and McNicholas, 1996).***

3- Altered Ventilation/Perfusion Relationships:

The reduction in accessory muscle contribution to breathing particularly during REM sleep result in a decreased FRC, and contribute to worsening ventilation/perfusion (V/Q) relationships during sleep, which also aggravate hypoxemia in COPD. We have found that transcutaneous PCO2 levels rise to a similar extent in those patients who developed major nocturnal oxygen desaturation as those who developed only a minor degree of desaturation, which suggests a similar degree of hypoventilation in both groups, despite the different degrees of nocturnal oxygen desaturation. The much larger fall in PaO2 among the major desaturators as compared with the minor desaturators, in conjunction with the similar rise in transcutaneous PCO2 in both patient groups, suggests that in addition to a degree of hypoventilation operating in all patients, other factors such as (V/Q) mismatching must also play a part in the excess desaturation of some COPD patients ***(Mulloy and McNicholas, 1996).***

4- Coexisting Sleep Apnea (the Overlap Syndrome):

The incidence of sleep apnea in patients with COPD is about 10 to 15%, which is higher than would be expected in a normal population of similar age. Factors that may predispose to sleep apnea in patients with COPD include impaired respiratory drive, particularly in blue-bloater-type COPD patients. Patients with coexisting COPD and sleep apnea typically develop more severe hypoxemia during sleep because such patients may be hypoxemic at the commencement of each apnea, whereas patients with pure sleep apnea tend to resaturate to normal SaO2 levels between apneas. Therefore, they are particularly prone to the complications of chronic hypoxemia, such as cor pulmonale and polycythemia ***(Chaouat et al., 1995).***

There is no universal agreement as to how and when COPD patients should be evaluated for nocturnal hypoxemia, because it is controversial what level of nocturnal hypoxemia merits treatment, who should be treated, and how aggressively to follow it. Both the Report of the Medical Research Council Working Party and the Nocturnal Oxygen Therapy Trial demonstrated improved survival with the continuous use of long-term oxygen therapy (LTOT) when including the hours of sleep. In the Nocturnal Oxygen Therapy Trial, the survival advantage also paralleled a reduced rate of progression for pulmonary hypertension. A joint effort by the American Thoracic Society and the European Respiratory Society is underway to revise the standards for evaluation and treatment of COPD patients. The standards will include those patients with NOD who do not meet current recommended criteria for treatment with continuous oxygen therapy. It is not expected that there will be major changes for this category, compared to the 1995 guidelines ***(Gay, 2004).***

Nocturnal oxygen should be prescribed to patients who suffer substantial desaturation (≤ 88%) during sleep. This can generally be predicted from daytime hypoxia (PaO2 < 55 mm Hg), and the goal is to maintain arterial oxygen saturation (SaO2) > 90% for 70% of the time.

In a large registry of patients who died with severe COPD after being treated with LTOT, death during sleep occurred in 20% of those deaths. One large study examined the relationship between NOD and mortality in 169 COPD patients with daytime PaO2 > 60 mm Hg, using 2 definitions. Definition 1 included patients with SpO2 < 90% for 5 min to a nadir of at least 85%, to focus on episodic desaturation associated mainly with REM sleep. Definition 2 enrolled patients who had > 30% of the time-in-bed with SpO2 below 90%. Patients with NOD spent a mean ± SD 134 ± 111 min below 90% SpO2, such that around 20 min reduction below that level included 90% of patients. The non-NOD subjects' survival (corrected for age) was significantly better, but when NOD subjects were stratified for supplemental oxygen use, survival remained better only in subjects separated by definition 1, with a nonsignificant trend toward better survival among the 35 oxygentreated subjects, compared to the 38 non-oxygen-treated subjects ***(Zielinski et al., 1997).***

The development of increased pulmonary vascular resistance and poorer survival has been correlated with more pronounced NOD, especially during REM sleep. Pulmonary artery pressure is more pronounced in patients who have NOD than in those who do not, and oxygen has a protective effect on supporting better nocturnal pulmonary hemodynamics. Mean pulmonary artery pressure actually fell in NOD patients who received (for 36 months) oxygen during sleep, compared to patients given sham treatment (defective oxygen concentrator) ***(Chaouat et al., 1997).***

NOD occurred in 82% of COPD patients and was predicted by both forced expiratory volume in the first second (FEV1) and PaCO2

level. Mean nocturnal SpO2 correlated with body mass index and PaCO2 during a wake but not with PaO2 ***(Fletcher et al., 1992).***

Little et al. (1999) has a study to identify factors which might predict nocturnal desaturation (defined as a fall of > 4% from awake baseline level for ≥ 5min) in normoxic or mildly hypoxic patients with stable COPD. Thirty three patients subdivided into 2 groups who had nocturnal desaturation and those who did not. There was a significant difference between these two groups in terms of mean and minimum nocturnal saturation. No significant difference in lung function between the two groups, but in the desaturating group daytime PaO_2 was significantly lower and $PaCO_2$ significantly higher than in those who did not desaturate. Similarly, the desaturators had a significantly lower daytime SaO_2 when compared with the non-desaturating group.

There were significant positive correlations between mean nocturnal saturation and daytime saturation. Statistically significant negative correlations were identified between mean nocturnal saturation and $PaCO_2$ and between mean nocturnal saturation and functional residual capacity Mean nocturnal saturation did not correlate with other lung function measurements, in particular FEV1. Regression analysis revealed that daytime SaO_2 was the only independent predictor of mean nocturnal desaturation, accounting for 61% of the variability in the mean nocturnal SpO_2 ***(Little et al., 1999).***

Chaout et al. (1997) demonstrated the Outcome of COPD patients with mild daytime hypoxaemia with or without sleep related oxygen desaturation to compare the evolution of pulmonary function tests, BMI and arterial blood gases in chronic obstructive pulmonary disease (COPD) patients with mild-to-moderate hypoxaemia, with or without sleep-related oxygen desaturation. The study done on 64 patients of COPD (35 were desaturator and 29 were non desaturator). According to the lung function criteria, all patients had moderate or severe airway obstruction and mild or moderate daytime hypoxaemia. The mean PaO2 of the group as a whole was 63.4, 3.1 mmHg (range 58–69 mmHg). Only 5 of the 64 patients had a PaO2 ≤ 60 mmHg. Apart from nocturnal oximetric data and body mass index (BMI), there were significant

difference observed between the two groups was a higher daytime PaCO2 in group 1 (desaturators) compared to group 2 (P = 0.001) with no significant difference in PaO2 between two groups and also there were a negative significant correlation between nocturnal O2 desaturation and BMI (P = 0.016) ***(Chaout et al., 1997).***

However, there is no significant difference between two groups in pulmonary function tests (FEV1%, FEV1/FVC, TLC% of predicted) ***(Chaout et al., 1997).***

The Impact of obstructive airway disease on Sleepiness and Sleep Variables in Participants with and without sleep apnea hypopnea:

To examine the impact of coexistent OAD and SAH on sleepiness and sleep architecture, with compared data from participants having both disorders with data from participants with each disorder alone. After adjusting for age, sex, height, weight, race, and smoking status, significant but small differences were observed between participants who had SAH alone and those who had both disorders (SAH + OAD). The former group had higher sleep efficiency and lower % of total sleep time in Stage 1. In contrast, differences between participants with both SAH and OAD and those with OAD alone were expressed more broadly across sleep variables. After adjusting for age, sex, height, weight, race, and smoking status, participants who had both SAH and OAD had significantly higher Epworth sleepness scale, lower TST, lower sleep efficiency, lower %TST in Stages rapid eye movement and 3, 4 sleep, greater % in Stage 2 sleep, and higher arousal index than those with OAD alone ***(Sanders et al., 2003).***

Comparison of participants with single disorders (e.g., OAD only, SAH only) indicated that those with SAH alone had greater perceived sleepiness by ESS, lower %TST in rapid eye movement as well as in Stage 3,4 sleep, and greater %TST in Stage 2 sleep than those with OAD alone. In addition, individuals with SAH alone had a markedly higher arousal index than those with only OAD. Thus, the most notable differences in sleep variables across the four participant groups were reflected in the comparisons between groups with and without SAH, regardless of whether or not there was coexistent OAD. To determine if

sleepiness and sleep architecture are influenced by the severity of OAD in the absence of SAH, data from the 976 participants with OAD (defined by an FEV1/FVC ratio < 70%) but without SAH were analyzed by quartile of percent-predicted FEV1. TST and sleep efficiency were slightly but statistically less in the lowest compared with highest FEV1 quartile ***(Sanders et al., 2003).***

The Impact of OAD on Sleep-related Oxyhemoglobin Saturation in Participants with and without Coexistent SAH:

To examine the degree to which OAD and SAH independently and conjointly contribute to desaturation during sleep we assessed the risk for spending more than 5% of TST with SaO2 less than 90% and less than 85%, respectively, in the presence of single and combined disorders. After adjusting for age, sex, height, weight, race, smoking status, and awake SaO2, the OR for oxyhemoglobin desaturation below threshold levels of less than 90% and less than 85% for more than 5% of TST was considerably increased in the presence of SAH with OAD with % 42.9 of participants with a relatively lower in patient of OAD in absence of SAH (11.2%) of participants ***(Saunders et al., 2003).***

Management of Obstructive Sleep Apnea (OSA)

Treatment for symptomatic OSA syndromes is influenced by the severity of sleep apnea, relative efficacy of treatment options, the presence of comorbid conditions, and patient and physician preference. For mild forms of OSA, nonsurgical options include (1) weight loss; (2) avoidance of sleep deprivation, alcohol, nicotine, and sedatives; (3) positional therapy (avoidance of the supine posture); and (4) treatment of comorbid conditions, such as hypothyroidism. Pharmacologic treatment of sleep apnea has not been very successful ***(Veasey, 2002).*** The use of stimulants, however, such as modafinil, 200 to 400 mg/d, may be useful as adjunctive therapy for daytime sleepiness that persists despite optimization of CPAP therapy. Oral appliances are useful for mild OSA and for patients with moderate or severe OSA who are unable or unwilling to tolerate CPAP and who have failed surgery or are not surgical candidates. Oral appliances work by increasing airway space, providing a stable anterior position of the mandible, advancing the tongue or soft palate, and possibly by changing genioglossus muscle activity. These device are not well tolerated by patients with significant temporomandibular joint symptoms ***(Lowe and Schmidt-Nowara, 2002).*** Positive airway pressure therapy (continuous, bilevel, and autotitrating): CPAP therapy can be used for all categories of OSA and represents first-line therapy for moderate to severe OSA. Based on the risk of increased pulmonary hypertension documented in the Wisconsin sleep cohort data CPAP therapy is recommended for all OSA patients with RDI of 30 events per hour. Similarly, based on documented improvement in symptoms and daytime function in CPAP-treated patients, CPAP therapy for patients with RDI of 5 to 30 events per hour associated with symptoms of excessive daytime sleepiness; impaired cognition; mood disorders; insomnia; documented cardiovascular diseases (including hypertension and ischemic heart disease); or stroke. Treatment with CPAP is not indicated for asymptomatic, mild OSA patients without evidence of cardiovascular disease ***(Loube et al., 1999).***

Effective CPAP therapy reduces nocturnal respiratory disturbances and improves nocturnal oxygenation, sleep architecture, daytime sleepiness, neurocognitive performance, driving performance, and perceived health status. Cardiovascular end points, such as hypertension, cardiac arrhythmia, nocturnal ischemia, left ventricular function, and

mortality, may also improve with CPAP therapy. Health care use is also reduced in OSA patients on CPAP therapy compared with untreated patients ***(Roux and Hilbert, 2003).***

Kribbs et al. defined CPAP failure as usage of CPAP less than 4 hours per night on 70% of the nights or lack of symptomatic improvement. Objectively measured CPAP usage adjusted to reflect mask-on time demonstrated average nightly use to be only 4.97 hours (range 2.8 – 6.9). The hallmark for eventual nonadherence and rejection of CPAP is use of CPAP less than 4 hours per night. Reasons for nonadherence cited by patients at the Stanford Sleep Disorders Clinic are similar to those reported by others: (1) nuisance factors (noise, partner intolerance, inconvenience); (2) mask problems (leaking mask, mask rubbing, skin rash or abrasion, conjunctivitis); (3) side effects (nasal congestion, rhinorrhea, epistaxis, sinus discomfort, oronasal dryness, chest discomfort, aerophagia, claustrophobia, difficulty exhaling, pneumothorax [rare], pneumocephaly [rare]); and (4) incomplete resolution of symptoms (frequent awakening, persistent fatigue or sleepiness). CPAP pressure has not been found to be a determinant of long-term use ***(Roux and Hilbert, 2003).***

Interventions to improve CPAP use are based on patient education and behavioral principles of positive reinforcement. These include providing literature addressing sleep apnea and good sleep habits; disseminating information on CPAP use, benefits, and potential side-effects; organizing group educational sessions and support groups (eg, AWAKE groups); teaching adaptation skills to the patient and bed partner; scheduling regular clinic follow-up to monitor CPAP meter readings, discuss patient-perceived problems, and initiate treatment plans

addressing identified problems; and implementing regular follow-up telephone calls (initially weekly, then monthly). Interventions mostly involve spending time with patients to determine the best nasal interface with least amount of sleep disruption, having common sense, and taking into consideration age and health status of the patient ***(Loube et al., 1999).***

Bilevel positive airway pressure allows independent adjustment of inspiratory and expiratory pressures. Indications for a trial of bilevel positive airway pressure may include OSA patients who cannot tolerate CPAP because of persistent massive nasal mask air leak or discomfort exhaling against positive pressure, or have concomitant nocturnal breathing disorders, such as restrictive thoracic disorders, chronic obstructive pulmonary disease, or nocturnal hypoventilation ***(Loube et al., 1999).***

Autotitrating positive airway pressure devices detect snoring, apneas, hypopneas, flow limitation, and changes in airway resistance or impedance, which are then interpreted by a central processing unit based on specific diagnostic algorithms to determine the resultant voltage for the autotitrating positive airway pressure blower in response to these signals ***(Roux and Hilbert, 2003).*** The 2002 American Academy of Sleep Medicine practice parameters on autotitrating positive airway pressure indicate that (1) the diagnosis of OSA must be established by an acceptable method; (2) autotitrating positive airway pressure may be used during attended titration to identify a single effective pressure for use with standard CPAP; (3) autotitrating positive airway pressure may be used in self-adjusting mode for unattended treatment of OSA after an initial successful attended CPAP or autotitrating positive airway pressure

titration; (4) patients being treated with fixed CPAP on the basis of an autotitrating positive airway pressure titration or being treated with autotltrating positive airway pressure require follow-up to determine treatment efficacy and safety; and (5) if symptoms do not resolve or if autotitrating positive airway pressure therapy is inefficacious, re-evaluation should be performed, and if needed, a standard CPAP titration should be done ***(Berry et al., 2002).*** Autotitrating positive airway pressure devices are not recommended for split-night studies or for patients with congestive heart failure; significant lung disease (chronic obstructive pulmonary disease); daytime hypoxemia; respiratory failure; or prominent nocturnal oxygen desaturation other than from OSA. Autotitrating positive airway pressure devices that rely on vibration or sound in the device's algorithm should not be used in patients who snore ***(Berry et al., 2002).***

The principle of auto-CPAP:

Auto-CPAP relies on a built-in event detector, which identifies respiratory events. When such an event is detected the pressure in the mask is automatically increased. However, to ensure the system does not permanently stay at high levels of pressure, it is necessary that the pressure is eventually decreased. This is done periodically, until events are detected again at which point the pressure increases again. Thus, the system is by essence unstable, as it constantly moves from high-pressure levels which eliminate the events to low-pressure levels at which events reappear. The instability of the system depends mainly on the time constant with which the algorithm increases the pressure when events are detected or decreases the pressure when no event is detected and on the nature of the detected events. These time constants have to satisfy two conflicting requirements: if they are long, the patients will not get all the

expected advantages, if they are short the resulting instability will be increased. Generally algorithms use shorter time constants to increase the pressure than to decrease it, as it is not desirable to leave the patient with persistent respiratory events, whereas it may be acceptable that the patient stays at a higher pressure level than actually required, the time constants usually being shorter, and the steps by which the pressure is increased larger, when apneas or hypopneas are detected than when more subtle events are detected. The importance of the instability also depends on the nature of the detected events. When the events are apneas (or hypopneas), there are necessarily "residual" events of some importance. When the events are more subtle ones, like snoring or inspiratory flow limitation, which are thought to precede the occurrence of obstructive hypopneas or apneas, then the residual events may be less important ***(Krieger, 1999).***

Titration with auto-CPAP

To find out which will be the optimal fixed CPAP for a given patient, without using supervized polysomnography where availability is limited. The choice of the fixed pressure depends on the philosophical choice between the lowest possible pressure or the most efficient possible pressure. The choice is indeed a philosophical one, as there is no demonstration that higher pressures result in more side effects or lower compliance, nor that more efficient pressures result in better outcomes or compliance ***(Krieger, 1999).***

The first automatic nasal CPAP calibration procedure actually did not use an intelligent auto-CPAP machine, but more simply a device in which CPAP was started at 4 cm H2O and increased in 1 cm H2O steps each 5 min for 30 min. The recording obtained from a portable Vitalog

was then reviewed to choose the most appropriate pressure. The same procedure was repeated 3 to 4 weeks later, starting with the previously set optimal pressure minus 1 cm H2O ***(Krieger, 1999).***

However, be noted that the endpoint with autotitration was elimination of inspiratory flow limitation, whereas it was elimination of apneas and hypopneas without considering snoring nor inspiratory flow limitation during manual titration; therefore, it is not unexpected that pressures were higher and residual events lower with autotitration ***(Krieger, 1999).***

Surgical treatment of obstructive sleep apnea:
Surgical therapy of OSA is directed toward site-specific obstruction in the upper airway. The three major anatomic regions of obstruction for OSA are (1) the nose; (2) the palate (oropharynx); and (3) the base of the tongue (hypopharynx). Fujita classified the sites of obstruction as follows: Fujita type I (palate with normal base of the tongue; Fujita type II (palate and base of the tongue obstruction); and Fujita type Ill (base of the tongue obstruction with normal palate) ***(Sher and Goldberg, 2002).***

Surgical techniques involve either extirpation of soft tissue, secondary soft tissue repositioning through primary skeletal mobilization, or bypass of the pharyngeal airway ***(Li, 2003).*** Procedures resulting in extirpation of soft tissue include uvulopalatopharyngoplasty (UPPP); modified UPPP-extended uvulopalatal flap; UPPP; laser midline glossectomy; and lingualpiasty. UPPP, the most commonly used technique, enlarges the retropalatal airway through tonsillectomy (if present); trimming and reorientation of the posterior and anterior tonsillar pillars; and excision of the uvula and the posterior portion of the palate. UPPP has a surgical response rate (defined as 50% reduction in AHI or RDI) and a RDI below 20 ranging from 40% to 65%. Analyzing 37 papers with a total of 640 patients, complications of UPPP include: velopharyngeal insufficiency greater than 1 month (14 of 640);

postoperative bleeding (7 of 640); nasopharyngeal stenosis (5 of 640); voice change (4 of 640); vague foreign body sensation (1 of 640); successfully managed airway obstruction (2 of 640); and death secondary to upper airway obstruction (1 of 640). UPPP has reported success rates ranging from 43% to 67% ***(Sher and Goldberg, 2002).***

Surgical techniques involving primary skeletal mobilization include transpalatal advancement pharyngoplasty, mandibular advancement, maxillomandibular advancement, genioglossal advancement, and hyoid myotomy and suspension. Transpalatal advancement pharyngoplasty involves resection of the posterior hard palate with antenor advancement of the soft palate into the bony defect, thereby enlarging the retropalatal airway; it is used for persistent retropalatal obstruction after UPPP, but its role in the surgical armamentarium is still vague. Mandibular advancement uses sagittal mandibular osteotomies to mobilize the tongue anteriorly and advance its insertion at the genioid tubercle; this procedure is beneficial for a small group of patients with class II dental occlusion and significant mandibular deficiency. Maxillomandibular advancement involves Le Fort I maxillary and sagittal-split mandibular osteotodmies with simultaneous advancement of both maxilla and mandible, thereby producing maximal enlargement of the retrolingual airway and some enlargement of the retropalatal airway ***(Sher and Goldberg, 2002).***

Tracheotomy may be used to bypass the pharyngeal airway in OSA patients with morbid obesity; severe facial skeletal deformity (mandibular deficiency) with excessive daytime somnolence; hypoxemia (SaO_2 < 70%); or significant cardiac arrhythmias ***(Li, 2003).*** The tracheotomy tube is plugged when the patient is awake to allow speech and

swallowing. Although tracheotomy is easy to perform and is effective for OSA, inconvenience and hygiene issues preclude its more widespread use ***(Li, 2003).***

The Stanford Protocol (Riley-Powell) surgical approach consists of a two-phased approach to direct surgical treatment of suspected regions of obstruction. In conjunction with the clinical evaluation, patients undergo lateral cephalometry and fiberoptic endoscopy with Muller's maneuver. Phase I surgical intervention includes nasal reconstruction, UPPP or uvulopalatal flap, and limited mandibular osteotomy with genioglossus advancement. Nasal reconstruction is performed for patients with significant obstruction of the nasal airway (deviated septum, collapsed ala, or enlarged turbinates). In a series of 33 patients who underwent the modified UPPP-extended uvulopalatal flap surgery, the reported success rate was 81.8%, compared with the overall reported success rate of 60% for phase I surgery. Phase II surgery involves maxillomandibular advancement osteotomy to treat refractory hypopharyngeal (base of the tongue) obstruction by advancing the mandible at least 10 mm. The reported success rate for phase II surgery in 350 patients was 90%. In a subgroup of 175 patients who underwent maxillomandibular advancement between 1998 and 1995, the mean age was 43.5 years, the cure rate was 97%, the mean hospital stay was 2.4 days, and the mean postoperative RDI was 7.2 compared with mean preoperative RDI of 72.3 ***(Li, 2003).***

Radio frequency volumetric tissue reduction has been used for the treatment of turbinate hypertrophy and to reduce the base of the tongue ***(Riley et al., 2003).*** In 18 patients treated with radio frequency tongue-base reduction under local anesthesia with a mean of 5.5 sessions mean

RDI improved from 39.5 ± 32.7 to 17.8 ± 15.6 at 2.6 ± 0.7 months postoperatively. Long-term follow-up (mean 28 ± 4 months) showed increase of RDI to 28.7 ± 29.4, with persistent improvement of the mean apnea index but with worsening hypopnea index and with mean weight increase of 3.1 ± 7.9 kg. Performance of extra sessions improved results ***(Li, 2003).***

In the recent past orthognathic surgery has been performed. Maxillary expansion is routinely performed orthodontically, when there is constriction of the maxilla where posterior crossbite often exists. Although the width of the maxilla can be improved by expansion ***(Cistulli et al., 1998).***

It usually remains narrowed after expansion because the extent of expansion is limited by the width of the mandible, and mandibular constriction often coexists. Distraction osteogenesis, a process of bone lengthening by gradually separation of bone segments performed by simple osteotomy, has improved the ability to expand the mandible simultaneously with the maxilla. It has been performed by Li and Guilleminault in six patients, improvement of SDB based on polysomnography and clinical results were seen in all six patients following maxillo-mandibular expansion, and no complications were encountered. The ideal candidate for this treatment may be an adolescent and young adult with isolated SDB who may be contemplating or are already in orthodontic treatment where lifelong CPAP treatment seems a limited afternative ***(Cistulli et al., 1998).***

Surgery remains a viable alternative to nasal CPAP in OSA patients. The indications, risks, and complications of surgery, the

possibility of multiple and staged procedures, and alternative forms of therapy need to be discussed with the patient. The selection of surgical procedures should be driven by the site of obstruction and the patient's airway anatomy, medical status, severity of sleep apnea, overall clinical status, age, patient preference, relative efficacy of the surgery, and the surgeon's experience and skill ***(Cistulli et al., 1998).***

Management of COPD with OSAS;
The major process barriers encountered by the clinician during the management of sleep-related breathing disorders in COPD patients can best be discussed first in terms of deciding about specific treatment goals or targets. The implementation of treatment must also be carefully thought out to avoid additional difficulties for delivery of optimal care. The therapies under consideration here involve oxygen therapy and NPPV. Although the comments that follow regarding reimbursement will soon be outdated because of the frequent reappraisals, the necessity for the clinician to keep in touch with current coverage criteria can easily be appreciated ***(Gay, 2004).***

Oxygen:

The threshold saturation and vigor of saturation maintenance may be influenced by the presence and degree of pulmonary hypertension, especially in patients with more severe COPD and NOD. Where to make the decisions is usually a practical concern, but oxygen therapy is typically determined during an office visit when continuous LTOT is needed. Home overnight oximetry before and after selection of nocturnal oxygen flow rates should usually be done for optimal management. Given the paucity of data to enlighten practitioners in either regard, however, it is understandable that both targets are not clear-cut. Each of these decisions is probably best individualized by the treating caregiver, but some more specific guidelines are offered below ***(Gay,2004).***

Current and Draft Oxygen Coverage Criteria.

Home oxygen therapy is currently covered only if all of the following conditions are met:

- Group I criteria include awake $PaO_2 \leq 55$ mm Hg or $SaO_2 \leq 88\%$.

- Group II criteria include the presence of criterion A or B (below) plus criterion 1, 2, or 3 (below).
    - A: Awake (at-rest or during exercise) PaO2 of 56–59 mm Hg or SaO2 ≤ 89%

    Or

    - B: SaO2 decrease of > 5% for at least 5 continuous minutes, with a nadir of ≤ 85% during sleep

    1. Dependent edema due to congestive heart failure, or
    2. Pulmonary hypertension or cor pulmonale, determined by measurement of pulmonary artery pressure, gated blood pool scan, echocardiogram, or "P pulmonale" on electrocardiogram, or
    3. Erythrocythemia with hematocrit > 56%

(Gay,2004)

The draft policy initially proposed qualification criteria similar to the above but included a clause to consider mandating recertification for LTOT. Under scrutiny are patients who were given LTOT during recovery from a COPD exacerbation and who may not need continued LTOT yet keep it for "convenience" and subjective benefit, which further increases the high costs of LTOT delivery and should probably be curtailed. Although recertification is proposed in the draft policy, it is unlikely this will be acceptable, given that oximetry reimbursement is limited at best and would pose an additional cost and inconvenience. Another alternative would be to consider attaching more specific payment methods to the various oxygen delivery systems (liquid oxygen, compressed gas, and oxygen concentrator) ***(Gay, 2004).***

Pharmacologic Therapy:

1- Anticholinergics:

Cholinergic tone is increased at night, and it has been proposed that this contributes to airflow obstruction and deterioration in gas exchange during sleep in patients with obstructive airways disease. There is recent evidence that ipratropium improves SaO2 in addition to sleep quality in patients with COPD, although other studies have shown conflicting results on the ability of ipratropium to block nocturnal bronchoconstriction in asthma ***(Catterall et al., 1988).***

Tiotropium bromide is a long acting anticholinergic drug that has a unique kinetic selectivity with very slow dissociation from M_1 and M_3 muscarinic receptors ***(Barnes, 2000).*** Clinical studies in COPD now indicate that inhaled tiotropium once daily is an effective bronchodilator in patients with COPD and is more effective than conventional ipratropium bromide four times daily ***(Littner et al., 2000).*** Tiotropium is likely to become the bronchodilator of choice in COPD and may have additive effects with long acting $ß_2$ agonists ***(Barnes, 2003).***

2- Theophylline:

In addition to being a bronchodilator, theophylline has important effects on respiration that may be particularly beneficial in patients with chronic hypoventilation, including central respiratory stimulation and improved diaphragmatic contractility, and improves gas exchange during sleep in COPD. In COPD, the benefits appear to be more likely caused by a reduction in trapped gas volume than by bronchodilation. However, theophyllines have an adverse effect on sleep quality in contrast with ipratropium bromide, and also have a relatively high incidence of gastrointestinal intolerance ***(Martin et al., 1999).***

3- β_2-Agonists:

There are only limited data on the efficacy of β_2-agonists on the management of sleep-related breathing abnormalities in COPD. One report found a long-acting theophylline superior to salbutamol in terms of nocturnal gas exchange and overnight fall in spirometry. However, there are no studies of the impact of long-acting β_2-agonists on sleep and breathing in COPD ***(Man et al., 1996).***

4- Almitrine:

This agent is a powerful carotid body agonist that stimulates ventilation. Almitrine also improves (V/Q) relationships within the lung, probably by an enhancement of hypoxic pulmonary vasoconstriction. The overall effect is to lessen hypoxemia awake and asleep, and is beneficial in hypoxemic patients with COPD. Important side effects include pulmonary hypertension, dyspnea, and peripheral neuropathy ***(Howard, 1989).***

Noninvasive Positive-Pressure Ventilation

The treatment goals of NPPV are primarily determined by what must be done to address individual patient complaints or requests for symptom relief. Since evidence does exist for improved sleep quality, especially for those with OSA, but also for those with COPD alone, this goal may be reasonable and achievable in patients with severe sleep disruption. How this is best accomplished with NPPV is more problematic, as questions remain regarding whether ventilator settings that achieve maximum minute ventilation also optimize sleep quality. Where to initiate and assess optimal NPPV settings is easily determined when more obvious overlap and obesity hypoventilation clinical features are present. There is a clear need to achieve upper-airway patency and increased inspiratory flow for hypoventilation in this subset of COPD patients. A recent intriguing finding is that patients who demonstrate improved sleep quality on initial use of CPAP have much better long-

term CPAP-therapy adherence, so clinicians should strive to create an optimal initial CPAP experience. The use of hypnotic medications to facilitate the adjustment to NPPV has not been formally studied but should be ***(Drake et al., 2003).***

PATIENTS AND METHODS

Patients:

This study was performed on fifty male patients with COPD with age ranged from 40 to 67 years with mean age (52.26 ± 8.59) years. This study was carried out at Thoracic Medicine Department, Mansoura University Hospitals in the period between June 2005 to June 2006.

Inclusion criteria:

1. All patients were fulfilling the criteria of COPD according to ***GOLD, 2004*** (irreversible obstructive airway disease i.e. FEV1/FVC < 70%) and <12% improvement in FEV1 expressed as percentage of predicted after inhalation of B_2 agonists.
2. Clinically stable COPD condition ***(Yoshikawa et al., 1999)***
3. COPD patients with $PaO_2 \geq 60$ mmHg.

Exclusion criteria:

Subjects were excluded from the study for:

1. COPD patients with exacerbation within 4 weeks.
2. COPD patients with coexisting illness (renal impairment, Liver impairment, Thyroid diseases).

Methods:

All patients were subjected to:

1- **Full history taking** with stress on:

- Age.
- Epworth sleepiness scale.
- Nocturnal shocking.
- Witnessed apnea.
- Berlin questionnaire.
- Chest symptoms.
- Special habits specially smoking and alcohol intake.

2- Physical examinations with stress on:

- Neck circumference.
- BMI.
- Chest and heart examination.

3- Plain chest X- ray.

4- Laboratory tests:

- Complete blood picture.
- Liver function tests.
- Serum creatinine.
- Arterial blood gases.
- Random blood sugar.

5- Pulmonary function tests:

Forced vital capacity (FVC% of predicted), forced expiratory volume in the first second (FEV_1 % of predicted), FEV1/FVC% ratio were measured by standard spirometric technique (Spiro-Jaeger, Germany), the highest value from at least three spirometric maneuvers was selected

6- Calculation of Body mass index:

- The used method for estimation of the body mass index was the weight- height index according to the following equation (BMI = weight (kg) / height^2 (m^2).
- According to the WHO classification of BMI the patients were classified into the following ***(Seidell and Flegal, 1997):***
    - Under weight: BMI < 18.5 kg/m^2.
    - Normal: BMI 18.5 – 24.9 kg/m^2.
    - Pre-obese: BMI 25 – 29.5 kg/m^2.
    - Obese class I: BMI 30 – 34.9 kg/m^2.
    - Obese class II: BMI 35 – 39.9 kg/m^2.
    - Obese class III: BMI > 40 kg/m^2.

8- Polysomnography:

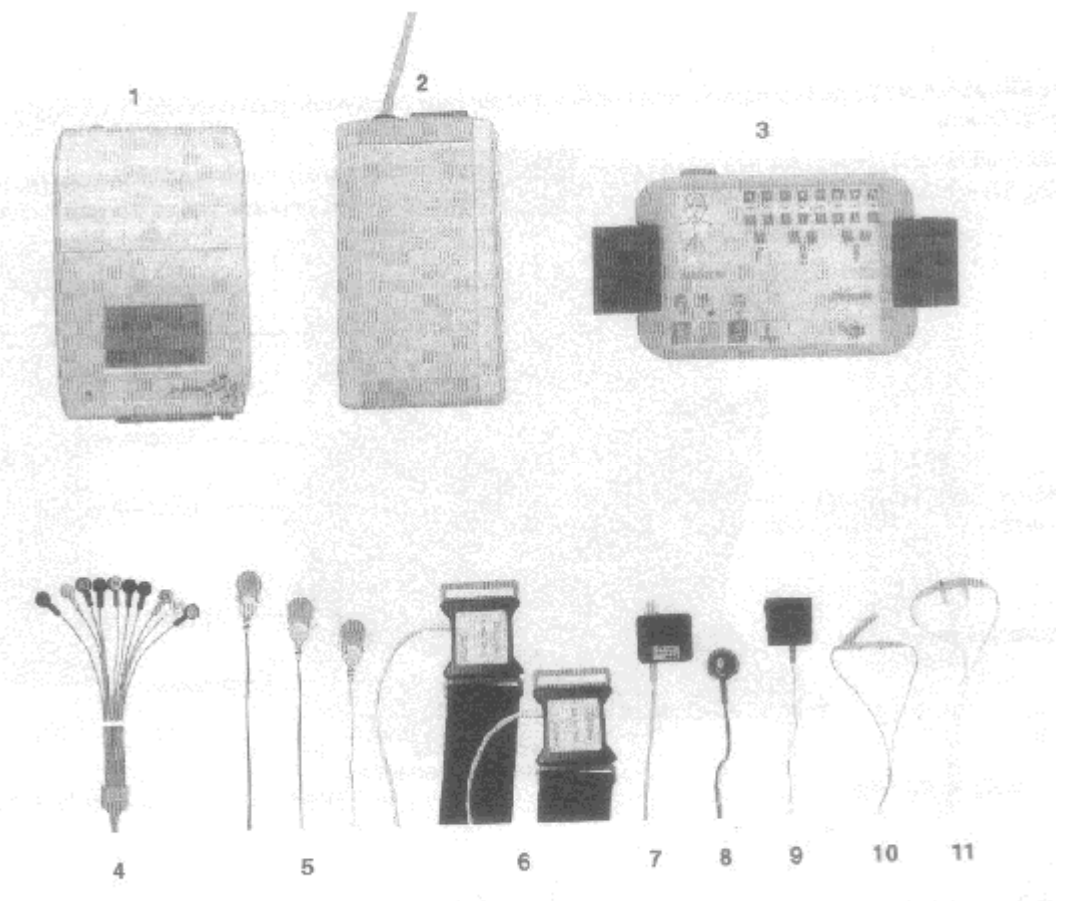
Full night polysomnography involves the recording of electroencephalography (EEG) electro-oculography (EOG), submental and anterior tibial electromyography (EMG), electrocardiography (ECG), respiratory effort (abdominal and thoracic effort), nasal & oral airflow sensor and oxygen saturation (pulse oxymetry).

Polysomnography used in this study is a full night polysomnography (Jaeger Sleep Screen). Various sensors can be connected to the sleep screen for measuring and recording.

- Oxygen saturation, pulse rate
- Body position
- Snoring
- Respiratory airflow
- Pressure sensor for the determination of CPAP/BiPAP and respiratory airflow (option: connection of nasal cannula possible)
- Light

- Respiratory effort (thoracic and abdominal)
- PLM (Periodic leg movement) (electromyogram of tibialis muscles)
- EEG (electroencephalogram)
- EMG (etectromyogram of chin muscles, for sleep staging)
- EOG (eleclro-oculogram, measurement of eye movement, for sleep staging)
- ECG (electrocardiogram)

Components of basic sleep screen:



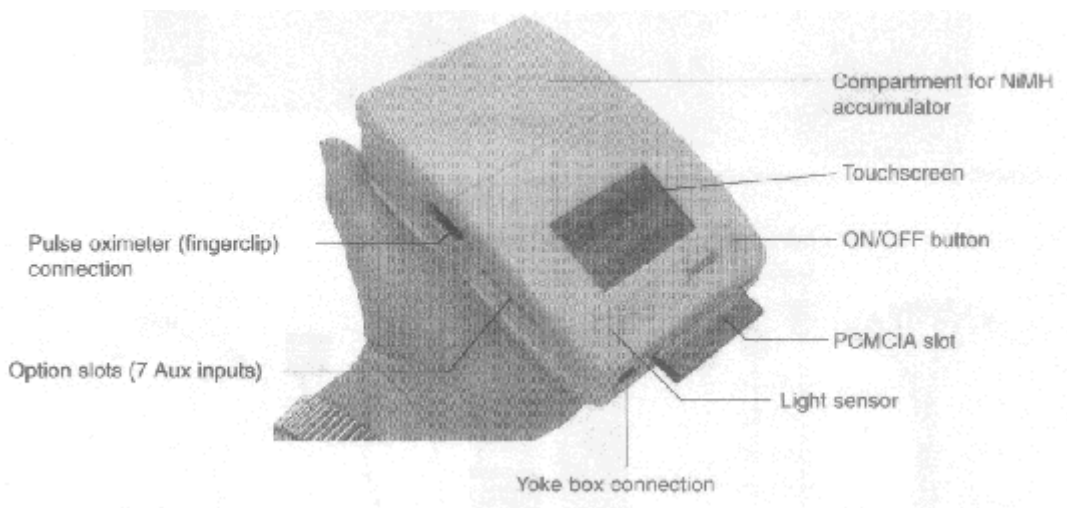
The following is included in the delivery:

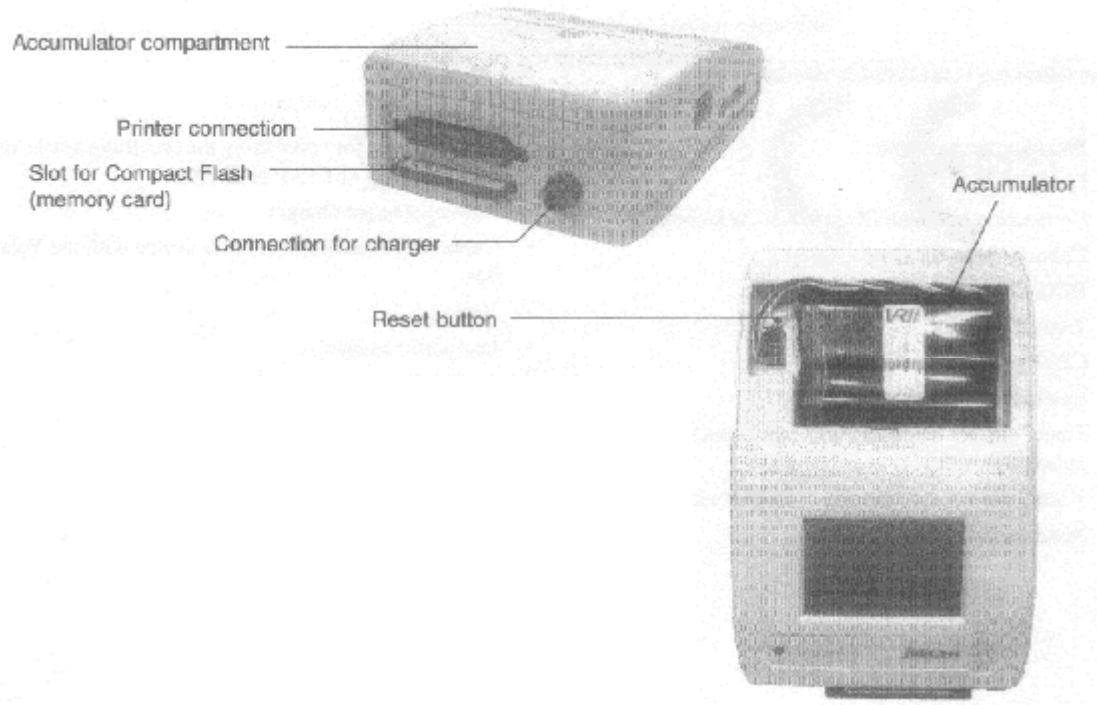
1. Sleep screen base unit
2. Charger
3. Connection belt with Sleep Screen Yoke box

4. Cable for sleep staging
5. One ECG electrode and two PLM electrodes
6. Two respiratory effort belts (thoracic and abdominal)
7. CPAP pressure sensor
8. External tracheal microphone
9. Finger clip for determining oxygen saturation and pulse rate
10. Thermistor for determining nasal-oral airflow
11. Nasal cannula (option)

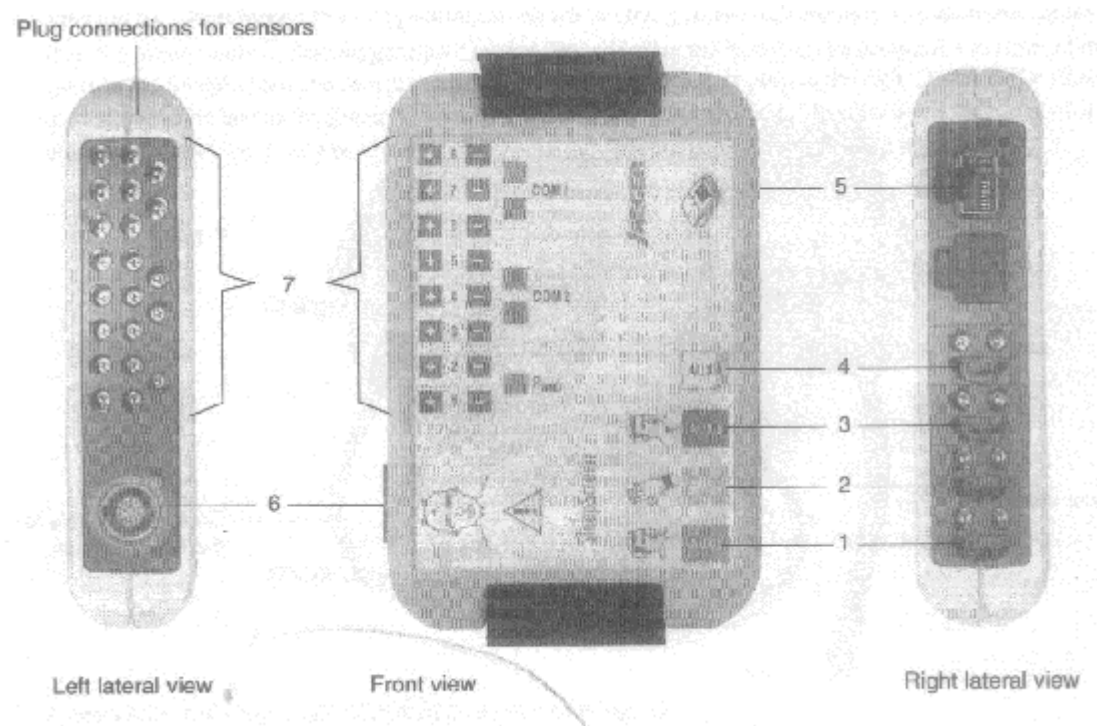
Sleep screen: Basic Device:

The basic sleep screen system is designed for recording and analysis of physiological data which are acquired with the sleep Yoke box. Furthermore, additional accessories and printer can be connected. The software is menu-guided and can be operated by pressing the activated fields on the integrated touch screen.



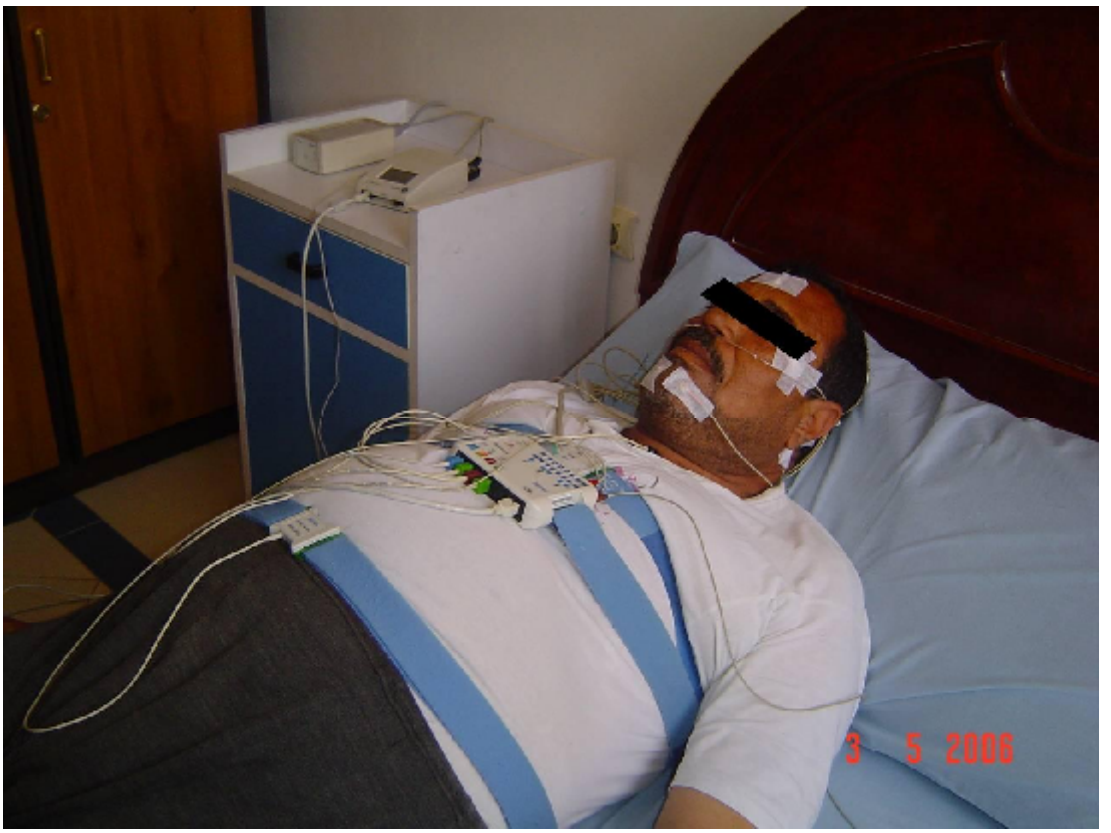


Yoke box for sleep screen:



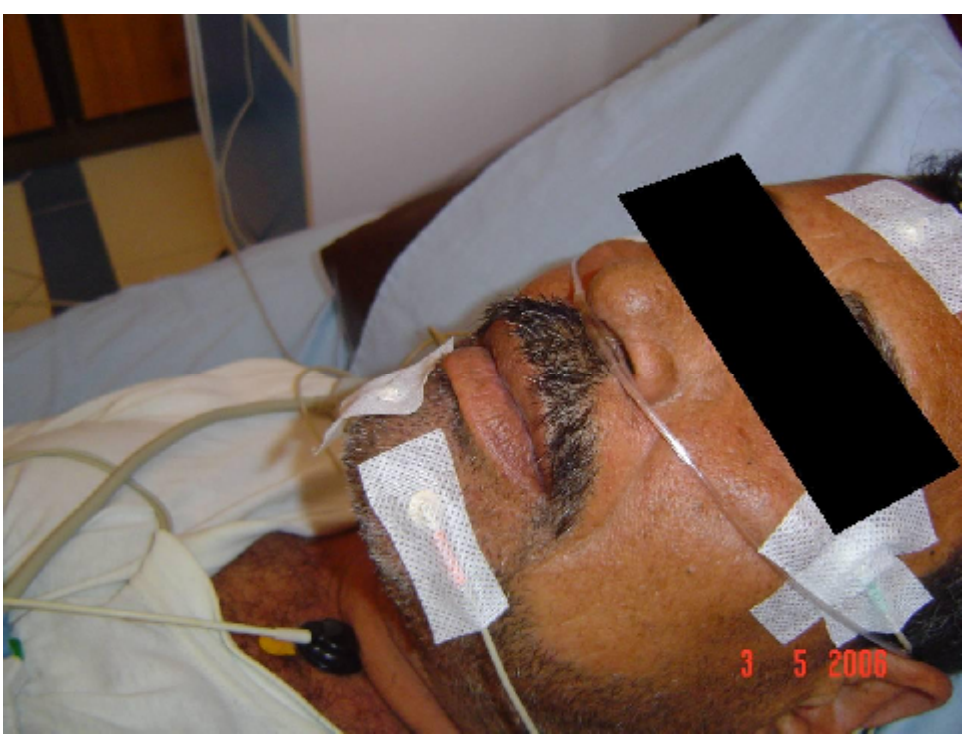
1. Connection for thermistor or CPAP-pressure sensor (flow) [Aux 1]
2. Connection for thoracic effort (or activity sensor) [Aux 2]
3. Tracheal microphone [Aux 3]
4. Connection for abdominal effort [Mix 4]

5. Connection to basic device
6. Connection for cable harness (EEG electrodes)
7. Additional connections for any electrophysiologicai signal



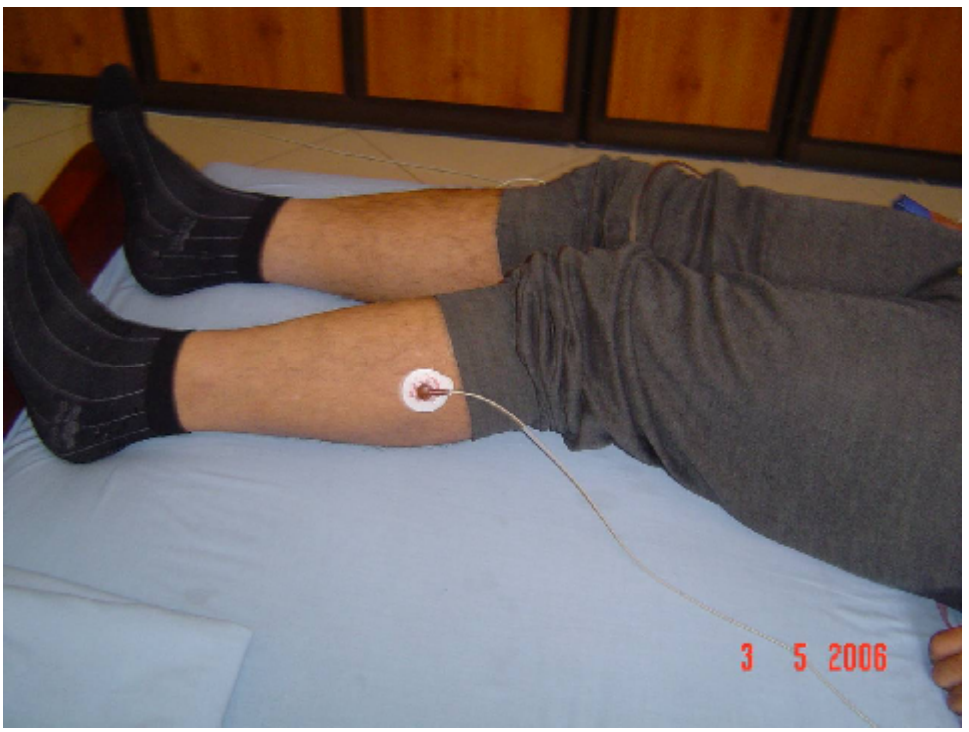
Yoke box for sleep screen

Abdominal and thoracic respiratory effort

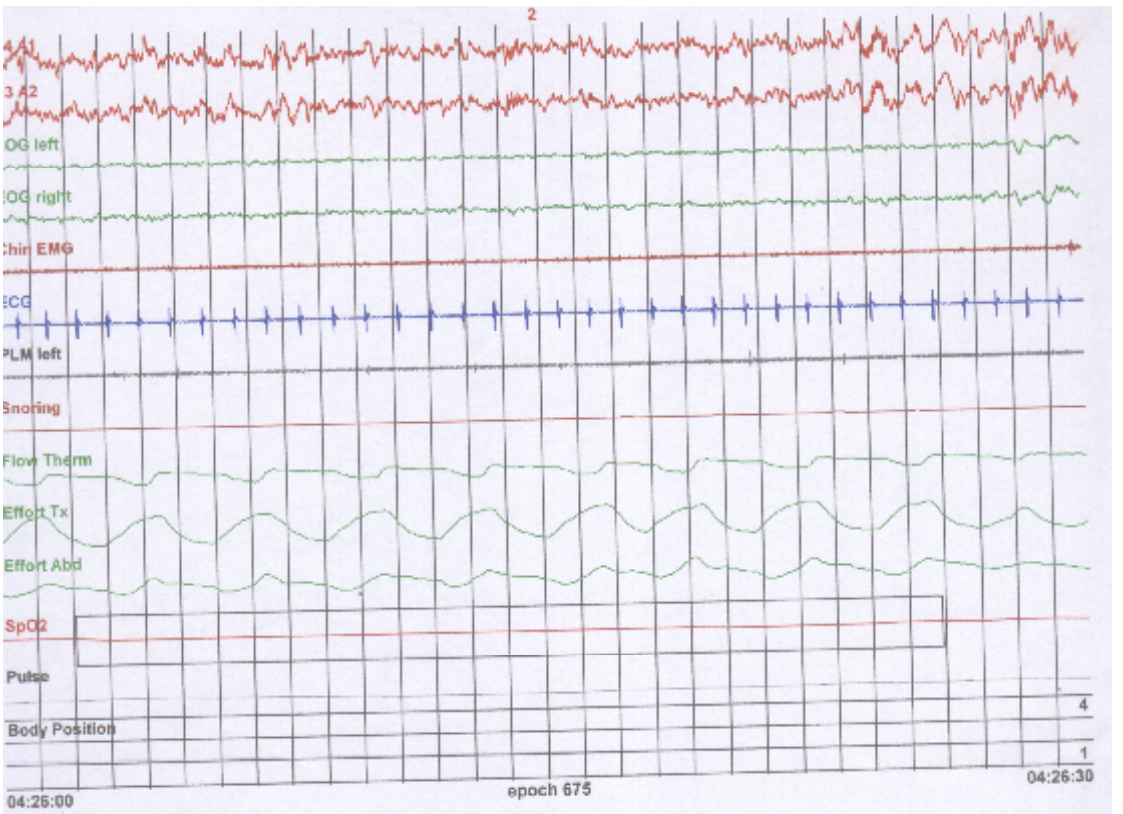


Nasal canula for respiratory airflow

(EMG) electrode
Tracheal microphone



BLM electrode of left leg



Epoch of polysomnography (30 seconds)

Patients subgroups:

- COPD patients were subdivided according AHI into two groups:
  - COPD patients with AHI ≥ 5 (i.e. COPD patients with OSAHS).
  - COPD patients with AHI < 5 (i.e. COPD patients without OSAHS) ***(Guilleminault and Chowdhuris, 2000).***
- And also subdivided according to Berlin questionnaire score into two groups:
  - High risk group to OSA i.e. Berlin score ≥ 2.
  - Low risk group to OSA i.e. Berlin score < 2.

(Netzer et al., 1999)

- Also subdivided according to nocturnal oxygen desaturation (NOD) in to two groups:
  - NOD i:e spending ≥30% of TST with SaO2 <90%
  - Non NOD (i.e. spending < 30% of TST with SaO2 < 90%) ***(Gay 2004).***

Statistical analysis:

- Data was analyzed using SPSS (Statistical Package for Social Sciences) version 10.
- Qualitative data was presented as number and percent. Comparison between groups was done by Chi-square test.
- Quantitative data was tested for normality by Kolmogrov-Smirnov test.
- Normally distributed data was presented as mean ± SD. Student t-test was used to compare between two groups. Non parametric variables were presented as Median (min – max) and Mann-Whitney test (U test) was used to compare between two groups.

- Pearson's correlation coefficient was used to test correlation between variables. A statistical index of the degree of linear dependence between the pair of values taken by observation of two variables. By definition, this must lie between +1 and –1, being positive if the two variables increase or decrease together. A zero correlation coefficient (r) implies a complete absence of correlation.
- $P < 0.05$ was considered to be statistically significant.

Results

This study was done on 50 patients of stable COPD (irreversible obstructive airway disease (FEV1/FVC < 70%) and < 12% improvement in FEV1 expressed as percentage of predictor after inhalation of B_2 agonists.

Table (1): Demographic data of the studied COPD patients.

	Studied COPD patients Mean ± SD
Age (years) Smoking indices (pack/years) Duration of COPD (years) BMI (kg/m^2) Neck circumference (cm)	**52.26 ± 8.02** **24.24 ± 10.07** **8.24 ± 3.96** **29.48 ± 5.04** **42.0 ± 4.55**

This table demonstrates the demographic data of the studied COPD patients, the mean ages of COPD patients was 52.26 ± 8.02 years, the mean smoking indices was 24.24 ± 10.07 packs/year, mean duration of COPD patients was 8.24 ± 3.96 years, mean BMI was 29.48 ± 5.04 kg/m^2, and the mean neck circumference was 42.0 ± 4.55 cm.

Table (2): Stages of COPD in the studied COPD patients.

Stages of COPD	Studied COPD patients	
	No	**%**
Stage I	**0**	**0%**
Stage II	**26**	**52%**
Stage III	**24**	**48%**

Stage IV	**0**	**0%**
Total	**50**	**100%**

This table shows stages of COPD patients in the studied group, 26 patients (52%) were in stage II, 24 patients (48%) were in stage III, however, there were no cases in stage I and stage IV.

Table (3): Distribution of the studied COPD patients according to AHI.

	No	%
AHI ≥ 5 (OSAHS)	**38**	**76%**
AHI < 5	**12**	**24%**
Total	**50**	**100%**

COPD patients were subdivided into two groups [COPD patients with AHI ≥ 5 (38 cases out of 50) (76%) which define overlap syndrome (COPD with OSAHS) and COPD with AHI < 5 (12 cases out of 50) (24%)].

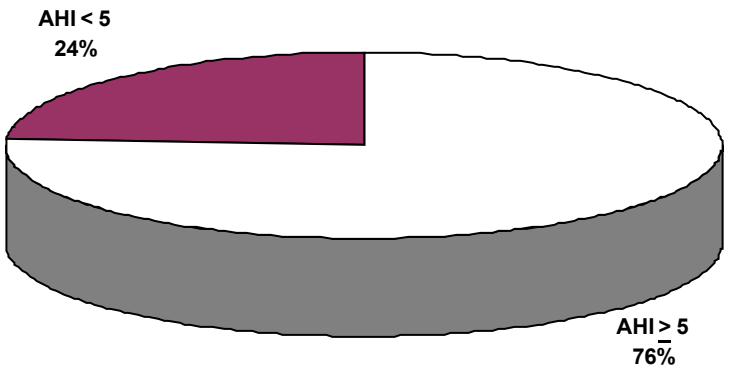


Fig (1): Distribution of the studied COPD patients according to AHI.

Table (4): Berlin questionnaire score in COPD patients with AHI ≥ 5 versus COPD patients with AHI < 5.

Berlin questionnaire score	**COPD with AHI ≥ 5 (n = 38)**		**COPD with AHI < 5 (n = 12)**	
	No	**%**	**No**	**%**
0	**3**	**7.9%**	**10**	**83.3%**
1	**2**	**5.3%**	**1**	**8.3%**
2	**7**	**18.4%**	**0**	**0%**
3	**26**	**68.4%**	**1**	**8.3%**

This table shows score of Berlin questionnaire in COPD patients with AHI ≥ 5 versus COPD patients with AHI < 5. The majority of COPD with AHI ≥ 5 (68.4%) were having the highest Berlin score (3). However, the majority of COPD patients with AHI < 5 (83.3%) were having the lowest Berlin score (0).

Table (5): Comparison between high risk group to OSA versus low risk group to OSA according to Berlin Questionnaire as regard to neck circumference, BMI, Epworth score and AHI.

	Berlin Questionnaire		**Test of significance**
	High risk to OSA (n = 34)	**Low risk to OSA (n = 16)**	
Neck circumference Mean ± SD	42.38 ± 4.9	41.18 ± 3.74	t = 0.863 P = 0.4
BMI Mean ± SD	30.7 ± 4.69	26.8 ± 4.8	t = 2.7 P = 0.009
Epworth score Mean ± SD	11.47 ± 3.75	4.69 ± 2.47	t = 6.574 P = 0.000
AHI Median (min – max)	30.35 0.0 – 98.2	4.5 1 – 10	U = 29.0 P = 0.001

* High risk to OSA i.e. have Berlin score ≥ 2
* Low risk to OSA i.e. have Berlin score < 2

This table shows a significant higher BMI in high risk group to OSA (30.7 ± 4.69) versus low risk group to OSA (26.8 ± 4.8) (P = 0.009) and there were a significant higher Epworth score in high risk group to OSA (11.47 ± 3.75) versus low risk group to OSA (4.69 ± 2.47) (P = 0.000), also there were a significant higher Median AHI in high risk group to OSA 30.35 versus low risk group to OSA 4.5 (P = 0.001). However, there were no significant difference in neck circumference between high risk group to OSA (42.38 ± 4.9) versus low risk group to OSA (41.81 ± 3.7) (P = 0.4).

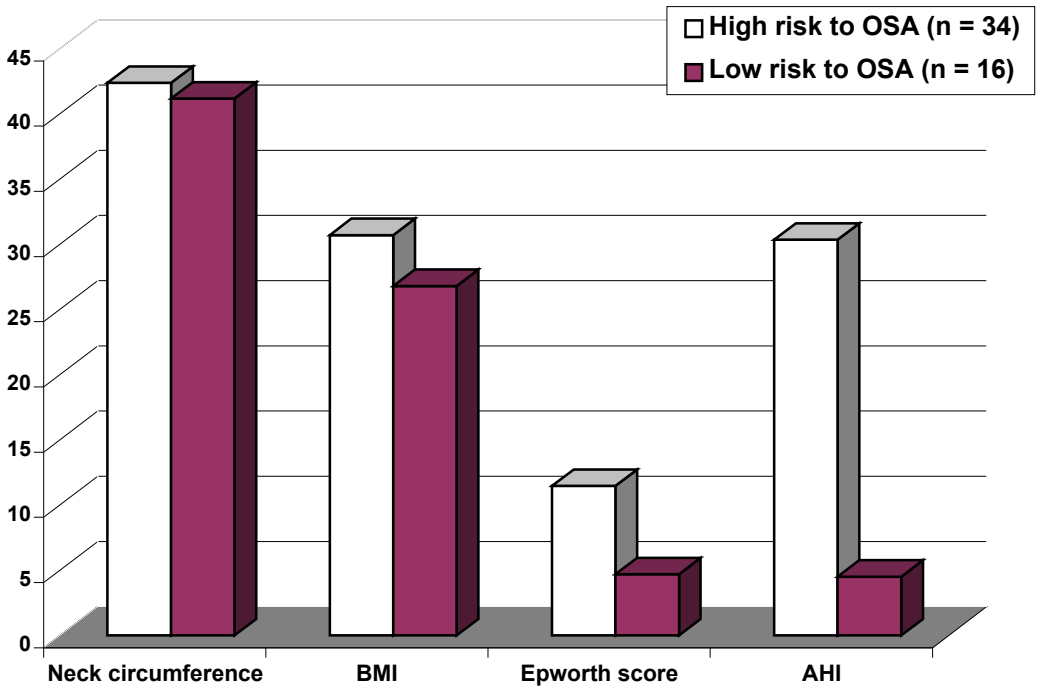


Fig (2): Comparison between high risk group to OSA versus low risk group to OSA according to Berlin Questionnaire as regard to neck circumference, BMI, Epworth score and AHI.

Table (6): Comparison between high risk group to OSA versus low risk groups to OSA according to Berlin questionnaire as regard spirometric pulmonary function tests.

	Berlin Questionnaire		**Test of significance**
	High risk to OSA (n = 34) Mean ± SD	**Low risk to OSA (n = 16) Mean ± SD**	
FEV1/FVC%	51.3 ± 10.69	58.73 ± 11.8	t = 2.07 P = 0.04
FEV1% of predicted	46.5 ± 10.5	54.4 ± 13.69	t = 2.2 P = 0.03

This table shows that there were a significant lower FEV1/FVC% in high risk group to OSA versus low risk group to OSA (51.3 ± 10.69 versus 58.23 ± 11.8, P = 0.04) and also there were a significant lower FEV1% of

predicted in high risk group to OSA versus low risk group to OSA (46.5 ± 10.5 versus 54.4 ± 13.69, P = 0.03).

Table (7): Comparison between high risk group to OSA versus low risk group to OSA according to Berlin questionnaire as regard awake arterial blood gases.

	Berlin Questionnaire		
	High risk to OSA (n = 34) **Mean ± SD**	**Low risk to OSA (n = 16) Mean ± SD**	**Test of significance**
PaO2	66.4 ± 6.4	66.9 ± 6.9	t = 0.172 P = 0.86
PaCO2	42.14 ± 6.2	41.69 ± 5.8	t = 0.250 P = 0.803
pH	7.38 ± 2.89	7.39 ± 2.76	t = 1.3 P = 0.192

This table shows no significant difference in PaO2 in high risk group to OSA (66.4 ± 6.4) versus low risk group to OSA (66.9 ± 6.9) (P = 0.86) and also there were no significant difference in PaCO2 in high risk group to OSA (42.14 ± 6.2) versus low risk group to OSA (41.69 ± 5.8) (P = 0.803) and there were no significant difference in pH in high risk group to OSA (7.38 ± 2.39) versus low risk group to OSA (7.39 ± 2.76) (P = 0.192).

Table (8): Comparison between high risk group to OSA versus low risk group to OSA according to Berlin questionnaire as regard parameters of nocturnal O2 desaturation.

	Berlin Questionnaire		**Test of significance**
	High risk to OSA (n = 34)	**Low risk to OSA (n = 16)**	
Basal SaO2 **Mean ± SD**	91.9 ± 1.8	91.9 ± 1.9	t = 0.001 P = 0.999
Minimum SaO2 **Mean ± SD**	75.94 ± 14.5	78 ± 16.63	t = 0.43 P = 0.67
Index of nocturnal oxygen desaturation (events/hrs) Median **(min – max)**	15.5 0.0 – 103	2.0 0.0 – 58.0	U = 113.5 P = 0.001
Average duration of nocturnal oxygen desaturation (seconds/event) Median **(min – max)**	40 (0 – 98)	33 (0 – 86)	U = 240.3 P = 0.313

This table shows a higher significant Median of index of nocturnal O2 desaturations in high risk group to OSA (15.5) versus low risk group to OSA (2) (P = 0.001). However, there were no significant difference in basal SaO2 between high risk group to OSA (91.9 ± 1.8) versus low risk to OSA group (91.9 ± 1.9) (P = 0.99), there were no significant difference in minimum SaO2 between high risk group to OSA (75.94 ± 14.5) versus low risk group to OSA (78 ± 16.63) (P = 0.67) and also there were no significant difference in Median of average duration of nocturnal O2 desaturation in high risk group to OSA (40) versus low risk group to OSA (33) (P = 0.313).

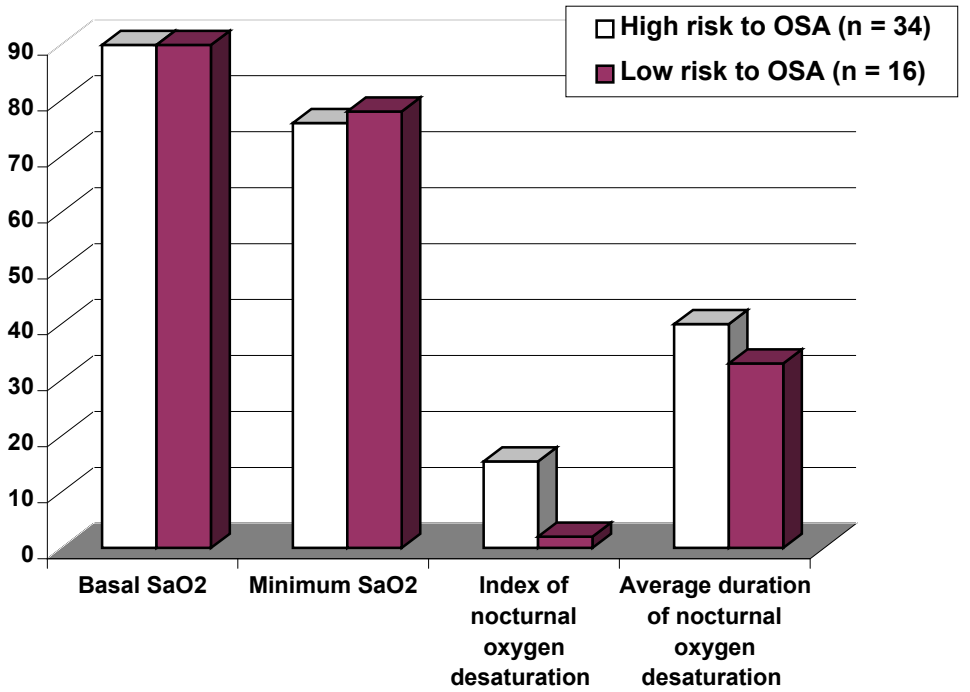


Fig (3): Comparison between high risk group to OSA versus low risk group to OSA according to Berlin questionnaire as regard parameters of nocturnal O2 desaturation.

Table (9): Sensitivity and specificity of Berlin questionnaire score in comparison to AHI score.

Berlin questionnaire score	**AHI score**		**Total**
	Positive to OSA (AHI ≥ 5)	Negative to OSA (AHI < 5)	
Positive (High risk to OSA)	33	1	34
Negative to (Low risk to OSA)	5	11	16
Total	38	12	50

Sensitivity = 86.8% Specificity = 91.7%
Positive predictive value = 97.1% Negative predictive value = 68.8%

This table shows sensitivity and specificity of Berlin questionnaire score in comparison to AHI score there were 33 COPD patients with true positive (positive by both Berlin questionnaire score and AHI score) while there were 11 COPD patients with true negative (negative by both Berlin questionnaire score and AHI score), 5 COPD patients were false negative (negative by Berlin questionnaire score and positive by AHI

score) and only one COPD patient was false positive (positive by Berlin questionnaire score and negatives by AHI score). So sensitivity of Berlin questionnaire was 86.8%, specificity of Berlin questionnaire was 91.7%, positive predictive value was 97.1% and negative predictive value was 68.8%.

Table (10): Percentage of mixed apneas versus obstructive apneas in studied COPD patients with abnormal AHI.

	Mixed apneas No (%)	**Obstructive apneas No (%)**	**Total No (%)**
AHI ≥ 5	21 (42%)	17 (34%)	38 (76%)
AHI ≥ 10	20 (40%)	7 (12%)	27 (54%)
AHI ≥ 15	19 (38%)	1 (2%)	20 (40%)
AHI ≥ 20	19 (38%)	0 (0%)	19 (38%)

Thirty eight patients (76%) of COPD patients were having AHI ≥ 5 (21 COPD patients with mixed apneas "42%" and 17 COPD patients with obstructive apneas "34%"). If we consider AHI ≥ 10, there were 27 cases (54%) of COPD patients (20 COPD patients with mixed apneas "40%" and 7COPD patients with obstructive apneas "14%"), if we consider AHI ≥ 15 there were 20 COPD patients (40%) (19 COPD patients with mixed apneas "38%" and only one COPD patient with obstructive apneas "2%"), and if we consider AHI ≥ 20 there were 19 COPD patients (38%) all were mixed apneas.

Table (11): Correlations between AHI and neck circumference, BMI, Epworth score and Berlin questionnaire score.

	AHI	
	r	P
Neck circumference (cm)	0.353	0.001
BMI (kg/m^2)	0.391	0.005

Epworth score	0.733	0.000
Berlin questionnaire score	0.627	0.000

This table shows correlations between AHI and neck circumference, BMI, Epworth score, and Berlin questionnaire score. There were a significant positive correlation between AHI and neck circumference, BMI, Epworth score and Berlin questionnaire (r = 0.353, P = 0.001; r = 0.391, P = 0.005; r = 0.733, P = 0.000 and r = 0.627, P = 0.000 respectively).

Table (12): Correlations between AHI and spirometric pulmonary function tests.

	AHI	
	r	P
FEV1/FVC %	- 0.384	0.006
FEV1 % of predicted	- 0.326	0.02

This table shows correlations between AHI and spirometric pulmonary function tests. There were a significant negative correlations between AHI and both FEV1/FVC % (r = - 0.384, P = 0.006) and FEV1 % of predicted (r = - 0.326, P = 0.02).

Table (13): Correlations between AHI and awake arterial blood gases.

	AHI	
	r	P
PaO2	- 0.150	0.287
PaCO2	0.241	0.09
pH	0.149	0.303

This table shows correlations between AHI and awake arterial blood gases. There were no significant correlation between AHI and PaO2, PaCO2 & pH (r = -0.150, P = 0.287; r = 0.240, P = 0.09; r = 0.303, P = 0.303 respectively).

Table (14): Correlations between AHI and parameter of nocturnal O2 desaturation.

	AHI	
	r	P
Basal SaO2	- 0.214	0.126
Minimum SaO2	- 0.284	0.04
Index of nocturnal O2 desaturation	0.739	0.000
Average duration of nocturnal oxygen desaturation	0.034	0.817

This table shows correlations between AHI and parameters of nocturnal O2 desaturation. There were a significant positive correlation between AHI and index of nocturnal O2 desaturation (r = 0.739, P = 0.000) and there were a significant negative correlation between AHI and minimum SaO2 (r = - 0.284, P = 0.04), however there were no significant correlations between AHI with both basal SaO2 and average duration of nocturnal oxygen desaturation (r = - 0.214, P = 0.126; r = 0.034, P = 0.817 respectively).

Table (15): Comparison of COPD patients with AHI ≥ 5 versus COPD patients with AHI < 5 as regard to neck circumference, BMI, Epworth score and Berlin questionnaire score.

	COPD with AHI ≥ 5 (n = 38) Mean ± SD	**COPD with AHI < 5 (n = 12) Mean ± SD**	**Test of**

			significance
Neck circumference (cm)	42.29 ± 4.65	41.68 ± 4.3	t = 0.797 P = 0.4
BMI (kg/m^2)	30.23 ± 5.02	27.17 ± 4.7	t = 1.87 P = 0.06
Epworth score	11.03 ± 3.96	3.83 ± 0.72	t = 10.67 P = 0.000
Berlin questionnaire score	2.47 ± 0.92	0.33 ± 0.89	t = 7.068 P = 0.000

Thirty eight patients (76%) of COPD patients were having AHI ≥ 5 while 12 patients (24%) of COPD patients were having AHI < 5.

The Epworth score was significantly higher in COPD patients with AHI ≥ 5 versus COPD patients with AHI < 5 (11.03 ± 3.96 vs 3.83 ± 0.72, P = 0.000) and also Berlin questionnaire score was significantly higher in COPD patients with AHI ≥ 5 versus COPD patients with AHI < 5 (2.47 ± 0.92 vs 0.33 ± 0.89, P = 0.000). However, there were no significant difference in BMI in COPD patients with AHI ≥ 5 (30.23 ± 5.01) versus COPD with AHI < 5 (27.2 ± 4.7) (P = 0.06) and also there were no significant difference in neck circumference in COPD patients with AHI ≥ 5 (42.3 ± 4.7) versus COPD patients with AHI < 5 (41.68 ± 4.3) (P = 0.4).

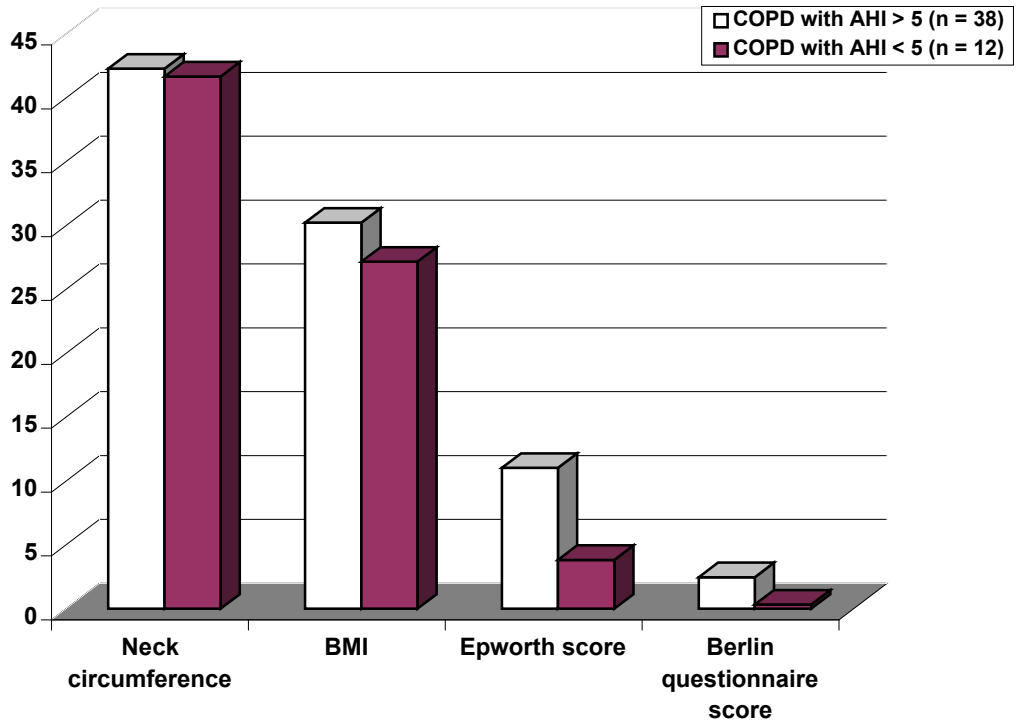


Fig (4): Comparison of COPD patients with AHI ≥ 5 versus COPD patients with AHI < 5 as regard to neck circumference, BMI, Epworth score and Berlin questionnaire score.

Table (16): Comparison of COPD patients with AHI ≥ 5 versus COPD patients with AHI < 5 as regard to spirometric pulmonary function tests.

	COPD with AHI ≥ 5 (n = 38) Mean ± SD	**COPD with AHI < 5 (n = 12) Mean ± SD**	**Test of significance**
FEV1/FVC %	52.09 ± 11.39	57.95 ± 10.79	t = 1.57 P = 0.122
FEV1 % of predicted	47.37 ± 11.81	54.2 ± 11.79	t = 1.74 P = 0.08

This table shows comparison between COPD patients with AHI ≥ 5 and COPD patients with AHI < 5 as regard spirometric pulmonary function tests. There were no significant difference in FEV1/FVC% in COPD patients with AHI ≥ 5 (52.09 ± 11.39) versus COPD patients with AHI < 5 (57.95 ± 10.79) (P = 0.12) and also there were no significant difference in FEV1% of predicted in COPD patients with AHI ≥ 5 (47.37 ± 11.8) versus COPD with AHI < 5 (54.2 ± 11.8) (P = 0.08).

Table (17): Comparison of COPD patients with AHI ≥ 5 versus COPD patients with AHI < 5 as regard awake arterial blood gases.

	COPD with AHI ≥ 5 (n = 38) Mean ± SD	**COPD with AHI < 5 (n = 12) Mean ± SD**	**Test of significance**
PaO2	65.6 ± 5.6	69.58 ± 9.13	t = 1.4 P = 0.164
PaCO2	42.29 ± 6.3	41.08 ± 5.09	t = 0.603 P = 0.549
pH	7.39 ± 2.99	7.40 ± 2.22	t = 1.78 P = 0.08

This table shows comparison between COPD patients with AHI ≥ 5 versus COPD patients with AHI < 5 as regard awake arterial blood gases. There were no significant difference in PaO2 in COPD patients with AHI ≥ 5 (65.6 ± 5.6) versus COPD patients with AHI < 5 (69 ± 9.13) (P = 0.16), also there were no significant difference in PaCO2 in COPD patients with AHI ≥ 5 (42.23 ± 6.3) versus COPD patients with AHI < 5 (41.08 ± 5.09) (P = 0.54) and there were no significant difference in pH in COPD patients with AHI ≥ 5 (7.39 ± 2.9) versus COPD patients with AHI < 5 (7.4 ± 2.2) (P = 0.08).

Table (18): Comparison of COPD patients with AHI ≥ 5 versus COPD patients with AHI < 5 as regard to parameters of nocturnal O2 desaturation.

	COPD with AHI ≥ 5 (n = 38)	**COPD with AHI < 5 (n = 12)**	**Test of significance**
Basal SaO2 (Mean ± SD)	92.57 ± 2.5	93.7 ± 3.0	t = 0.03 P = 0.97
Minimum SaO2 (Mean ± SD)	76.8 ± 11.005	83 ± 6.4	t = 0.353 P = 0.7
Index of nocturnal oxygen desaturation (events/hrs) Median (min – max)	24.5 (1 – 103)	2.0 (0.0 – 23.0)	U = 40.0 P = 0.000
Average duration of nocturnal oxygen desaturation (seconds/event) Median (min – max)	40 (12 – 98)	30 (0 – 86)	U = 167 P = 0.165

This table shows comparison between COPD patients with AHI ≥ 5 versus COPD patients with AHI < 5 as regard to parameters of nocturnal O2 desaturation. There were a significant higher Median of index of nocturnal O2 desaturation in COPD patients with AHI ≥ 5 (24.50) versus COPD with AHI < 5 (2.0) (P = 0.000). There were no significant difference in mean of basal SaO2 in COPD patients with AHI ≥ 5 (92.57 ± 2.5) versus COPD patients with AHI < 5 (93.7 ± 3.0) (P = 0.97). There were no significant difference in the mean of minimum SaO2 in COPD patients with AHI ≥ 5 (76.8 ± 11.005) versus COPD patients with AHI < 5 (83.0 ± 6.4) (P = 0.7) and there was no significant difference in Median of average duration of nocturnal oxygen desaturation in COPD patients with AHI ≥ 5 (40.0) versus COPD with AHI < 5 (30) (P = 0.165).

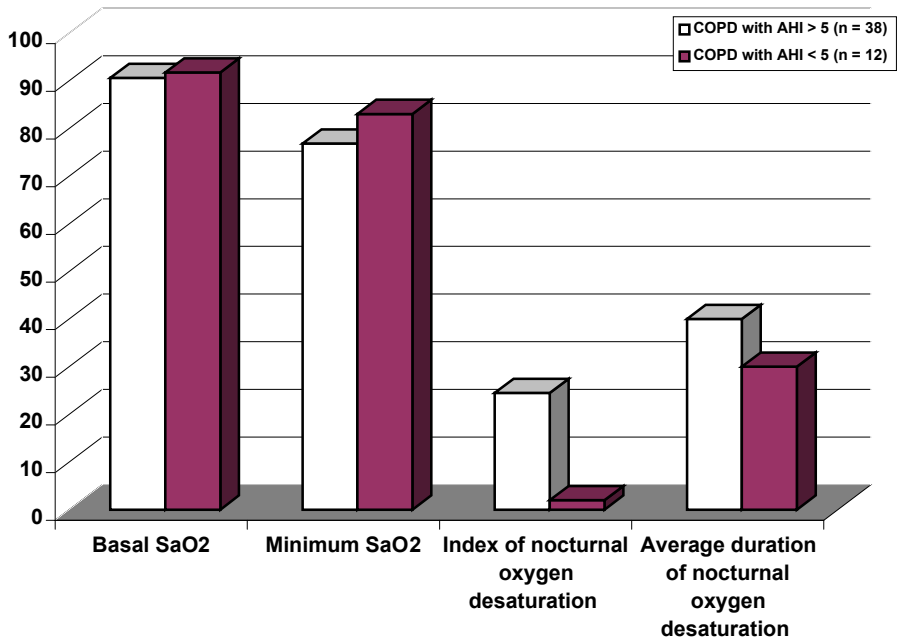


Fig (5): Comparison of COPD patients with AHI ≥ 5 versus COPD patients with AHI < 5 as regard to parameters of nocturnal O2 desaturation.

Table (19): Comparison between COPD patients with AHI ≥ 5 versus COPD patients with AHI < 5 as regard to NOD.

	AHI > 5 (n = 38)		AHI < 5 (n = 12)		P value
	No	**%**	**No**	**%**	
Nocturnal O2 desaturator (n = 32)	**32**	**84.2**	**0**	**0**	**$\chi 2 = 28.07$ < 0.001**
Non nocturnal O2 desaturator (n = 18)	**6**	**15.8**	**12**	**100**	

NOD in COPD patients with AHI ≥ 5 (32 out of 38) were significantly higher than COPD patients with AHI < 5 (0 out of 12) (84.2% vs 0% P < 0.001). NOD in COPD patients were found in 32 cases out of 50 (64%) with all cases were found in those with AHI ≥ 5.

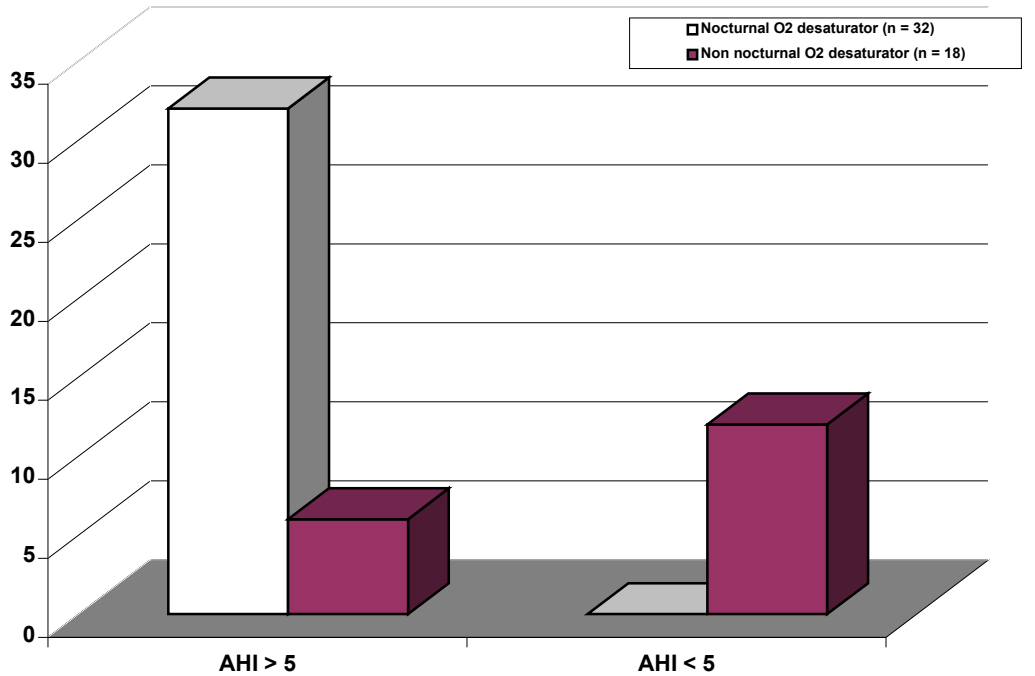


Fig (6): Comparison between COPD patients with AHI ≥ 5 versus COPD patients with AHI < 5 as regard to NOD.

Table (20): Comparison of COPD patients with nocturnal O2 desaturator versus COPD patients without nocturnal O2 desaturator as regard to neck circumference, BMI, Epworth score and Berlin questionnaire score.

	Nocturnal O2 desaturator (n = 32) Mean ± SD	**Non nocturnal O2 desaturator (n = 18) Mean ± SD**	**Test of significance**
Neck circumference (cm)	42.5 ± 4.52	41.1 ± 4.6	T = 1.036 P = 0.305
BMI (kg/m^2)	30.53 ± 4.97	27.6 ± 4.7	T = 2.030 P = 0.058
Epworth score	11.09 ± 3.7	6.1 ± 4.4	T = 4.221 P = 0.000
Berlin questionnaire score	2.5 ± 0.87	1.0 ± 1.3	T = 4.180 P = 0.000

Thirty two patients (64%) of COPD patients were having nocturnal O2 saturation < 90% for ≥ 30% of total sleep time (desaturators) while 18 patients (36%) of COPD patients were non desaturators.

Epworth score was significantly higher in nocturnal O2 desaturators (11.09 ± 3.7) vs non desaturator (6.0 ± 4.4) (P = 0.000) and also Berlin questionnaire was significantly higher in nocturnal O2 desaturators (2.5 ± 0.87) vs non desaturators (1 ± 1.3) (P = 0.000). However, neck circumference was not significantly different in nocturnal O2 desaturators (42.5 ± 4.52) vs non desaturators (41.1 ± 4.6) (P = 0.3). BMI was not significantly different in nocturnal O2 desaturators (30.53 ± 4.97 vs non desaturators 27.6 ± 4.7, P = 0.058).

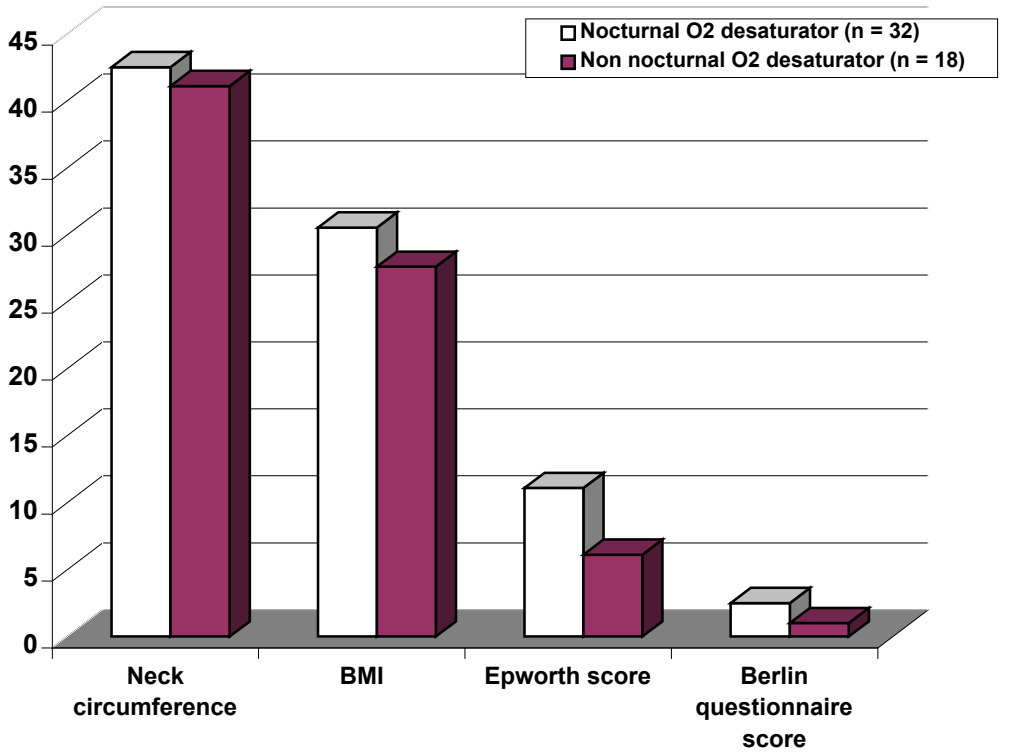


Fig (7): Comparison of COPD patients with nocturnal O2 desaturator versus COPD patients without nocturnal O2 desaturator as regard to neck circumference, BMI, Epworth score and Berlin questionnaire score.

Table (21): Comparison of COPD patients with nocturnal O2 desaturator versus COPD patients without nocturnal O2 desaturator as regard to spirometric pulmonary function tests.

	Nocturnal O2 desaturator (n = 32) Mean ± SD	**Non nocturnal O2 desaturator (n = 18) Mean ± SD**	**Test of significance**
FEV1/FVC %	51.9 ± 11.6	56.28 ± 10.69	T = 1.303 P = 0.199
FEV1 % of predicted	48.04 ± 11.79	51.05 ± 12.04	T = 0.860 P = 0.394

There was no significant difference in FEV1/FVC% in nocturnal O2 desaturators (51.9 ± 11.6) vs non desaturators (56.28 ± 10.69) (P = 0.19) and also FEV1% of predicted was not significantly different in nocturnal

O2 desaturators (48.04 ± 11.79) vs non desaturators (51.05 ± 12.04) (P = 0.39).

Table (22): Comparison of COPD patients with nocturnal O2 desaturator versus COPD patients without nocturnal O2 desaturator as regard to awake arterial blood gases.

	Nocturnal O2 desaturator (n = 32) Mean ± SD	**Non nocturnal O2 desaturator (n = 18) Mean ± SD**	**Test of significance**
PaO2	66.08 ± 5.84	68.53 ± 8.15	T = 1.293 P = 0.202
PaCO2	43.2 ± 6.39	39.83 ± 4.6	T = 2.157 P = 0.036
pH	7.38 ± 3.0	7.39 ± 2.6	T = 0.623 P = 0.536

There were significantly higher PaCO2 in nocturnal O2 desaturators (43.2 ± 6.39) vs non desaturators (39.83 ± 4.6) (P = 0.03). However, there were no significant difference in PaO2 in nocturnal O2 desaturators (66.08 ± 5.84) vs non desaturators (68.53 ± 8.15) (P = 0.3) and also there were no significant difference in pH in nocturnal O2 desaturators (7.38 ± 3.0) vs non desaturators (7.39 ± 2.6) (P = 0.53).

Table (23): Comparison of COPD patients with nocturnal O2 desaturator versus COPD patients without nocturnal O2 desaturator as regard to parameters of nocturnal O2 desaturation.

	Nocturnal O2 desaturator (n = 32) Mean ± SD	**Non nocturnal O2 desaturator (n = 18) Mean ± SD**	**Test of significance**
Basal SaO2 (Mean ± SD)	92.08 ± 2.08	94.17 ± 2.88	T = 1.682 P = 0.099
Minimum SaO2 (Mean ± SD)	76.59 ± 10.75	81.22 ± 9.25	T = 1.534 P = 0.132
Index of nocturnal oxygen desaturation (events/hrs) Median (min – max)	31 (13 – 103)	3.5 (0.0 – 35.0)	U = 61.500 P = 0.000
Average duration of nocturnal oxygen desaturation Median (seconds/event) (min – max)	47 (16 – 98)	27.5 (0 – 77)	U = 166.50 P = 0.014

There were significantly higher median index of nocturnal O2 desaturation in nocturnal O2 desaturators (31) vs non desaturators (3.5) (P = 0.000) and also there were significantly higher median of average duration of nocturnal O2 desaturation in nocturnal O2 desaturators (47) vs non desaturators (27.5) (P = 0.01). While, there were no significant difference in basal SaO2 in nocturnal O2 desaturators (92.08 ± 2.08) vs non desaturators (94.17 ± 2.88) (P = 0.09) and also there were no significant difference in minimum SaO2 in nocturnal O2 desaturators (76.59 ± 10.75) vs non desaturators (81.22 ± 9.25) (P = 0.132).

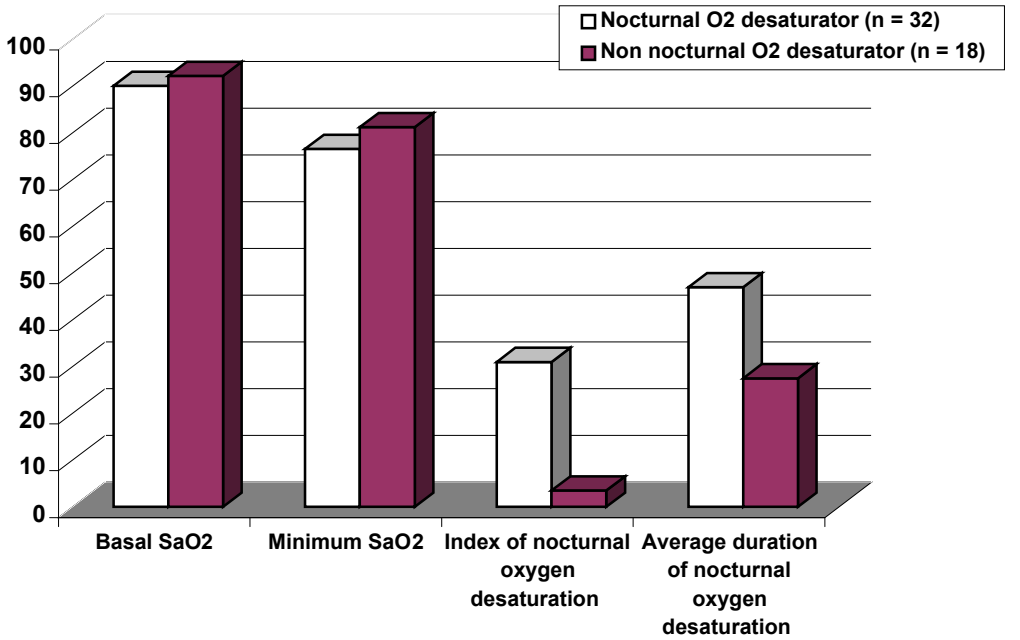


Fig (8): Comparison of COPD patients with nocturnal O2 desaturator versus COPD patients without nocturnal O2 desaturator as regard to parameters of nocturnal O2 desaturation.

Case No (2)

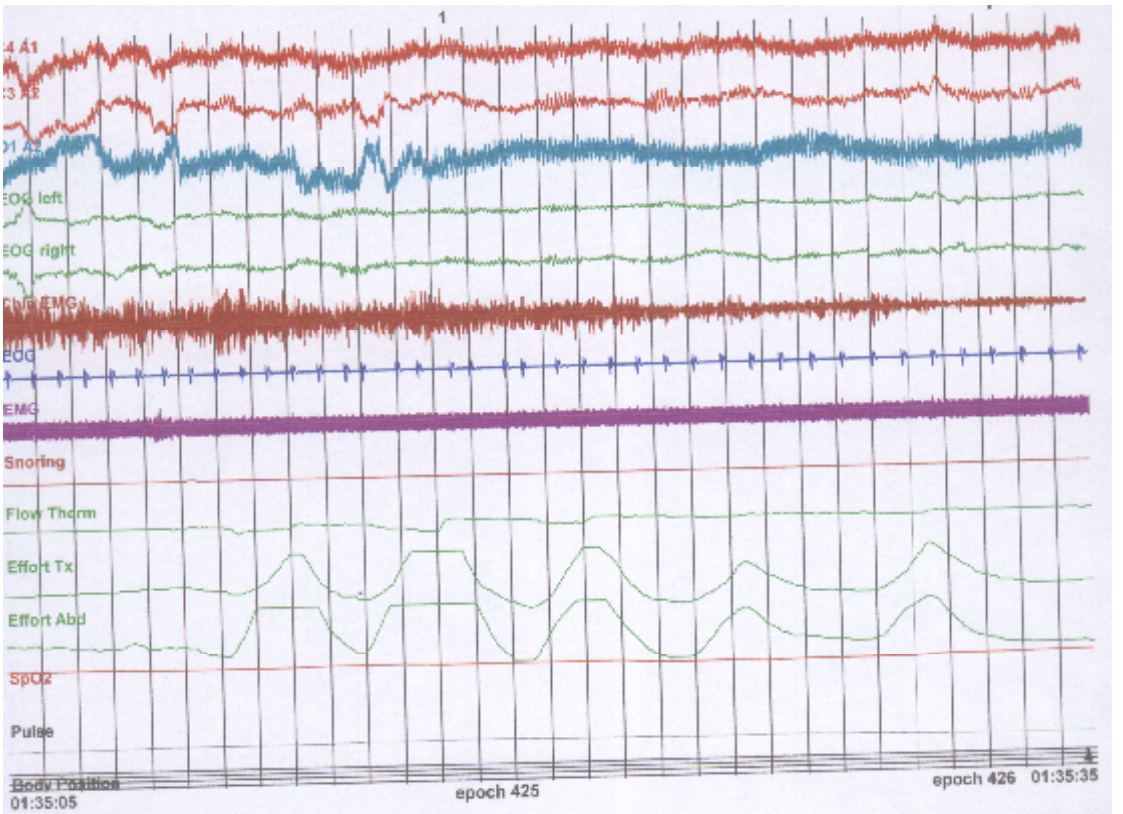


Fig (9): Epoch of polysomnography (Obstructive apnea).

Case No (6)

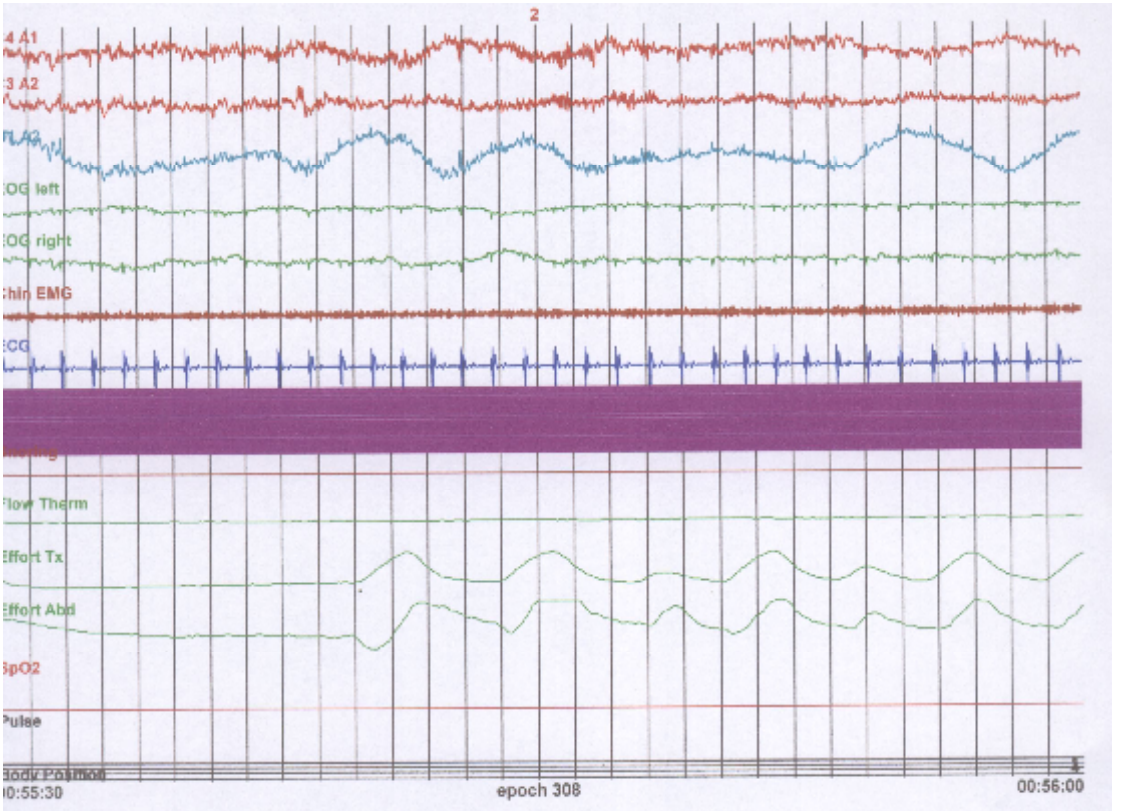


Fig (10): Epoch of polysomnography (Mixed apnea).

Case No (8)

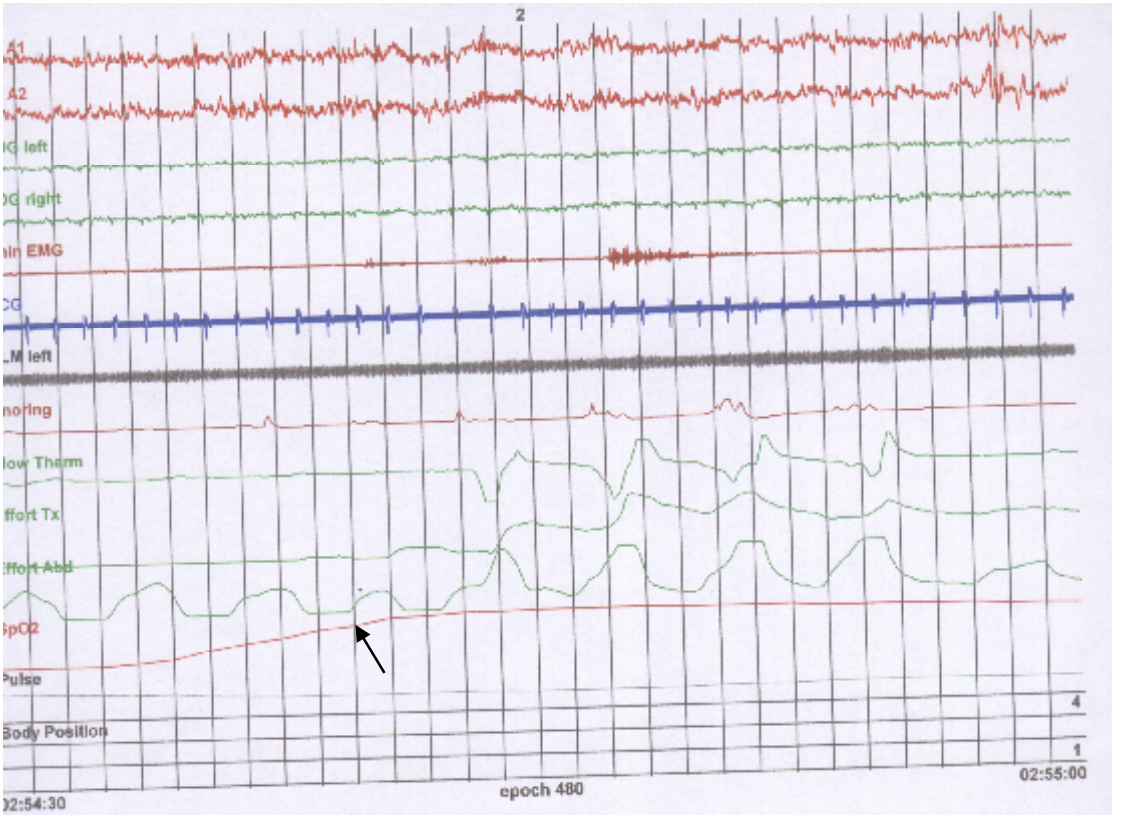


Fig (11): Epoch of polysomnography (nocturnal oxygen desaturator).

DISCUSSION

Sleep has well recognized effect on breathing, including changes in central respiratory control, airway resistance, and muscular contractility which don't have an adverse effect in healthy individuals but may cause problems in patients with COPD. Sleep related hypoxemia and hypercapnia are well recognized in COPD and are most pronounced in REM, however sleep studies are usually only indicated in patients with COPD when there is a possibility of sleep apnea or when corpulmonale and/or polycythemia are not explained by the awake PaO2 level ***(Mcnicholas, 2000).***

Nocturnal O2 desaturation (NOD) has long been recognized in COPD patients, who may spend ≥ 30% of sleep time with oxygen saturation < 90% mostly during REM sleep. The degree of nocturnal O2 desaturation differs markedly among COPD patients and is often difficult to predict, nocturnal hypoxaemia is affected by comorbidities such as OSA ***(Gay, 2004).***

The aim of this study was to determine the rate of occurrence of nocturnal oxygen desaturators in COPD patients with or without OSAHS and to determine the predictors of OSAHS and nocturnal oxygen desaturators in COPD patients.

This study was done on 50 patients of stable COPD (irreversible obstructive airway disease i:e FEV1/FVC < 70%) and < 12% improvement in FEV1 expressed as percentage of predictor after inhalation of B2 agonists.

The mean age of the studied group was 52.26 ± 8.02 years with mean BMI was 29.48 ± 5.04 kg/m2 and the mean neck circumference was 42 ± 4.55 cm. The highest percentage of COPD patients in this study were in stage II (52%) while with lower percentage of COPD patients in this study were in stage III (48%), with no cases in stage I and IV (0%). The studied COPD patients were subdivided according to AHI into two groups. COPD with AHI ≥ 5 events/hour (38 cases out of 50) 76%, which define overlap syndrome (COPD with OSAHS) and COPD with AHI < 5 events/hour (12 cases out 50) 24%.

Also subdivided according to Berlin questionnaire into high risk group to OSA and low risk group to OSA. High risk group were having

Berlin score ≥ 2 (34 cases), low risk group were having Berlin score < 2 (16 cases).

This study shows that the majority of studied COPD patients with AHI ≥ 5 (68.4%) were having the highest Berlin score (3) while the majority of COPD patients with AHI < 5 (83.3%) were having the lowest Berlin score (0). This signify that the high Berlin score can predict COPD patients with AHI ≥ 5.

There were significantly higher BMI in high risk group to OSA vs low risk group to OSA (30.7 ± 4.69) vs (26.8 ± 4.8) (P = 0.009). This signify that the results of category of high risk to OSA according to Berlin questionnaire was in accordance to a known risk factor for OSA like higher BMI. Also, there were significantly higher Epworth score in high risk to OSA vs low risk to OSA (11.47 ± 3.75 vs 4.69 ± 2.47) (P = 0.000). This signify that the Berlin questionnaire results were in accordance to the results of the previously known Epworth score, which consider values above 10 is abnormal ***(Schwab et al., 1998).*** The median of AHI was significantly higher in high risk group to OSA vs low risk to OSA [30.35 vs 4.5 P = 0.001]. This demonstrate that Berlin questionnaire was considered a good subjective test for OSA.

However, neck circumference was not significantly different in high risk group to OSA vs low risk group to OSA (42.38 ± 4.9 vs 41.18 ± 3.74, P = 0.4). This can be explained by the total mean of neck circumference of all studied COPD patients was small (42 ± 4.55) which was lower than reported to be risky to OSA in male as reported by ***Schwab et al. (1998)*** who report 42.5cm, also in ***Woodson et al. (1997)*** who reported that a neck circumference larger than 43.7 cm in male

increase the odds (2.2) of OSA syndrome due to increase amount of fat in the neck.

There were a significantly lower FEV1/FVC% in high risk group to OSA vs low risk group to OSA (51.3 ± 10.69 vs 58 ± 11.8, P = 0.04) and also there were significantly lower FEV1% of predicted in high risk to OSA vs low risk to OSA (46.5 ± 10.5 vs 54.4 ± 13.69, P = 0.03). This mean that Berlin questionnaire consider the more severe airway obstruction was considered a risk factor for OSA.

Arterial blood gases (PaO2, PaCO2 and pH) were not significantly different between high risk to OSA vs low risk to OSA (P = 0.8, 0.8, 0.1 respectively). This illustrate that Berlin questionnaire did not consider arterial blood gases a good predictor to OSA.

The only significant difference between high risk to OSA vs low risk to OSA as regard to parameters of nocturnal O2 desaturation was the median index of nocturnal O2 desaturation [15.5 vs 2, P = 0.001]. While no significant difference between high risk to OSA vs low risk to OSA as regard to basal SaO2, minimum SaO2 and average duration of nocturnal O2 desaturation (P = 0.59, 0.67, 0.31 respectively).

Berlin questionnaire score is a good subjective test for detection of AHI ≥ 5 with sensitivity 86.8% and specificity 91.7%, PPV 97.1% and NPV 68.8% and this was in accordance to ***Alauya-Lamping et al. (2006)*** who reported that Berlin questionnaire is a good subjective test for AHI ≥ 5 with sensitivity 86%, specificity 95%, PPV of 96% and NPV 82%.

Thirty eight patients (76%) of COPD patients were having AHI ≥ 5 (21 COPD patients with mixed apneas “42%” and 17 COPD patients with

obstructive apneas "34%"), while ***Chaouts (2001)*** study reported that 33% of COPD patients were having AHI ≥ 5. If we consider AHI ≥ 10, there were 27 cases (54%) of COPD patients (20 COPD patients with mixed apneas "40%" and 7 COPD patients with obstructive apneas "14%"). While, ***Sander's et al. (2003)*** reported that 13.9% of COPD patients were having AHI ≥ 10, if we consider AHI ≥ 15 there were 20 COPD patients (40%) (19 COPD patients with mixed apneas "38%" and only one COPD patient with obstructive apneas "2%"), while Sander's study reported that 22% of COPD patients were having AHI ≥ 15, and if we consider AHI ≥ 20, there were 19 COPD patients (38%) (all of them were mixed apneas), while ***Alauya-Lamping (2006)*** reported that 11% to 20% of COPD patients with AHI ≥ 20. Our results were higher than reported by ***Chaouts (2001); Sander's (2003) and Alauya-Lamping (2006)*** and this may be due to different number of cases and different severity of COPD patients in different studies, as chaout's study was done on 98 COPD patients with 34% in stage II and 52% in stage IV, while Sander's and Alauya-Lamping studies were done on multicenter study with large number of cases (980, 720 patients respectively) with different stages of COPD, while our study was done on 50 COPD patients with highest percentage in stage II (50%) and low percentage in stage III (48%) and no cases in stage IV.

There were a significant positive correlation between neck circumference and AHI (P = 0.001) this can be explained by the fact that increase amount of fat in the neck plays the largest role in OSA ***(Schwab et al., 1998).*** Also there were a significant positive correlation between BMI and AHI (P = 0.005), this was in accordance to ***Chaout et al. (2001)*** who reported that a significant positive correlation between BMI and AHI (P = 0.02).

Epworth score was also significantly positive correlated with AHI (P = 0.000), this was in accordance to ***Sander's et al. (2003)*** who reported that Epworth score was significantly positive correlated with AHI (P = 0.001). Berlin questionnaire was significantly positive correlated with AHI (P = 0.000), this was in accordance to ***Alaua-Lamping et al. (2006)*** which report that Berlin questionnaire was useful in prediction of AHI ≥ 5 with sensitivity 86% and specificity 95%.

Spirometric pulmonary function tests (FEV1% of predicted and FEV1/FVC%) were significantly negative correlated with AHI (P = 0.02, 0.006 respectively). This was in accordance to ***Chaout (1997)*** who reported that a significant negative correlation between AHI and (FEV1% of predicted and FEV1/FVC%) (P = 0.02, 0.05 respectively). This signify that the more obstructive ventilatory defect, the more AHI and so the more OSA.

Arterial blood gases (PaO2, PaCO2, pH) were not significantly correlated with AHI (P = 0.3, 0.09, 0.31 respectively). This was in accordance to ***Chaout et al. (2001)*** who reported that PaO2 was not significantly correlated with AHI (P = 0.07) however PaCO2 was significantly positive correlated with AHI (P = 0.01). This can be explained by the Chaout's study was done on a larger number of COPD patients (98 patients) with 34% in stage II and 52% in stage IV, while our study was done on 50 patients only categorized mainly in stage II (52%) and with lowest percentage in stage III (48%) with no cases in stage IV.

Minimum SaO2 was significantly negative correlated with AHI (P = 0.04), this was in accordance to ***Little's et al. (1999)*** who reported that minimum SaO2 was significantly negative correlated with AHI (P =

0.001). Also index of nocturnal O2 desturation was significantly positive correlated with AHI (P = 0.000) while no significant correlation between both Basal SaO2 and average duration of nocturnal O2 desaturation and AHI (P = 0.1, 0.8 respectively). While, ***Little's (1999)*** study reported that basal SaO2 was significantly negative correlated with AHI (P = 0.01), while index of nocturnal O2 desaturation and average duration of nocturnal O2 desturation were not reported by Little's study and his study done on 33 patients only i.e. a very small number of COPD patients with mild to normoxic COPD patients.

Epworth score was significantly higher in COPD with AHI ≥ 5 vs COPD with AHI < 5 (11.03 ± 3.96 vs 3.83 ± 0.72, P = 0.000). Berlin questionnaire score was also significantly higher in COPD with AHI ≥ 5 vs COPD with AHI < 5 (2.47 ± 0.92 vs 0.33 ± 0.89 P = 0.000) this was in accordance to ***Alauya-Lamping et al. (2006)*** who reported that Berlin questionnaire was useful in prediction of AHI ≥ 5 with a sensitivity 86% and specificity 95%,in our study neck circumference was not significantly different between COPD with AHI ≥ 5 versus COPD with AHI < 5 (42.29 ± 4.65 vs 41.08 ± 4.3, P = 0.4). This can be explained by the total mean of neck circumference of all studied COPD patients was (42 cm) which was lower than reported to be risky to OSA in male as reported by ***Schwab et al. (1998)*** who report 42.5cm, also ***Woodson et al. (1997)*** reported that a neck circumference larger than 43.7 cm in male increase the odds (2.2) of OSA syndrome due to increase amount of fat in the neck.

BMI was not significantly different in COPD with AHI ≥ 5 vs COPD with AHI < 5 (30.23 ± 5.02 vs 27 ± 9.7, P = 0.06) and also this can be explained by the total mean of BMI in all studied COPD patients

was (29.48) which is below the level of obesity this was in accordance to WHO classification which considered obesity ≥ 30 kg/m2.

There were no significant difference between COPD with AHI ≥ 5 and COPD with AHI < 5 in spirometric pulmonary function tests. FEV1/FVC% (52.09 ± 11.39 vs 57.95 ± 10.79) (P = 0.1) and FEV1% of predicted (47.37 ± 11.81 vs 54.2 ± 11.79) (P = 0.08). These were in accordance to ***Chaout et al. (2001)*** who reported that FEV1/FVC% (36.2 ± 10.3 vs 34.8 ± 8.9, P > 0.05) and FEV1% of predicted (35.4 ± 10.8 vs 33.4 ± 11.6, P > 0.05). So, the spirometric pulmonary function tests were not considered a good predictor to OSA.

There was no significant difference between COPD with AHI ≥ 5 and COPD with AHI < 5 as regard to PaO2 (65.6 ± 5.6 vs 69.58 ± 9.13, P 0.2). This was in accordance to ***Chaout et al. (2001)*** who showed also no significant difference between the two groups as regard to PaO2 (62.8 ± 3 vs 64.2 ± 3.2, P = 0.07). But, ***Little's et al. (1999)*** showed that PaO2 was significantly lower in COPD patients with AHI ≥ 5 vs COPD patients with AHI < 5 (66.2 ± 3.6 vs 74.25 ± 6.2). This can be explained by Little's et al. study was done on small number of cases (only 33 patients of COPD).

As regard to PaCO2, there were no significant difference between COPD patients with AHI ≥ 5 vs COPD with AHI < 5 (42.29 ± 6.3 vs 41.08 ± 5.09, P = 0.5), but ***Chaout's study (2001)*** reported that PaCO2 was significantly higher in COPD patients with AHI ≥ 5 vs COPD with AHI < 5 (44.9 ± 4.9 vs 41 ± 4.1). This difference may be due to Chaout's study was done on (98) patients with 34% in stage II and 52% in stage IV

while our study was done on 50 COPD patients only with highest percentage of cases was in stage II (52%) and with lower percentage of cases of stage III (48%) and no cases in stage IV.

As regard to pH, there was no significant difference between COPD patients with AHI ≥ 5 vs COPD patients with AHI < 5 (7.39 ± 2.99 vs 7.4 ± 2.22, P = 0.08). While, pH was not reported by both Chaout's and Little's studies. So arterial blood gases were not considered a good predictor of OSA in our study.

There were no significant difference between COPD with AHI ≥ 5 and COPD patients with AHI < 5 as regard to Basal SaO2 (92.57 ± 2.5 vs 93.7 ± 3) (P = 0.9), minimum SaO2 (76.8 ± 11.005 vs 83 ± 6.4) and average duration of nocturnal oxygen desaturation (40 vs 30) (P = 0.16), while the median index of nocturnal oxygen desaturation was significantly higher in COPD patients with AHI ≥ 5 vs COPD patients with AHI < 5 (24.5 vs 2) (P = 0.000). While, ***Chaout et al. (2001)*** reported that there were significantly lower basal SaO2 in COPD patients with AHI ≥ 5 vs COPD patients with AHI < 5 (95 ± 1.7 vs 92 ± 1.6, P = 0.005) and also minimum SaO2 was significantly lower in COPD patients with AHI ≥ 5 vs COPD patients with AHI < 5 (72 ± 13 vs 85 ± 4, P = 0.001). And also average duration of nocturnal oxygen desaturation was significantly higher in COPD patients with AHI ≥ 5 vs COPD patients with AHI < 5 (69.9 ± 23.6 vs 6.8 ± 7.2, P = 0.001) but index of NOD was not reported by chaout et al 2001 and this difference may be explained by ***Chaout's et al. (2001)*** study was done on 98 patients with 34% in stage II and 52% in stage IV, while our study done on 50 patients only with highest percentage of cases in stage II (52%) and with lower percentage of cases in stage III (48%) and no cases in stage IV. So, the index of

nocturnal oxygen desaturation was considered the most important parameter of NOD in our study.

NOD in COPD patients with AHI ≥ 5 (32 out of 38) were significantly higher than COPD patients with AHI < 5 (0 out of 12) (84.2% vs 0% P < 0.001). NOD in COPD patients were found in 32 cases out of 50 (64%) with all cases found in those with AHI ≥ 5 (P = 0.001). This signify that the predictor of OSA can predict NOD in COPD patients to large extent.

Epworth score was significantly higher in nocturnal O2 desaturators vs non desaturators (11.09 ± 3.7) vs (6.0 ± 4.4) (P = 0.000), also Berlin questionnaire was significantly higher in nocturnal O2 desaturators vs non desaturators (2.5 ± 0.87) vs (1 ± 1.3) (P = 0.000). This signify that Epworth score and Berlin questionnaire were considered good predictors of NOD in our study. Neck circumference was not significantly different in nocturnal O2 desaturators vs non desaturators (42.5 ± 4.52) vs (41 ± 4.6) (P = 0.3). This can be explained by the total mean of neck circumference of all studied COPD patients was (42 cm) which was lower than reported to be risky to OSA in male as reported by ***Schwab et al. (1998)*** who report 42.5cm, also ***Woodson et al. (1997)*** reported that a neck circumference larger than 43.7 cm in male increase the odds (2.2) of OSA syndrome due to increase amount of fat in the neck. BMI was not significant difference in nocturnal O2 desaturators vs non desaturators (30.53 ± 4.97) vs (27.6 ± 4.7) (P = 0.058). This was in accordance to ***Chaout et al. (1997)*** who reported that BMI was not significantly different in nocturnal O2 desaturators vs non desaturators (27 ± 4.9) vs (24.7 ± 5.5) (P > 0.05) and also this can be explained by the total mean of BMI in all studied COPD patients was (29.48) which is below the level of obesity this was in accordance to WHO classification which considered obesity ≥ 30 kg/m^2.

There were no significant difference in spirometric pulmonary function tests in nocturnal O2 desaturators vs non desaturators. FEV1/FVC% (51.9 ± 11.6) vs (56.28 ± 10.69) (P = 0.19) and FEV1% of predicted (48.04 ± 11.79) vs (51.05 ± 12.04) (P = 0.08), these were in accordance to ***Chaout et al. (1997)*** who reported that FEV1/FVC% (40 ± 0.12 vs 37 ± 0.10) (P = 0.06) and FEV1% of predicted (46.05 ± 12.2 vs 50.9 ± 12.3) (P > 0.05) so spirometric pulmonary function tests were not considered a good predictors for nocturnal O2 desaturators.

There was no significant difference between nocturnal O2 desaturators and non desaturators as regard to PaO2 (66.08 ± 5.84 vs 68.53 ± 8.15) (P = 0.3) this was in accordance to Chaout et al. (1997) who reported that PaO2 was not significantly different in desaturators vs non desaturators (62.8 ± 4.4 vs 62.9 ± 2.9) (P > 0.05) as regard to PaCO2 there was significantly higher PaCO2 in nocturnal desaturators vs non desaturators (43.2 ± 6.39 vs 39.83 ± 4.6) (P = 0.03) and this was in accordance to ***Chaout et al. (1997)*** who reported that PaCO2 was significantly higher in nocturnal desaturators vs non desaturators (44.7 ± 5.3 vs 39.6 ± 3.8) (P < 0.001). About pH there was no significant difference between nocturnal O2 desaturators vs non desaturators (7.38 ± 3 vs 7.39 ± 2.6) (P = 0.5) while pH was not reported by ***Chaout et al. (1997).*** This mean that the only important parameter of awake arterial blood gases for NOD in our study was PaCO2.

There were significantly higher median index of nocturnal O2 desaturation in nocturnal O2 desaturators vs non desaturators (31 vs 3.5) (P = 0.000) and also there were significantly higher average duration of nocturnal O2 desaturation in nocturnal O2 desaturators vs non desaturators (47 vs 27.5) (P = 0.01) this was in accordance to ***Chaout et al. (1997)*** who reported that significantly higher average duration of nocturnal O2 desaturation in nocturnal O2 desaturators vs non

desaturators (69 ± 24 vs 8 ± 11) (P < 0.001). While there were no significant difference between nocturnal O2 desaturators vs non desaturators as regard to both basal SaO2 (92.08 ± 2.08 vs 94.17 ± 2.88) (P = 0.09) and minimum SaO2 (76.59 ± 10.75 vs 81.22 ± 9.25) (P = 0.13) in our study. This signify that the only reliable parameter of nocturnal O2 desaturation was index of nocturnal O2 desaturation and average duration of nocturnal O2 desaturation.

Summary

- Nocturnal O2 desaturation (NOD) has long been recognized in COPD patients, who may spend ≥ 30% of sleep time with oxygen saturation < 90% mostly during REM sleep (Gay, 2004).

The aim of this work was to determine the rate of occurrence of nocturnal oxygen desaturators in COPD patients with or without OSAHS and to determine the predictors of OSAHS and nocturnal oxygen desaturators in COPD patients.

- This study was done on 50 patients of stable COPD (irreversible obstructive airway disease i.e. FEV1/FVC < 70%) and < 12% improvement in FEV1 expressed as percentage of predicted after inhalation of β2 agonists.

All patients were subjected to the following:

1) Full history taking with stress on:
    - Epworth score.
    - Berlin questionnaire score.
2) Physical examination with stress on:
    - Neck circumference.

- Body mass index (BMI).

3) Plain chest x-ray.
4) Laboratory tests.
5) Spirometric pulmonary function tests.
6) Calculation of BMI.
7) Polysomnography.

This study revealed the following:

- The mean age of the studied group was 52.26 ± 8.02 years, the mean BMI was 29.48 ± 5.04 kg/m2 and the mean neck circumference was 42 ± 4.55 cm.

- The highest percentage of patients were in stage II (52%) while a low percentage of patients were in stage III (48%).

- There were 38 COPD patients (76%) having AHI ≥ 5 which define overlap syndrome (COPD with OSAHS) while there were 12 COPD patients (24%) having AHI < 5.

- According to Berlin questionnaire, there were 34 COPD patients (68%) with high risk to OSA and 16 COPD patients (32%) with low risk to OSA.

- The majority of COPD patients with AHI ≥ 5 (68.4%) were having the highest Berlin score (3) however the majority of COPD patients with AHI < 5 (83.3%) were having the lowest Berlin score (0).

- According to Berlin questionnaire, BMI, Epworth score and AHI were significantly higher in high risk group to OSA vs low risk group to OSA (P = 0.009, 0.000, 0.001 respectively), while neck circumference

was not significantly different in high risk group to OSA vs low risk group to OSA (P = 0.4).

- According to Berlin questionnaire, Spirometric pulmonary function tests (FEV1% of predicted and FEV1/FVC%) were significantly lower in high risk group to OSA vs low risk group to OSA (P = 0.03, 0.04 respectively).

- According to Berlin questionnaire, Awake arterial blood gases (PaO2, PaCO2, pH) were not significantly different in high risk group to OSA vs low risk to OSA (P = 0.96, 0.8, 0.1 respectively).

- According to Berlin questionnaire, the index of nocturnal O2 desaturation (evens/hr) was significant higher in high risk group to OSA vs low risk group to OSA (P = 0.001) while (basal SaO2, minimum SaO2 and average duration of nocturnal oxygen desaturation) were not significantly different in high risk group to OSA vs low risk group to OSA (P = 0.99, 0.67, 0.3 respectively).

- Sensitivity of Berlin questionnaire score was 86.8%, specificity was 91.7%, with PPV 97.1%, and NPV 68.8%.

- 38 patients (76%) of COPD patients were having AHI ≥ 5, 27 (54%) of COPD patients were having AHI ≥ 10, while 20 (40%) of COPD patients were having AHI ≥ 15 and lastly 19 (38%) of COPD patients were having AHI ≥ 20.

- Neck circumference, BMI, Epworth score and Berlin questionnaire score were significantly positively correlated with AHI (P = 0.001, 0.005, 0.000, 0.000 respectively).

- Spirometric pulmonary function tests (EFV1% of predicted and FEV1/FVC%) were significantly negative correlated with AHI (P = 0.02, 0.006 respectively).

- Awake arterial blood gases (PaO2, PaCO2, pH) were not significantly correlated with AHI (P = 0.2, 0.09, 0.3 respectively).

- The index of nocturnal O2 desaturation was significantly positive correlated with AHI (P = 0.000) and also minimum SaO2 was significantly negatively correlated with AHI (P = 0.04). While basal SaO2 and average duration of nocturnal O2 desaturation were not significantly correlated with AHI (P = 0.12, 0.8 respectively).

- Epworth score and Berlin questionnaire were significantly higher in COPD with AHI ≥ 5 vs COPD with AHI < 5 (P = 0.000, 0.000 respectively), while neck circumference and BMI were not significantly different in COPD with AHI ≥ 5 vs COPD with AHI < 5 (P = 0.4, 0.06 respectively).

- Spirometric pulmonary function tests (FEV1% of predicted and FEV1/FVC%) were not significantly different in COPD with AHI ≥ 5 vs COPD with AHI < 5 (P = 0.08, 0.1 respectively).

- Awake arterial blood gases (PaO2, PaCO2, pH) were not significantly different in COPD with AHI ≥ 5 vs COPD with AHI < 5 (P = 0.16, 0.54, 0.08 respectively).

- The index of nocturnal O2 desaturation was significantly higher in COPD with AHI ≥ 5 vs COPD with AHI < 5 (P = 0.000). While basal SaO2, minimum SaO2 and average duration of nocturnal O2

desaturation were not significantly different in COPD with AHI ≥ 5 vs COPD with AHI < 5 (P = 0.97, 0.7, 0.16 respectively).

- NOD in COPD patients with AHI ≥ 5 were significantly higher than COPD patients with AHI < 5 (84.2% vs 0% P < 0.001). NOD in COPD patients were found in 32 cases out of 50 (64%) with all cases were found in those with AHI ≥ 5.

- Epworth score and Berlin questionnaire score were significantly higher in nocturnal O2 desaturators vs non desaturators (P = 0.000, 0.000 respectively), while neck circumference and BMI were not significantly different in nocturnal O2 desaturators vs non desaturators (P = 0.3, 0.058 respectively).

- Spirometric pulmonary function tests (FEV1/FVC% and FEV1 of predicted) were not significantly different in nocturnal O2 desaturators vs non desaturators (P = 0.1, 0.39).

- PaCO2 was significantly higher in nocturnal O2 desaturators vs non desaturatos (P = 0.03) while PaO2 and pH were not significantly different in nocturnal O2 desaturators vs non desaturators (P = 0.3, 0.53).

- Both index of nocturnal O2 desaturation and average duration of nocturnal O2 desaturation were significantly higher in nocturnal O2 desaturators vs non desaturators (P = 0.000, 0.01 respectively) while both basal SaO2 and minimum SaO2 were not significantly different in nocturnal O2 desaturators vs non desaturators (P = 0.09, 0.13 respectively).

Conclusion:

- OSAHS and nocturnal oxygen desaturation were common in COPD patients with prevalence (76% and 64% respectively) in our study.
- Berlin questionnaire score and Epworth score were good subjective test for prediction of OSAHS and nocturnal oxygen desaturators.
- Spirometric pulmonary function tests was not considered a good predictor to OSAHS and nocturnal oxygen desaturation.
- Awake arterial blood gases were not considered a good predictor to OSAHS.
- PaCO2 was the only reliable predictor of awake arterial blood gases for NOD.

Recommendations:

1) Administration of Berlin questionnaire and Epworth score prior to polysomnography study to identify high risk subject and also to avoid unnecessary polysomnography studies.
2) Multicenter studies of COPD patients are needed for better assessment of the prevalence of OSAHS and nocturnal oxygen desaturators in COPD patients by surveying large number of COPD patients and for use of mean nocturnal oxygen desaturation as an important parameter of nocturnal oxygen desaturation and also for detection of nocturnal oxygen desaturators in both NREM and REM stages of sleep.

References

AASM (American Academy of Sleep Medicine) Task Force. Sleep related breathing disorders in adults: recommendations for

syndrome definition and measurement techniques in clinical research. Sleep 1999; 22: 667-89.

Alauya Lamping AM, Jorge MC, Fernandez LC, De Los Reyes VS. Sleep: advances in obstructive sleep apnea, continued. Chest 2006; 130(4): 265S.

Al-Delaimy WK, Manson JE, Willett WC, et al. Snoring as a risk factor for type II diabetes mellitus: a prospective study. Am J Epidemiol 2002; 155: 387-93.

American Thoracic Society. Standards for the diagnosis and care of patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 1995; 152: S77-S121.

ASDA Atlas Task Force. Arousals: scoring rules and examples. Sleep 1992; 15: 173-84.

Astrom C, Christensen L, Gjerris F, et al. Sleep in acromegaly before and after treatment with adrenalectomy. Neuroendocrinology 1991; 53: 328-31.

Badr S and Strohi KP. Pathophysiology of sleep disordered breathing. In: Baum's Textbook of Pulmonary Diseases. By: Crapo JD, Glassroth J, Karlinsky JB, King TE (editors). 7th edition, Lippincott Williams and Wilkins, Ch 69, 2004; PP: 1400-1423.

Barnes PJ. Chronic obstructive pulmonary disease. 12: New treatments for COPD. Thorax 2003; 58: 803-808 .

Barnes PJ. Chronic Obstructive Pulmonary Disease. The New England Journal of Medicine 2000; 343(4):269-280.

Bassetti C, Chervin R. Cerebrovascular diseases. In: Kryger M, Roth T, Dement W, editors. Principles and practice of sleep medicine. 3rd edition. Philadelphia: WB Saunders; 2000. p. 1072-86.

Bassiri AG, Guilleminault C. Clinical features and evaluation of obstructive sleep apnea-hypopnea syndrome. In: Kryger MH,

Rother T, Dement WC, editors. Principles and practice of sleep medicine Philadelphia: WB Saunders 2000; PP: 869-78.

Benumof J. Obstructive sleep apnea in the adult obese patient: implications for airway management. Anesthesiol Clin North America 2002; 20: 789-811.

Berry RB, Parrish JM, Hartse KM. The use of auto-titrating continuous positive airway pressure for treatment of adult obstructive sleep apnea: an American Academy of Sleep Medicine review. Sleep 2002; 25: 148-73.

Block AJ, Boysen PG, Wynne JW, et al. Sleep apnea, hypopnea, and oxygen desaturation in normal subjects. N Engl J Med 1997; 300: 513-517.

Bonsignore MR, Marrone O, Insalaco G, Bonsignore G. The cardiovascular effects of obstructive sleep apnoeas: analysis of pathogenic mechanisms. Eur Respir J 1994; 7: 786-805.

British Thoracic Society. Guidelines for the management of COPD. Thorax 1997; 52: suppl 5, 57.

Catterall JR, Rhind GB, Whyte KF, et al. Is nocturnal asthma caused by changes in airway cholinergic activity? Thorax 1988; 43: 720-724.

Chaouat A, Weitzenblum E, Kessler R, Charpentier C, Ehrhart M, Levi-Valensi P, et al. Sleep-related O_2 desaturation and daytime pulmonary haemodynamics in COPD patients with mild hypoxaemia. Eur Respir J 1997; 10(8): 1730-1735.

Chaouat A, Weitzenblum E, Kessler R, Schott R, Charpentier C, Levi-Valensi P, Zielinski J, Delaunois L, Cornudella R, dos Santos JM. Outcome of COPD patients with mild daytime hypoxaemia with or without sleep-related oxygen desaturation. Eur Respir J 2001; 17: 848-855.

Chaouat A, Weitzenblum E, Krieger J, Ifoundza T, Oswald M, Kessler R. Association of chronic obstructive pulmonary disease and sleep apnea syndrome. Am Rev Respir Dis 1995; 151: 82-86.

Chesson AL Jr, Ferber RA, Fry JM, et al. The indications for polysomnography and related procedures. Sleep 1997; 20: 423-487.

Cistulli PA, Palmisano RG, Poole MD. Treatment of obstructive sleep apnea syndrome by rapid maxillary expansion. Sleep 1998; 21: 831-5.

Crapo RO. Pulmonary function testing: In Baum's textbook of pulmonary disease 7th ed. Chapter 11; 35-54, 2004.

Dalmasso F, Prota R. Snoring: analysis, measurement, clinical implications and applications. Eur Respir J 1996; 9: 146-59.

Dart RA, Gregoire JR, Gutterman DD, Woolf SH. The association of hypertension and secondary cardiovascular disease with sleep-disordered breathing. Chest 2003; 123: 244-60.

David M. Epidemiology and Global Impact of Chronic Obstructive Pulmonary Disease. Seminars in Respiratory and Critical Care Medicine 2005; 26(2): 204-210.

De Miguel J, Cabello J, Sanchez-Alarcos JM, et al. Long-term effects of treatment with nasal continuous positive airway pressure on lung function in patients with overlap syndrome. Sleep & Breathing 2002; 6: 3-10.

Dempsey JA, Skatrad JB. Apnea following mechanical ventilation may be caused by nonchemical neuromechanical influences. Am J Respir Crit Care Med 2001; 163: 1297-1298.

Dempsey JS, Skatrad JB. A sleep-induced apneic threshold and its consequences. Am Rev Respir Dis 1986; 133: 1163-1170.

Douglas NJ, Calverley PMA, Leggett RJE, et al. Transient hypoxaemia during sleep in chronic bronchitis and emphysema. Lancet 1979; 1: 1-4.

Douglas NJ, Flenley DC. Breathing during sleep in patients with obstructive lung disease. Am Rev Respir Dis 1990; 141: 1055-69.

Drake CL, Day R, Hudgel D, Stefadu Y, Parks M, Syron ML, et al. Sleep during titration predicts continuous positive airway pressure compliance. Sleep 2003; 26(3): 308-311.

Dyken ME, Somers VK, Yamada T, Ren ZY, Zimmermann MB. Investigating the relationship between stroke and obstructive sleep apnea. Stroke 1996; 27: 401-7.

Fleetham J, West P, Mezon B, Conway W, Roth T, Kryger M. Sleep, arousals, and oxygen desaturation in chronic obstructive pulmonary disease: the effect of oxygen therapy. Am Rev Respir Dis 1982; 126(3): 429-433.

Flemons WW, Whitelaw WA, Brant R, et al. Likelihood ratios for a sleep apnea clinical prediction rule. Am J Respir Crit Care Med 1999; 150(5 Pt 1): 1279-1285.

Flenley DC. Sleep in chronic obstructive lung disease. Clin Chest Med 1985; 6: 651-661.

Fletcher EC, Donner CF, Midgren B, et al. Survival in COPD patients with a daytime PaO_2 greater than 60 mm Hg with and without nocturnal oxyhemoglobin desaturation. Chest 1992; 101: 649-655.

Fletcher EC, Gray BA, Levin DC. Nonapneic mechanisms of arterial oxygen desaturation during rapid-eye-movement sleep. J Appl Physiol 1983; 54: 632-9.

Fletcher EC, Luckett RA, Goodnight-White S, Miller CC, Qian W, Costarangos-Galarza C. A double-blind trial of nocturnal

supplemental oxygen for sleep desaturation in patients with chronic obstructive pulmonary disease and a daytime PaO2 above 60 mm Hg. Am Rev Respir Dis 1992; 145(5): 1070-1076.

Gay PC. Chronic obstructive pulmonary disease and sleep. Respiratory Care 2004; 49(1): 49-51.

Gibson GJ and MacNee W. Chronic obstructive pulmonary disease: Investigations and assessment of severity. In: Postma DS. and Siafakas N.M: Management of chronic obstructive pulmonary disease, 1st edition, ch.5, Chapman and Hall, London; 1998; pp: 126-140.

Girault C, Muir JF, Mihaltan F, et al. Effects of repeated administration of zolpidem on sleep, diurnal and nocturnal respiratory function, vigilance, and physical performance in patients with COPD. Chest 1996; 110: 1203-11.

Glenville M, Broughton R. Reliability of the Stanford Sleepiness Scale compared to short duration performance tests and the Wilkinson Auditory Vigilance Task. Adv Biosci 1978; 21: 235-244.

GOLD. Global initiative for chronic obstructive lung disease. Global strategy for diagnosis, management and prevention of chronic obstructive pulmonary disease (based on April 1998 NHLBI/WHO workshop). National Heart, Lung and Blood Institute, April 2001(Updated, 2004).

GOLD. Global initiative for chronic obstructive lung disease. Global strategy for diagnosis, management and prevention of chronic obstructive pulmonary disease (based on April 1998 NHLBI/WHO workshop). National Heart, Lung and Blood Institute, April 2001(Updated, 2003).

Goldstein RS, Ramcharan V, Bowes G, et al. Effects of supplemental oxygen on gas exchange during sleep in patients with severe obstructive lung disease. N Engl J Med 1984; 310: 425-429.

Gottlieb DJ. Obstructive Sleep Apnea. In: A Practical Approach to Pulmonary Medicine, By: Goldstein RH, O'Connell JJ, Karlinsky JB (editors). Lippincott Rave 1999; Ch 20; PP: 309-322.

Graf KI, Karaus M, Heinemann S, et al. Gastroesophageal reflux in patients with sleep apnea syndrome. Z Gastroenterol 1995; 33: 689-93.

Green BT, Broughton WA, O'Connor JB. Marked improvement in nocturnal gastroesophageal reflux in a large cohort of patients with obstructive sleep apnea. Arch Intern Med 2003; 163: 41-5.

Grunstein R. Neuroendocrine changes in sleep apnea. In: Pack A, editor. Sleep apnea pathogenesis diagnosis and treatment. New York: Marcel Dekker; 2002. p. 411-41.

Grunstein RR, Ho KY, Sullivan CE. Sleep apnea in acromegaly. Ann Intern Med 1991; 115: 527-32.

Guilleminault C and Abad VC. Obstructive sleep apnea syndromes. Medical Clinics of North America 2004; 88(3): 611-630.

Guilleminault C, Chowdhuri S. Upper airway resistance syndrome is a distinct syndrome. Am J Respir Crit Care Med 2000; 161: 1412-3.

Guilleminault C, Cummiskey J, Motta J. Chronic obstructive airflow disease and sleep studies. Am Rev Respir Dis 1980; 122: 397-406.

Guilleminault C, Partinen M, Hollman K, et al. Familial aggregates in obstructive sleep apnea syndrome. Chest 1995; 107: 1545-1551.

Han F, Strohi KP. Inheritance of ventilatory behavior in rodent models. Respir Physiol 2000; 121: 247-256.

Harsch IA, Pour Schahin S, Radespiel-Troger M, Weintz O, Jahreiss H, Fuchs FS, et al. CPAP treatment rapidly improves insulin sensitivity in patients with OSAS. Am J Respir Crit Care Med 2004; 169: 159-62.

Henke KG, Depsey JA, Badr MS, et al. Effect of sleep-induced increases in upper airway resistance on respiratory muscle activity. J Appl Physiol 1991; 70: 158-168.

Hoffstein V. Relationship between smoking and sleep apnea in clinic population. Sleep 2002; 25: 519-526.

Hofstein V, Szalai JP. Predictive value of clinical features in diagnosing obstructive sleep apnea. Sleep 1993; 16: 118-122.

Howard P. Hypoxia, almitrine, and peripheral neuropathy. Thorax 1989; 44: 247-250.

Hudgel DW, Martin RJ, Capehart M, et al. Contribution of hypoventilation to sleep oxygen desaturation in chronic obstructive pulmonary disease. J Appl Physiol 1983; 55: 669-77.

Ip MS, Lam B, Ng MM, Lam WK, Tsang KW, Lam KS. Obstructive sleep apnea is independently associated with insulin resistance. Am J Respir Crit Care Med 2002; 165: 670-6.

Javaheri S. Heart failure and sleep apnea: emphasis on practical therapeutic options. Clin Chest Med 2003; 24: 207-22.

Johns MW. A new method for measuring daytime sleepiness: The Epworth Sleepiness Scale. Sleep 1991; 14: 540-545.

Kadotani H, Kadotani T, Young T, et al. Association between apolipoprotein E e4 and sleep-disordered breathing in adults. JAMA 2001; 285: 2888-2890.

Kaynak D, Goksan B, Kaynak H, Degirmenci N, Daglioglu S. Is there a link between the severity of sleep-disordered breathing and atherosclerotic disease of the carotid arteries? Eur J Neurol 2003; 10: 487-93.

Klein JS, Gamsu G, Webb WR, Golden JA, Muller NL. High-resolution CT diagnosis of emphysema in symptomatic patients with normal chest radiographs and isolated low diffusing capacity. Radiology 1992; 182: 817-821.

Krachman SL, Quaranta AJ, Berger TJ, Criner GJ. Effects of noninvasive positive pressure ventilation on gas exchange and sleep in COPD patients. Chest 1997; 112(3): 623-628.

Krieger J. Therapeutic use of auto-CPAP. Sleep Medicine Reviews 1999; 3(2): 159-174.

Kulnis R, Nelson S, Strohl K, et al. Cephalometric assessment of snoring and nonsnoring children. Chest 2000; 118: 596-603.

Lavie P, Herer P, Peled R, et al. Mortality in sleep apnea patients: a multivariate analysis of risk factors. Sleep 1995; 18: 149-157.

Lee-Chiong T. Monitoring respiration during sleep. In: Lee-Chiong T, Sateia M, Carskadon M, editors. Sleep medicine. Philadelphia: Hanley & Belfus; 2002. p. 639-46.

Levi-Valensi P, Weitzenblum E, Rida Z, et al. Sleeprelated oxygen desaturation and daytime pulmonary hemodynamics in COPD. Eur Respir J 1992; 6: 301-307.

Li KK. Surgical management of obstructive sleep apnea. Clin Chest Med 2003; 24: 365-70.

Little SA, Elkholy MM, Chalmers GW, Farouk A, Patel KR and Thomson NC. Predictors of nocturnal oxygen desaturation in patients with COPD. Respiratory Medicine 1999; 93: 202-207.

Littner MR, Ilowite JS and Tashkin DP. Long-acting bronchodilation with once-daily dosing of tiotropium (Spiriva) in stable chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2000;161: 1136-42.

Logan AG, Thacova R, Perlikowski SM, Leung RS, Tisier A, Floras JS, et al. Refractory hypertension and sleep apnoea: effect of CPAP on blood pressure and baroreflex. Eur Respir J 2003; 21: 241-7.

Loube D, Gay P, Strohl K, Pack A, White D, Collop N. Indications for positive airway pressure treatment of adult obstructive sleep apnea patients. Chest 1999; 115: 863-6.

Lowe A, Schmidt-Nowara W. Oral appliance therapy for snoring and sleep apnea. In: Pack A, editor. Sleep apnea pathogenesis diagnosis and treatment. New York: Marcel Dekker; 2002. p. 555-73.

Man GC, Chapman KR, Ali SH, et al. Sleep quality and nocturnal respiratory function with once-daily theophylline (Uniphil) and inhaled salbutamol in patients with COPD. Chest 1996; 110: 648-653.

Mannino DM. COPD: Epidemiology, Prevalence, Morbidity and Mortality, and Disease Heterogeneity. Chest 2002; 121: 121S-126S.

Manser RL, Rochford P, Pierce RJ, Byrnes GB, Campbell DA. Impact of different criteria for defining hypopneas in the apnea-hypopnea index. Chest 2001; 120: 909-14.

Martin RJ, Bartelson BL, Smith P, et al. Effect of ipratropium bromide on oxygen saturation and sleep quality in COPD. Chest 1999; 115: 1338-1345.

Martin RJ. Nocturnal asthma: circadian rhythms and therapeutic interventions. Am Rev Respir Dis 1993; 147: 525-8.

Mathur R, Douglas NJ. Family studies in patients with the sleep apnea-hypopnea syndrome. Ann Intern Med 1995; 122: 174-8.

McGrath JJ, Prochazka J, Pelouch V, et al. Physiological responses of rats to intermittent high-altitude stress: effects of age. J Appl Physiol 1973; 34: 289-293.

McKeon JL, Murree-Allen K, Saunders NA. Prediction of oxygenation during sleep in patients with chronic obstructive lung disease. Thorax 1988; 43: 312-317.

McNicholas WT, Fitzgerald MX. Nocturnal deaths among patients with chronic bronchitis and emphysema. Br Med J (Clin Res Ed) 1984; 289(6449): 878.

McNicholas WT. Impact of sleep in COPD. Chest 2000; 117: 48S-53S.

Mezzanotte WS, Tangel DJ, Fox AM, et al. Nocturnal nasal continuous positive airway pressure in patients with chronic obstructive pulmonary disease. Influence on waking respiratory muscle function. Chest 1994; 106: 1100-1108.

Mezzanotte WS, Tangel DJ, White DP. Influence of sleep onset on upper-airway muscle activity in apnea patients versus normal controls. Am J Respir Crit Care Med 1996; 153(6 pt 1): 1880-1887.

Moller DS, Lind P, Strunge B, Pedersen EB. Abnormal vasoactive hormones and 24-hour blood pressure in obstructive sleep apnea. Am J Hypertens 2003; 16: 274-80.

Mulloy E, McNicholas WT. Ventilation and gas exchange during sleep and exercise in severe COPD. Chest 1996; 109(2): 387-394.

National Emphysema Treatment Trial Research Group. Patients at high risk of death after lung-volume-reduction surgery. N Engl J Med 2002; 345: 1075-83.

National Heart Lung & Blood Institute. Morbidity and mortality: 2002 chart book on cardiovascular, lung and blood disorders. Available at www.nhlbi.nih.gov/resources/docs/02_chtbk.pdf

Netzer NC, et al. Using the Berlin Questionnaire to identity patients at risk for the sleep apnea syndrome. Ann Intern Med 1999; 131: 485-491.

Nocturnal Oxygen Therapy Trial Group. Continuous or nocturnal oxygen therapy in hypoxemic chronic obstructive lung disease. Ann Intern Med 1980; 93: 391-8.

Okubadejo AA, Jones PW, Wedzicha JA. Quality of life in patients with chronic obstructive pulmonary disease and severe emphysema. Thorax 1996; 51: 4447.

Pack AI, Kubin L, Davies RD. Changes in cardiorespiraotry system during sleep. In: Pulmonary Diseases and Disorders. By: Fishman AP (ed). McGraw-Hill, 3rd edition, Ch 102, PP: 1630, 1998.

Panettieri RA and Fishman AP. Chronic obstructive pulmonary disorders. In Fishman AP, Ellas JA and Grippi MA: Manual pulmonary disease and disorders 3rd edition, (vol 1), ch6, McGraw -Hill Co., North America 2002, pp6.

Partinen M. Epidemiology of obstructive sleep apnea syndrome. Cur Opin Pulm Med 1995; 1: 482-7.

Pauwels RA, Buist AS, Calverley PMA, Jenkins CR, Hurd SS. On behalf of 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: 1256-76.

Pelttari L, Rauhala E, Polo O, et al. Upper airway obstruction in hypothyroidism. J Intern Med 1994; 236: 177-81.

Peppard P, Young T, Palta M, et al. Longitudinal study of moderate weight change and sleep-disordered breathing. JAMA 2000; 284: 3015-3021.

Petty TL, Silver GW, Stanford RE, Baird MD and Mitchell RS. Small airway pathology is related to increased closing capacity and abnormal slope of phase III in excised human lungs. Am Rev Respir Dis 1980; 121: 449-56.

Philips BA, Anstead MI, Gottlieb DJ. Monitoring sleep and breathing: methodology. Part I: Monitoring breathing. Clin Chest Med 1998; 1: 203-12.

Philips BG, Somers VK. Sleep disordered breathing and risk factors for cardiovascular disease. Curr Opin Pulm Med 2002; 8: 516-20.

Quanjer PH, Tommeling GJ, Cotes JE, Pedersen OF, Peslin R, Yernault JC. Lung volumes and forced ventilatory flows. Eur Respir J 1994; 6 (suppl 16): 5-40.

Ramirez JM, Richter DW. The neuronal mechanisms of respiratory rhythm generation. Curr Opin Neurobiol 1996; 6: 817-825.

Redline S, Kapur VK, Sanders MH, Quan SF, Gotlieb DJ, Rapoport DM, et al. Effects of varying approaches for identifying respiratory disturbances on sleep apnea assessment. Am J Respir Crit Care Med 2000; 161: 369-74.

Redline S, Strohl KP. Recognition and consequences of obstructive sleep apnea hypopnea syndrome. Clin Chest Med 1998; 19: 1-19.

Redline S, Tishler PV, Hans MG, Tosteson TD, Strohl KP, Spry K. Racial differences in sleep-disordered breathing in African-Americans and Caucasians. Am J Respir Crit Care Med 1997; 155: 186-92.

Redline S, Tosteson T, Tishler PV, et al. Studies in the genetics of obstructive sleep apnea. Familial aggregation of symptoms associated with sleep-related breathing disturbances. Am Rev Respir Dis 1992; 145(2 pt 1): 440-4.

Resta O, Foschino Barbaro MP, Bonfitto P, et al. Hypercapnia in obstructive sleep apnoea syndrome. Neth J Med 2000; 56: 215-222.

Resta O. Sleep-related breathing disorders, loud snoring and excessive daytime sleepiness in obese subjects. Int J Obes 2001; 25: 669-675.

Reynolds HY. Antibiotic treatment of bronchitis and chronic lung disease. In: Cherniack NS. Chronic Obstructive Pulmonary Disease. W. B. Saunders, Philadelphia, 1991: 456-461.

Richter DW, Spyer KM. Studying rhythmogenesis of breathing: comparison of in vivo and in vitro models. Trends Neurosci 2001; 24: 464-472.

Riley RW, Powell NB, Li KK, Weaver EM, Guilleminault C. An adjunctive method of radiofrequency volumetric tissue reduction of the tongue for OSAS. Otolaryngol Head Neck Surg 2003; 129: 37-42.

Rochester DF and Braun NT. Determinants of maximal inspiratory pressure in chronic obstructive pulmonary disease. Am Rev Respir Dis 1985; 132: 42-47.

Ronald J, Delaive K, Manfreda J, Bahammam A, Kryger MH. Health care utilization in the 10 years prior to diagnosis in obstructive sleep apnea syndrome patients. Sleep 1999; 22: 225-229.

Roux F, Hilbert J. Continuous positive airway pressure: new generations. Clin Chest Med 2003; 24: 315-42.

Rowley JA, Zahn BR, Babcock MA, et al. The effect of rapid eye movement (REM) sleep on upper airway mechanisms in normal human subjects. J Physiol 1998; 510(pt 3): 963-976.

Rowley JA, Zhou X, Vergine I, et al. Influence of gender on upper airway mechanics: upper airway resistance and P_{crit}. J Appl physiol 2001; 91: 2248-2254.

Sanders C. The radiographic diagnosis of emphysema. Radiol Clin North Am 1991; 29: 1019-1030.

Sanders MH, Newman AB, Haggerty CL, Redline S, Lebowitz M, Samet J, O'Connor GT, Punjabi NM, Shahar E. Sleep and sleep-disordered breathing in adults with predominantly mild obstructive airway disease. Am J Respir Crit Care Med 2003; 167: 7-14.

Schafer H, Pauleit D, Sudhop T, Gouni-Berthold I, Ewig S, Berthold HK. Body fat distribution, serum leptin, and cardiovascular risk factors in men with obstructive sleep apnea. Chest 2002; 122: 829-39.

Schellenberg JB, Maislin G, Schwab RJ. Physical findings and the risk for obstructive sleep apnea. The importance of oropharyngeal structures. Am J Respir Crit Care Med 2000; 162(2 pt 1): 740-748.

Schwab RJ, Goldberg AN, Pack AI. Sleep apnea syndromes. In: Pulmonary Diseases and Disorders. By: Fishman AP (ed). McGraw-Hill, 3rd edition, Ch 102, 1998; PP: 1617.

Selby C, Engleman HM, Fitzpatrick MF, Sime PM, Mackay TW, Douglas NJ. Inhaled salmeterol or oral theophylline in nocturnal asthma? Am J Respir Crit Care Med 1997; 155: 104-8.

Sharma SK, Reddy TS, Mohan A, et al. Sleep disordered breathing in chronic obstructive pulmonary disease. Indian J Chest Dis Allied Sci 2002; 44: 99-105.

Sher A, Goldberg A. Upper airway surgery for obstructive sleep apnea. In: Pack A, editor. Sleep apnea pathogenesis diagnosis and treatment. New York: Marcel Dekker; 2002; PP: 575-605.

Shipley JE, Schteingart DE, Tandon R, et al. Sleep architecture and sleep apnea in patients with Cushing's disease. Sleep 1992; 15: 514-8.

Siafakas NM, Vermeire P, Pride NB, Paoletti P, Gibson J, Howard P, Yernault JC, DeCramer M, Higenbottam T and Postma DS. Optimal assessment and management of chronic obstructive pulmonary disease (COPD). The European Respiratory Society Task Force. Eur Respir J 1995; 8: 1398-420.

Siedell and Flegal. Assessing obesity: Classification and epidemiology. BMJ 1997; 53(2): 238-52.

Somers V, Fletcher E. Mechanisms of hypertension in obstructive sleep apnea. In: Pack A, editor. Sleep apnea pathogenesis diagnosis and treatment. New York: Marcel Dekker; 2002. p. 353-76.

Spengler CM, Shea SA. Sleep deprivation per se does not decrease the hypercapnic ventilatory response in humans. Am J Respir Crit Care Med 2000; 161: 1124-1128.

Spiegel K, Leproult R, Van Cauter E. Impact of sleep debt on metabolic and endocrine function. Lancet 1999; 354: 1435-9.

Stevens D. Sleep Medicine Secrets. Hanley & Belfus, Inc., 2004.

Stradling JR, Crosby JH. Predictors and prevalence of obstructive sleep apnoea and snoring in 1001 middle-aged men. Thorax 1991; 46: 85-90.

Strohi KP, Cherniack NS, Gothe B. Physiologic basis of therapy for sleep apnea. Am Rev Respir 1986; 134: 791-802.

Suratt PM, McTier RF, Wilhoit SC. Upper airway muscle activation is augmented in patients with obstructive sleep apnea compared with that in normal subjects. Am Rev Respir Dis 1988; 137: 889-894.

Tishler PV, Larkin EU, Schluchter MD, Redline S. Incidence of sleep-disordered breathing in an urban adult population: the relative importance of risk factors. JAMA 2003; 289: 2230-7.

Van Lunteren E, Strohl KP. The muscles of the upper airway. Clin Chest Med 1986; 7: 171-188.

Veasey S. Pharmacotherapeutic trials for sleep-disordered breathing. In: Pack A, editor. Sleep apnea pathogenesis diagnosis and treatment. New York: Marcel Dekker; 2002; PP: 607-22.

Vgontzas AN, Bixler EO, Chrousos GP. Metabolic disturbances in obesity versus sleep apnoea: the importance of visceral obesity and insulin resistance. J Intern Med 2003; 254: 32-44.

Vos PJ, Folgering HThM, van Herwaarden CLA. Predictors for nocturnal hypoxaemia (mean SaO, < 90%) in normoxic and mildly hypoxic patients with COPD. Eur Respir J 1995; 8: 14-77.

Weersink EJM, Douma RR, Postma DS, Koeter GH. Fluticasone propionate, salmeterol xinafoate, and their combination in the treatment of nocturnal asthma. Am J Respir Crit Care Med 1997; 155: 1241-6.

Weitzenblum E, Krieger J, Apprill M, Vallee E, Ehrhart M, Ratomaharo J, Oswald M, Kurtz D. Daytime pulmonary hypertension in patients with obstructive sleep apnea syndrome. Am Rev Respir Dis 1988; 138: 345-349.

Wetter DW, Young TB, Bidwell TR, et al. Smoking as a risk factor for sleep-disordered breathing. Arch Intern Med 1999; 154: 2219-2224.

White JE, Drinnan MJ, Smithson AJ, et al. Respiratory muscle activity during rapid eye movement (REM) sleep in patients with chronic obstructive pulmonary disease. Thorax 1995; 50: 376-382.

Whyte KF, Douglas NJ. Peripheral edema in the sleep apnea/hypopnea syndrome. Sleep 1991; 14: 354-356.

Wiegand L, Mende CN, Zaidel G, Zwillich CW, Petrocella VJ, Yancey S, et al. Salmeterol vs Theophylline: sleep and efficacy outcomes in patients with nocturnal asthma. Chest 1999; 115: 1525-32.

Winkelman JW, Goldman H, Piscatelli N, et al. Are thyroid function tests necessary in patients with suspected sleep apnea? Sleep 1996; 19: 790-3.

Woodson BT, Conley SF. Prediction of uvulopalatopharyngoplasty response using cephalometric radiographs. Am J Otolaryngol 1997; 18: 179-184.

Wright JL, Cagle P, Churg A, Colby TV, Myers J. Diseases of the small airways. Am Rev Respir Dis 1992; 146: 240-262.

Wu DMH and Center DM. Chronic Bronchitis and Broncіectasis. In: A Practical Approach to Pulmonary Medicine, By: Goldstein RH, O'Connell JJ, Karlinsky JB (editors). Lippincott Rave 1997; Ch 15; PP: 240-252.

Yaggi H, Mohsenin V. Sleep-disordered breathing and stroke. Clin Chest Med 2003; 24: 223-37.

Yoshikawa M, Yoneda T, Kobayashi A, Fu A, Takenaka H, Narita N, and Nezu K. Body Composition Analysis by Dual Energy X-

ray Absorptiometry and Exercise Performance in Underweight Patients With COPD. Chest 1999; 115: 371-375.

Young T, Evans L, Finn L, Palta M. Estimation of the clinically diagnosed proportion of sleep apnea syndrome in middle-aged men and women. Sleep 1997; 20: 705-6.

Young T, Finn L, Austin D, Peterson A. Menopausal status and sleep-disordered breathing in the Wisconsin Sleep Cohort Study. Am J Respir Crit Care Med 2003; 167: 1181-5.

Young T, Palta M, Dempsey J, et al. The occurrence of sleep-disordered breathing among middle-aged adults. N Engl J Med 1993; 328: 1230-1235.

Zielinski J, MacNee W, Wedzicha J, Ambrosino N, Braghiroli A, Dolensky J, et al. Causes of death in patients with COPD and chronic respiratory failure. Monaldi Arch Chest Dis 1997; 52(1): 43-47.