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Sleep Disordered Breathing

Natural evolution and metabolism

Minireview based on a doctoral thesis

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INTRODUCTION

The need for sleep is common to all human beings throughout life. It is a fact that the time spent asleep occupies one third of our lives. Furthermore, it is common knowledge that if you sleep well you perform well the next day, and that if you do not, your performance suffers. We now know that sleep disordered breathing means fragmented and disrupted sleep, hypoxia of a peculiar intermittent or remittent manner, and respiratory effort with increased negative intrathoracic pressure. After three decades of exhaustive research work on sleep disordered breathing, we no longer need to ask questions such as whether sleep disordered breathing has anything to do with our physiology. Rather, we need to ask how sleep disordered breathing affects our physiology. If we accept as fact that the relationship between sleep disordered breathing and cardiovascular disease, such as hypertension, is more than a coincidence, then we should investigate the metabolic aspect of sleep disordered breathing.

SLEEP DISORDERED BREATHING

DEFINITIONS

Recently, the American Academy of Sleep Medicine has published new recommendations for classification, definitions, and severity rating of sleep disordered breathing syndromes. The aim was to facilitate comparability of studies for research purposes (1).

Snoring

Snoring is an inspiratory, or prevalently inspiratory, noise produced by vibration of the soft parts of the oropharyngeal walls during sleep (2). It can be classified as mild, moderate or severe on the basis of frequency and disturbance to other people such as a bed partner (3). The pathological importance of snoring is related to its intensity (dB), timing (continuous or interrupted), and the length of sleep time which is occuppied by snoring (snoring index) (3). Snoring can not be considered harmless to the sleeper. At least it is a potential marker for OSA. At worst, it is a disease characterized by daytime dysfunction and may increase the snorer's risk of vascular disease (4).

Apnea is an at least 10 sec pause in respiration during sleep. This pause may take the form of obstructive apnea caused by closure of the pharyngeal airway during inspiration, central apnea caused by lack of central respiratory drive or a combination of both (mixed apnea) with the central component preceding the obstructive component (5). However, apnea episodes that occur at sleep onset or during bursts of rapid eye movement in REM sleep should not be considered pathologic since they occur in normal populations (6).

Hypopnea

There is a very real confusion in the literature over the definition of hypopnea, as some describing the condition as a decrease in the airflow signal, some as a decrease in thoracoabdominal movement, and others as a decrease in airflow in association with a 4% drop in oxygen saturation and/or EEG or movement arousals (7). In a survey of 100 sleep laboratories accredited by the American Sleep Disorders Association, there was no consensus about either recording techniques or definitions of hypopnea (8).

Arousal

There is no universal agreement as to what exactly constitutes an arousal. An arousal represents a protective mechanism to restore ventilation and normalize blood gases whenever the upper airway is occluded (9). The mechanisms of arousal from sleep remain unclear and it is unlikely that any single factor is responsible for arousal (9). Different mechanisms have been suggested including pressure-sensitive mechanoreceptors (10), augmented carotid body output resulting from hypoxia (11), and receptors sensitive to hypercapnia (12, 13). Increased respiratory effort may be the direct stimulus to arousal as arousal occurred in normal subjects exposed to hypoxia, hypercapnia and inspiratory resistive loading during sleep, but the respiratory effort (peak Pes) for each subject was similar at the point of arousal regardless of the stimulus (14).

Obstructive Sleep Apnea (OSA)

An early definition of OSA was: more than 5/h of more than 10 second apneas (15) or the presence of 30 or more episodes of apnea per 7 hour sleep period (16). Recently, OSA is defined as recurrent episodes of obstructive hypopneas and/or apneas. The inadequate alveolar ventilation usually result in oxygen desaturations and in cases of prolonged events, a gradual increase in PaCO2. The events are often terminated by arousals (1). It is probably not useful to try to define a threshold for normality but rather to accept the existence of a continuum and quote prevalences for various levels of sleep apnea activity to allow correlations with manifestations, consequences and risk/benefit ratios for various treatments (17).

Obstructive Sleep Apnea-Hypopnea Syndrome (OSAHS)

An early definition of OSAS was: a potentially lethal condition characterized by multiple obstructive or mixed apneas during sleep associated with repetitive episodes of inordinately loud snoring and excessive daytime sleepiness (EDS) (18). The more recent definitions involved hypopneas; hence

the title OSAHS became more accepted. The syndrome is essentially a combination of recorded OSA events (see previous section) and daytime symptoms such as EDS and/or other physical or mental effects (1).

Upper Airway Resistance Syndrome (UARS)

The UARS is defined as the combination of a clinical complaint (daytime sleepiness, presence of abnormal multiple sleep latency test (MSLT)) with demonstration of flow limitation (esophageal pressure -Pes- monitoring) and demonstration of increased respiratory efforts related arousals (RERA) following peak negative inspiratory Pes (19). As there was not enough evidence to suggest that UARS was a distinct syndrome with unique pathophysiology, the American Academy of Sleep Medicine replaced UARS by RERA and include this under the definition of OSAHS (1).

Central Sleep Apnea

There is a small minority of patients who have true central sleep apneas. Such patients generally have coexisting cardiovascular or cerebrovascular disease (20).

EPIDEMIOLOGY

Epidemiology of Snoring

Prevalence studies were based on self-reported snoring. In Italy, habitual snorers (subjects who reported snoring every or almost every night) constitiute about 25% of men and 15% of women (21). In the age group of 41 to 65 years, about 60% of men and 40% of women are habitual snorers (2). In Finland, 30% of those between 40 and 69 years of age are habitual snorers (22). In Sweden, habitual snoring (loud and disturbing snoring often or very often) was found in 15% of a male population aged 30 to 69 years, increased to 20% after 10 years, with an age-related increase in snoring up to 60 years of age, followed by decline (23, 24). The different results in these studies was in part due to lack of standard defintions of snoring and habitual snoring.

Epidemiology of OSA and OSAHS

The 1993 study of Young et al. can be considered the most comprehensive polysomnographic prevalence study of OSA and OSAHS in men and women. They administered questionnaires to 4,284 subjects, followed by polysomnography on 602 habitual snorers. This study gave estimated prevalences of 9% for women and 24% for men for an apnea-hypopnea index (AHI) of ≥ 5. According to this study, 2% of women and 4% of men meet the minimal diagnostic criteria for OSAHS (25). The apparent OSAHS prevalence reported by the major prevalence studies varies from as little as 0.3% to as much as 15% (25-31). The results of Stradling & Crosby (30) and the study by Olson et al. (31) lie towards opposite ends of this spectrum (32). However, when the results of Stradling & Crosby were reanalysed after considering the effects of changes in disease definition, methodology and population characteristics, the prevalence exceeded the minimum prevalence reported by Olson et al. (32).

OSA in Specific Populations

OSA is very common among elderly people, patients with morbid obesity, acromegaly, asthma, hypertension and other cardiovascular disease, type 2 diabetes, and among patients with craniofacial abnormalities (33). Pediatric studies suggest that OSA occurs in approximately 17% of obese children and adolescents and is manifested by snoring, restlessness at night with difficult breathing, arousals and sweating, nocturnal enuresis, and EDS (34).

PATHOPHYSIOLOGY

Many risk factors that may contribute to the evolution of upper airway narrowing have been suggested (9, 17, 20) (Fig. 1).

General Factors

Airway size is affected by obesity, aging, and genetically-driven variability in jaw position, tonsillar tissue, tongue size, etc. (35, 36). Although it is widely believed that the risk of developing OSA increases with age in men, it is well accepted that an AHI ≥ 5/hour may be a normal finding in elderly subjects (37). Normal males have significantly higher pharyngeal and supraglottic resistance than normal females (9, 35). A familial aggregation of sleep-disordered breathing was reported in several studies (38-41). Smoking is a risk factor for snoring (24) and OSA (42). Alcohol intake influences snoring and OSA, both by inducing peripheral vasodilatation and the consequent swelling of the mucosa and by depressing the respiratory centers in the medulla (43) or by depressing the arousal response (44).

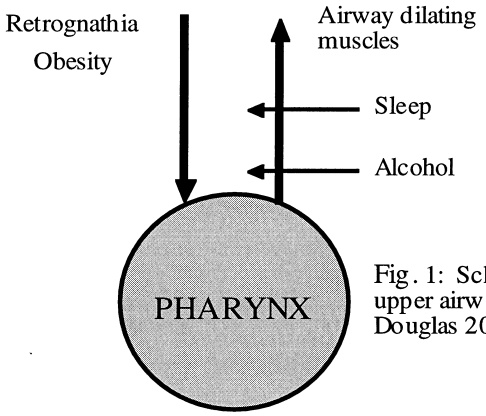

Fig. 1: Schematic diagram of upper airway physiology, from Douglas 2000 (20).

Reduced Upper Airway Calibre

Factors that reduce upper airway calibre lead to increased upper airway resistance with the generation of a more negative pharyngeal pressure during inspiration and thereby predispose to upper airway occlusion during sleep (45). The location of this occlusion is generally either behind the uvula and soft palate or behind the tongue (46). Conditions associated with facial dysmorphism

and/or mandibular abnormalities, such as micrognathia or retrognathia, show a predisposition to OSA (47-49). Also, infiltration of upper airway muscles and soft tissues, as seen in acromegaly or myxedema, can impair muscle function and reduce the upper airway lumen (9).

Mechanical Factors

The segment of the upper airway extending from the nasal choanae to the epiglottis in humans lacks rigid or bony support and may thus collapse in the absence of forces to maintain patency (46). Pharyngeal compliance in snorers with OSA is increased compared to non apneic snorers. Patients with OSA have more collapsible upper airway during wakefulness than control subjects (50).

Upper Airway Muscle Function

The activity of the upper airway muscles is modulated by chemical stimuli, vagal input, changes in upper airway pressure and baroreceptor activity (51). The upper airway is subjected to collapse when the force produced by these muscles, for a given cross-sectional area of the upper airway, is exceeded by the negative airway pressure generated by inspiratory activity of the diaphragm and intercostal muscles (52). Factors that interferes with increase in genioglossus activity, such as sleep, onset of REM sleep or periodicity of central drive, can predispose to upper airway collapse (36, 53).

Upper Airway Reflexes

Evidence suggests that these reflexes are pressure sensitive and interference with them could lead to an imbalance between intrapharyngeal pressure and the contraction of upper airway dilating muscles, resulting in OSA (9, 54-56).

Factors of the Central Nervous System

Upper airway resistance in OSA appears to be influenced by the intensity of the central respiratory drive, as determined by relating measurements of mouth occlusion pressure to mean inspiratory flow. At specific levels of respiratory drive, a similar decrease in central respiratory drive leads to a greater increase in pharyngeal resistance among OSA patients than among normal subjects, which is not explained by differences in weight and age (57).

Variability in inspiratory muscle timing among patients with OSA could result from periodicity of the central respiratory controller (58). During the hypopneic portion of the periodic breathing cycle, there is a greater fall in amplitude of upper airway muscle EMG than diaphragm EMG, and the normal preactivation of upper airway EMG is not apparent (58).

Arousal

Arousals lead to sleep fragmentation, which in itself can worsen the underlying OSA (59). Sleep deprivation selectively decrease genioglossus EMG activity (60) and sleep fragmentation leads to a higher upper airway collapsibility than does sleep deprivation (61). Arousals could potentially predispose to further apneas by virtue of the hyperventilation that occurs with relief of upper airway

obstruction. The resultant fall in PaCO2 and increase in oxygen saturation will predispose to further apneas (9).

DIAGNOSIS

Clinical Features of OSAHS

Possible clinical features include: male sex, age of more than 40 years, obesity, history of hypertension, EDS, loud habitual snoring, unrefreshing nocturnal sleep, fatigue, morning headaches, disturbed sleep, observed apneas, nocturnal gasping, choking, or resuscitative snorting, nocturia, cognitive impairment, impotence, depression, nocturnal esophageal reflux, secondary polycythemia or ankle swelling for which no other cause is known (1, 7, 62, 63).

Possible findings on clinical examination include the presence of upper airway abnormalities, such as an enlarged soft palate, tonsillar hypertrophy, or narrowed pharynx with an enlarged uvula, retrognathia, an increased body-mass index, an increased neck circumference, and hypertension (62, 63).

Differential Diagnosis

Other causes of EDS need to be considered, such as narcolepsy, idiopathic hypersomnolence, periodic limb movement disorder, post-traumatic hypersomnolence, Kleine-Levin syndrome, psychiatric illness, psychological sleepiness, insufficient sleep, shift work, and drug abuse (20).

Monitoring Techniques

1. Polysomnography

The OSAHS was originally diagnosed by polysomnography, which is still the gold standard for diagnosis (see page 34 for more details). However, the need for this relatively expensive investigation has been questioned as a result of both the limitation of health care budgets and the flood of patients being referred for investigation (62). EEG and EMG are essential for detection of arousals. It has, however, been suggested that from a clinical point of view it may be better to detect arousals by looking at changes in blood pressure or respiratory pattern than by EEG (62).

2. Oximetry

When tested against detailed polysomnography, using episodes of >4% drop of oxygen saturation detects about 20% fewer events than conventional criteria (64) and oximetry alone can detect only two thirds of patients with OSAHS (65). Oximetry is less useful in detecting patients with the UARS (62). Further, one third of the patients who had AHI of $\geq$ 15/ hour had < 5, 4% desaturations/hour (64).

3. Techniques to record Airflow Limitation

Temperature based systems (thermocouples and thermistors) are widely used although they underestimate changes in nasal flow, do not provide a quantitative estimation of ventilation, and can not detect UARS (7, 66). The use of nasal prongs connected to a pressure transducer is a useful

alternative (66). Other methods include expired carbon dioxide detectors, tracheal sounds, and measurement of true flow using a face mask and pneumotachograph system (62).

4. Techniques to record Thoracoabdominal Movement

These include inductance plethysmography, impedance pneumography, mercury strain gauges, piezoelectric systems, and static charge-sensitive beds (SCSB) (62).

5. Techniques to record Snoring

There is no standard technique for objective measurement of snoring. Different methods have been used for analysis of snoring sounds, such as Leq-Equivalent continuous sound level, or power spectrum with frequency values, formantic structure data and typical shape, which can help to distinguish simple snoring from heavy snoring with OSA (3). Using snoring and heart rate for the diagnosis of OSA have demonstrated high sensitivity of these variables (96 and 58%) but low specificity (27 and 39%) in comparison to polysomnography (3).

6. Diagnosis of UARS

This may be achieved by invasive recording techniques such as intraesophageal catheter to detect Pes along with EEG monitoring to detect arousals or, less invasively, by detecting airflow limitation (see above) or by SCSB or thoracoabdominal phase angle (62).

7. Limited Sleep Study Equipment

Most of these equipment contains an oximeter with varying combinations of sensors to detect snoring, heart rate, body position, airflow, and thoracoabdominal movement (3, 62, 67). High levels of feasibility, reliability, and reproducibility of measuring sleep disordered breathing with the Eden Tec (see page 32 for more details) were reported (67). Some authors suggested that the AHI can be used as an index of sleep fragmentation (68) and justified that by the high correlation (r=0.85) between the AHI and the EEG arousal index (69). Limited sleep study will usually suffice in the following situations: in patients highly likely to have OSAHS, habitual snorer who reports EDS and/or observed apneas, simple snorers with no features of OSAHS. Only if this limited study is equivocal should a polysomnography be carried out (62, 63).

Assessment of Upper Airway Calibre

Useful information relating to the anatomy of the upper airway can be obtained from a variety of imaging techniques, including lateral cephalometry (70), acoustic reflection (71), CT scanning, cine-CT, and ultrafast CT (72-74), and MRI (75, 76).

TREATMENT

Treatment of OSAHS is aimed primarily at controlling the complications of the disease; thus the treatment decisions should be based on EDS and cardiopulmonary function rather than on the AHI (32, 63). However, the goals of treatment should also aim at establishing normal nocturnal

oxygenation, abolishing snoring, and eliminating disruption of sleep due to upper airway closure (63).

Conservative Treatment

Weight loss, the most important conservative treatment, is quite effective in decreaseing the number of apneic events, the extent of arterial oxygen desaturation, and the amount of sleep disruption seen in patients with OSA (77, 78). Weight reduction surgery (gastric reduction or bypass surgery) has been found to be quite effective in treating obese individuals with OSA (79).

Continuous Positive Airway Pressure (CPAP)

CPAP provides a pneumatic splint that prevents narrowing and closure of the upper airway regardless of the site of obstruction (80). The main problem with this therapy is poor patient compliance (81, 82). Side effects reported by patients using CPAP include discomfort or irritation related to the nasal mask (77), nasal congestion and occasional rhinorrhea, nasal dryness, increased resistance to exhalation or sensation of too much pressure in the nose, claustrophobia, or air leaks from the mouth (63). A system that is fitted with a ramp (which allows a gradual increase in the positive pressure to the prescribed level over a period of 5 to 45 minutes) or Bilevel pressure system (BiPAP) may solve the problem of increased resistance to exhalation (63).

Oral Appliances

Patients with mild OSA who do not tolerate CPAP are good candidates for trying an oral appliance (63). A wide variety of appliances are available, differing both in construction and in the manner in which they alter the oral cavity, for example: the tongue-retaining device, and Herbst appliance which forces the mandible forward (63, 83).

Medications

Various pharmacologic agents have been tried to treat OSA, such as thyroxine, acetazolamide, medroxyprogesterone, theophylline, opioid antagonists, nicotine, angiotensin-converting enzyme inhibitors, protriptyline, fluoxetine, psychotropic agents, and benzodiazepines, but to date none has been very successful (77, 84-86). Nocturnal oxygen therapy is a possibility for patients who have severe desaturation and are intolerant of or will not accept other, more effective, treatments (87).

Surgical Treatment

1. Tracheostomy

Although tracheostomy can provide dramatic improvement and can be lifesaving (88), the availability and acceptance of CPAP have lessened the need for this therapy.

2. Upper Airway Reconstruction

The most commonly performed procedure, uvulopalatopharyngoplasty (UPPP), is curative in less than 50% of patients and even when the technical results of surgery are good, obstruction may continue at the site of surgery in the soft palate, or elsewhere in the upper airway (89). Laser-

assisted UPPP which has been introduced as an outpatient treatment for snoring, is not currently recommended for the treatment of OSA (63). Other procedures have been developed involving genioglossus advancement or maxillomandibular advancement, with or without resuspension of the hyoid bone, and may be performed in conjunction with UPPP (63, 90).

CONSEQUENCES OF OSA

Cerebrovascular Disease

In patients with OSA, intracranial pressure increases in a cyclical pattern, with the maximum immediately after the termination of apnea (91). The increase in intracranial pressure is secondary to both the cerebral vasodilatation caused by hypercapnia and the apnea-related increases in systemic blood pressure and central venous pressure. This increased intracranial pressure is probably the major contributing cause of the nocturnal and morning headaches and strokes in patients with sleep disordered breathing (91-93).

Excessive Daytime Sleepiness (EDS)

Using the Epworth Sleepiness Scale (ESS), MSLT or the maintenance of wakefulness test (MWT), it has been shown that patients with OSA tend to have EDS which is related to apnea severity and improves following CPAP therapy (94-96). Sleep fragmentation, lack of SWS, and recurrent hypoxemia have all been proposed as the cause of EDS in OSAHS (94). However, it is a common clinical observation that some patients with loud snoring and no OSA may have EDS, whereas some patients with severe OSA deny any sleepiness (19).

Psychological/Psychiatric Consequences

Sleepiness, fatigue, irritability and personality change have been attributed to nocturnal desaturation and the chronic sleep deprivation caused by sleep fragmentation (63). Intellectual deterioration, personality and behavioral changes, anxiety, and depression are well recognised features of sleep disordered breathing (94, 97, 98). Cognitive impairment is related to the severity of the sleep hypoxemia (99) and also to the sleep fragmentation (100).

Non-Diabetic Endocrine Consequences

In patients with OSA, decreased libido and impotence are not uncommon problems (16, 94). Sleep disordered breathing causes hypothalamic-pituitary dysfunction which is reversible following CPAP treatment (101). Sleep disordered breathing is associated with marked reduction in growth hormone (GH) concentrations, with a significant increase with CPAP therapy (102, 103). In children with tonsil hypertrophy, improvement of sleep breathing disorders by surgery was associated with a positive effect on the GH secretion (104). OSA is associated with elevated catecholamines and cortisol and decreased TSH and LH levels (105).

Hematological and Biochemical Consequences

The normal diurnal reduction in serum erythropoietin concentrations does not occur in patients with OSA (106). An elevated hematocrit was reported in OSA patients with a rapid reduction after CPAP

therapy (107). Excess production of atrial natriuretic peptide (ANP) with excessive nocturnal diuresis in OSA was also reported as improved after using CPAP (108). Other abnormalities were also reported, such as increased uric acid (109), abnormal prostaglandin biosynthesis (110), impaired endothelium-dependent vascular relaxation (111), abnormal renin-angiotensin function (112), low blood fibrinolytic activity (113), and increased platelet activation and aggregation (114).

Renal Consequences

Patients with sleep disordered breathing commonly complain of nocturia (16, 108). Patients with sleep disordered breathing are also more prone to have proteinuria (115). It is possible that OSA is an important cause of the progression of the chronic renal failure, as years of episodes of nocturnal hypertension, hypoxemia, hypercapnia as well as the daytime hypertension might cause or at least contribute to the progression of the disease (116).

Traffic and Occupational Accidents

OSA is a well recognised cause of both automobile and occupational accidents (117-119).

Mortality

There is an increased mortality in subjects with snoring and OSA, mostly in those younger than 50 years (120-122). The major cause of this increased mortality appears to be cardiovascular in nature (123).

SLEEP DISORDERED BREATHING: A PROGRESSIVE PROBLEM ?

Whether OSA is indeed a progressive condition has important implications for the care of patients and for public health policy (124). The hypothesis of evolution from just snoring when younger and lighter in weight to OSA when older and heavier was proposed early (125). Nevertheless, natural history studies are rare (126). The two studies that investigated severe OSA in more obese subjects failed to find any progression over a time span of years (124, 127). The other two, who investigated subjects with mild to moderate OSA with less obesity found a rapid progression within months (128, 129).

Possible mechanisms for producing disease progression involve the traumatizing effect of repeated loud snoring on the upper airway which causes structural remodelling, edema, myxomatous degeneration of the uvula, changes in the muscle fibres, and reduction in the upper airway sensation and reflex responses (130).

Undertaking research into the natural history of OSA is particularly difficult for several reasons, including the study material, ethical problems, and expense (126, 130). The most meaningful data would involve a large prospective community cohort with a wide range of OSA severity and access to full polysomnographic facilities (126).

SLEEP DISORDERED BREATHING AND CARDIOVASCULAR DISEASE

SNORING AND CARDIOVASCULAR DISEASE

Almost 50% of patients with cardiovascular disease are habitual snorers compared to 30% of controls (131). Among Swedish obese population, self-reported loud snoring and observed breathing pauses was associated with ischemic heart disease and blood pressure after adjustment for potential confounders (132). Habitual snoring was associated with a 10-year incidence of hypertension in a middle aged male population independent of confounders (133). In men and women who snored between the fifth and tenth decades of life, the association between snoring, hypertension, and ischemic heart disease persisted even after correction for smoking and obesity (134). Habitual snoring carries a significant risk for myocardial infarction even after adjusting for other factors (131) Snoring was not associated, however, with cardiovascular risk factors or clinical cardiovascular diseases in two elderly populations (135, 136).

Habitual snoring is an independent risk factor of ischemic stroke (131, 137, 138), except for the elderly (135). Furthermore, in a multiple stepwise logistic regression analysis, snoring was the only independent risk factor differentiating stroke occurring either during sleep or during the first 30 minutes after awakening from stroke occurring at other times of the day (92). Previous stroke and habitual snoring were the only two risk factors adversely to effect mortality of stroke (93).

Snoring significantly worsened the prognosis of patients with risk factors for cardiovascular disease (hypertension, diabetes, obesity, smoking, high serum cholesterol level) in comparison to non-snorers with the same risk factors (139). Although snoring was not associated wiht an increased risk of cardiovascular or all-cause mortality either in an elderly (135) or a middle aged population (120), snoring with EDS was significantly associated with mortality in the middle aged population (120).

OSA AND CARDIOVASCULAR DISEASE

There is a dose-response association between sleep disordered breathing and the development of hypertension independent of known confounding factors (140). The frequently reported association of OSA and essential hypertension led to the hypothesis of an etiological association between OSA and hypertension (116, 141, 142). This is further confirmed by animal models where repetitive apneas led to prolonged diurnal blood pressure elevation (143).

Further, secondary hypertension, caused by excessive alcohol intake, chronic renal failure, diabetes, hypothyroidism or acromegaly have a higher than normal prevalence of OSA and OSA may contribute to the hypertension and organ damage found in these conditions as well (116).

Sleep disordered breathing is an independent predictor of coronary artery disease, cardiac arrhythmia, and stroke (144-148). Left ventricular afterload increases during OSA and results in left ventricular hypertrophy or dysfunction in patients with OSA compared to control subjects (149). CPAP can result in improved left ventricular functions in patients with OSA (150, 151). OSA was found to be a significant predictor for all-cause mortality, most probably by being a risk factor for cardiovascular disease (152).

The prevalence of pulmonary hypertension in patients with OSA has been reported to be between 10% and 20% (153). The changes in pulmonary artery pressure are due both to the effects

of obstructed inspiratory efforts on pulmonary and cardiac dynamics, and to pulmonary hypoxic vasoconstriction (94). However, no significant decrease in pulmonary artery pressure was found following CPAP therapy (154). Right heart failure and hypercapnic respiratory failure both occur in severe OSA. These patients tend to be more obese, with daytime hypoxemia and associated airway obstruction (94).

SLEEP DISORDERED BREATHING AND OBESITY

Obesity is a complex multifactorial syndrome of appetite regulation and energy metabolism (155, 156). About one in every three persons is at least 20% above ideal body weight and 5% have direct obesity-related serious health problems (157). In the U.S.A., about 35% of women and 31% of men aged 20 and older are obese, as well as 25% of children and adolescents (155, 158).

Obesity raises the risk of morbidity and mortality from hypertension, dyslipidemia, coronary artery disease, stroke, gall bladder disease, insulin resistance and type 2 diabetes mellitus, degenerative osteoarthropathy, OSA and respiratory problems, and endometrial, breast, prostate, and colon cancers (158, 159). The scientific evidence suggests strongly that obese individuals who lose even relatively small amounts of weight are likely to decrease this risk (155, 160).

Health risks are generally associated with increased body mass index (BMI, a measure of whether weight is appropriate for height, measured in kg/m2) and more importantly with excess abdominal/visceral fat (as estimated by a waist-hip circumference ratio [WHR]) (155, 161). Central obesity is an independent risk factor for coronary heart disease and stroke (162). The importance of the WHR lies in its ability to discriminate risk at least among overweight individuals with BMI <30 kg/m2 (163). Males typically accumulate fat intraabdominally/viscerally while female adiposity is subcutaneous and particularly over the thighs (34).

Smoking is associated with lower body weight but higher WHR. These smoking-associated differences in body fat distribution may mediate, at least in part, the high prevalence of diabetes among smokers (164). Moreover, smoking cessation increased insulin sensitivity inspite of a modest increase in body weight (165).

OSA AND OBESITY

Assessment of cardiorespiratory consequences of OSA is difficult owing to confounding obesity that is strongly associated with OSA (166). Approximately 50% of morbidly obese subjects have OSA (167). Either obesity or central obesity (defined as WHR $\geq$ 1.0) was present in more than 50% of patients with OSA (168). The BMI, but not the WHR, was significantly correlated to the severity of respiratory disorders (168, 169). In subjects with massive obesity (BMI > 40 kg/m2), however, no significant differences were found in the BMI in OSA versus non-OSA groups (166). Gastric restriction procedures, a surgical treatment of choice for morbidly obese persons, is followed by a clear cut reduction or even disappearance of obesity-related OSAHS (170, 171).

The mechanism for the relationship between obesity and OSA may be mechanical obstruction or hypoxemia (172). Mechanical mechanisms include fat deposition in the pharyngeal walls (173), smaller lung volumes which can indirectly influence upper airway size (174), or external compression by increased neck circumference (175, 176).

Some evidence suggests, however, that sleep apnea may promote weight gain, mainly central obesity, or prevent weight loss by several mechanisms: reduction in anabolic (GH and testosterone) hormone secretion, influences on energy balance and insulin sensitivity, and altered central serotonergic tone (177) (Fig. 2).

More important, a synergestic interaction of both pathomechanisms favors the development of insulin resistance and arterial hypertension. Obese patients with OSA thus constitute a high-risk group for the development of cardiovascular disease (178). Morbidly obese men with OSA have a high risk of sudden cardiovascular death, despite the absence of other conventional risk factors (179).

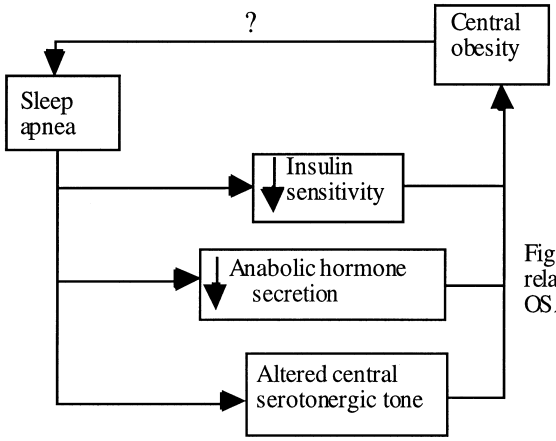

Fig. 2: Factors involved in the relationship between central obesity and OSA, from Grunstein 2000 (181).

OSA AND CENTRAL OBESITY - WHY?

There is a strong epidemiological link between central obesity and OSA (177, 180, 181) and OSA may contribute to morbidity in the metabolic syndrome observed in the centrally obese (1329. Thus, the observation of central obesity in OSA is possibly more important because of its links with insulin resistance and both macrovascular and microvascular disease than mechanical or reflex mediated effects on the upper airway due to its association with similar fat deposits in the neck (167, 180).

SLEEP DISORDERED BREATHING AND DIABETES MELLITUS

NEW DIAGNOSTIC CRITERIA FOR DIABETES MELLITUS

A major consistent epidemiologic finding is that type 2 diabetes is undiagnosed in about 50% of the prevalent cases based on the use of the oral glucose tolerance test (OGTT) (182, 183). In the interest of standardization and also to facilitate work in epidemiological studies, a fasting plasma glucose (FPG) $\geq$ 7.0 mmol/l or a fasting blood glucose $\geq$ 6.1 mmol/l has been recommended as a diagnostic cut-off point for diabetes (182, 184). A new group, defined as having 6.1$\leq$ FPG < 7.0 mmol/l (5.6 $\leq$ FBG < 6.1 mmol/l) was titled as impaired fasting glucose (IFG) (182, 184). An FPG $\geq$ 6.1 mmol/l (FBG $\geq$ 5.6 mmol/l) has been chosen as the upper level of normal because it is

near the level above which acute phase insulin secretion is lost in response to intravenous administration of glucose, is a risk factor for future diabetes and/or cardiovascular disease, and is associated with the insulin resistance syndrome (185,186).

EPIDEMIOLOGY OF DIABETES MELLITUS

The estimated worldwide number of people with diabetes is over 100 million (187). Diabetes is a major cause of cardiovascular disease and all-cause mortality (187, 188). The prevalence of diabetes was estimated to be 4.3% in a Swedish cohort (189), and 12.3% in U.S. adults aged 40-74 year (190). In two cohorts, the annual incidence rate of diabetes was 3.5/1000 and 2.2 /1000 person (189, 191).

Obesity, weight gain, and central adiposity are independent risk factors for insulin resistance and type 2 diabetes (163, 192-195). Other risk factors include age, hypertension, dyslipidemia, and family history of diabetes (185, 196). Smokers have been shown to exhibit insulin resistance and markers of the metabolic syndrome (165, 197). There is a dose response relationship between smoking and the risk of type 2 diabetes and a decrease in risk for those who quit smoking (191, 197, 198). The results regarding the association between moderate chronic alcohol consumption and diabetes are equivocal (192, 199). There is an inverse association between physical activity and type 2 diabetes (200, 201).

FROM SYNDROME X TO SYNDROME Z

The metabolic syndrome (also known as syndrome X or the insulin resistance syndrome) consists of insulin resistance, compensatory hyperinsulinemia to maintain glucose homeostasis, obesity (especially central obesity), dyslipedemia, and hypertension, and constitutes a major risk factor for the development of cardiovascular disease (182, 184, 202). Insulin resistance precedes the development of type 2 diabetes (203, 204), and insulin-mediated sympathetic stimulation may result in hypertension (205).

Insulin resistance is found in obesity, in 50% of essential hypertensives, in the majority of patients with type 2 diabetes, and in 25% of normal population (167, 204). As insulin sensitivity declines, insulin secretion increases more than proportionally to compensate for insulin resistance, and in obese subjects, larger amounts of insulin are needed to maintain glucose tolerance (206).

Insulin resistance may constitute a further risk factor for the development of cardiovascular disease in patients with sleep-disordered breathing (207). Patients with OSA have many features in common with those with syndrome X, including systemic hypertension, overweight (usually with a central pattern), and insulin resistance, and dyslipidemia is likely to be present (167). There may be specific effects of OSA which further increase the cardiovascular risk; thus, syndrome X may actually include OSA and could be better considered as syndrome Z (167).

SLEEP DISORDERED BREATHING AND DIABETES

There are common clinical features for OSA and diabetes, such as obesity, hypertension, cardiovascular disease, sleepiness, tiredness, and disorders of metabolism (207-209).

The prevalence of OSA is significantly high among patients with type 2 diabetes (209, 210). OSA patients had a higher prevalence of impaired glucose tolerance or diabetes than expected (168, 178, 210), especially in the presence of hypertension (141). There is evidence for an independent association between OSA and fasting insulin levels (132, 211). Snoring was associated with impaired glucose tolerance and diabetes in elderly populations (136, 212).

OSA AND DIABETES: POSSIBLE MECHANISMS

Is It Only Obesity?

A common hypothesis is that obesity is a common risk factor for breathing disorders and insulin resistance in type 2 diabetes (213). However, the independent associations between snoring, OSA, and diabetes or insulin resistance (see previous section) suggest that OSA has an effect on insulin reistance apart from the effects of co-existent obesity (167). Further, CPAP treatment in patients with OSA and diabetes improved insulin resistance and controled glycemia (209, 214) inspite the fact that it had no effect on weight or fat distribution (167).

Diabetic Autonomic Neuropathy

Another hypothesis is that the development of autonomic neuropathy, at least in type 1 diabetes, may predispose to OSA (213). This hypothesis was supported by small studies where diabetic subjects with autonomic neuropathy were found to have a higher prevalence of OSA than other groups (215-218). Besides, the hypoxic ventilatory drive was reported to be impaired in diabetics with autonomic neuropathy compared to diabetics without neuropathy (219). In contrast to these studies, others found no significant difference between diabetics with and without neuropathy in any parameter of sleep disordered breathing (220, 221). Further, the ventilatory response to hypoxia and to hypercapnia did not differ among groups of diabetics with or without autonomic neuropathy and normal controls (222).

OSA as a Risk for Diabetes ?

An alternative hypothesis is that the events in OSA, such as hypoxemia and/or arousals, trigger different, perhaps unique, adaptations in metabolic processes involving insulin action and glucose regulation (208).

Neonatal hypoxic stress is associated with the development of type 1 diabetes within the first year of life (223). Hypoxia induced insulin resistance, impaired glucose tolerance, and hyperglycemia in animals (223-225). The mechanisms of hypoxia-induced hyperglycemia may result from defects at a prereceptor, receptor, or postreceptor level (223). Prereceptor mechanisms include the effect of hypoxia on liver function, and insulin counterregulatory hormones such as catecholamines, hydrocortisone, glucagon, and GH (223, 225).

The stability of glucose levels during sleep and the normal daytime variation of glucose tolerance is achieved by a complex relationship between glucose regulation, sleep stages and sleep quality, and circadian rhythm (226, 227). Sleep quality markedly influences nocturnal brain and tissue glucose utilization (226). Alterations of the normal nocturnal and daytime glucose tolerance have been identified in aging, obesity, and diabetes (226, 227). Chronic sleep disturbances, such as

those occuring with OSA, may be associated with disturbances of glucose regulation, which in turn contribute to the development of insulin resistance and glucose intolerance (226, 227).

SLEEP DISORDERED BREATHING AND SYMPATHETIC FUNCTION

OSA AND SYMPATHETIC ACTIVITY

Several small studies reported significant associations between OSA and increased plasma and/or urinary catecholamines or increased muscle sympathetic nerve activity both during sleep and waking periods (105, 228,229). Marked reduction of catecholamine concentrations and sympathetic nerve activity during CPAP was also reported (230-232).

Increased sympathetic activity in OSA may play an important role in the development of hypertension and other cardiovascular complications of OSA (233, 234) as there is a strong association between hypertension and sympathetic activation (235-237). Iodine-123-MIBG cardiac scintigraphy, a specific test of cardiac sympathetic function, revealed impairment of this function in OSA patients in comparison to controls (238). The reported increased sympathetic activity in OSA can explain the frequently reported insulin resistance and impaired glucose tolerance in OSA patients (167, 210).

OSA AND SYMPATHETIC ACTIVITY: POSSIBLE MECHANISMS

In patients with sleep disordered breathing, the hypoxic episodes and sleep fragmentation may play the major role in sympathetic nervous system activation (68, 228, 239, 240). It was further suggested that although hypoxia contributes more during the early stages of the development of hypertension, once sustained levels of hypertension already exist, blood pressure is modulated by the degree of sleep fragmentation (68). It is also possible that while the accumulated nocturnal hypoxia determines blood pressure during the immediate period after awakening, the degree of sleep fragmentation sets the blood pressure level during the rest of the day (68). The role of hypercapnia as a stimulant of sympathetic activity in OSA is still to be investigated (228, 231, 241).

Negative intrathoracic pressure was also suggested as a possible trigger (231, 242). However, acute production of negative intrathoracic pressure has been shown to reduce muscle sympathetic nerve activity and blood pressure (242). Furthermore, central sleep apnea without such negative pressure elicits increases in muscle sympathetic nerve activity and blood pressure similar to those with OSA (242-244).

Hypoxia and Sympathetic Function

In OSA, norepinephrine levels correlated with severity of night hypoxemia (68, 245). When arterial catecholamines were measured at varying intervals during sleep in subjects with OSA, norepinephrine was released in response to oxygen desaturation (246). Patients with OSA might also have difficulty returning blood pressure to normal levels, after the acute pressor effect, because hypoxia impaired baroreflexes (247).

In several animal (248-250) and human studies (251-254), hypoxia led to a marked increase in sympathetic nerve activity and catecholamines concentrations. Catecholamine concentrations in

plasma and in urine increased significantly in response to altitude hypoxia (255, 256). Insulin action decreases markedly in response to altitude hypoxia, with increases in insulin and glucose levels (255, 257, 258) which could be explained by the increase in the circulating catecholamines (256, 257).

Sleep Fragmentation and Sympathetic Function:

The circadian blood pressure rhythm appears to be mediated mainly by the circadian rhythm of the sympathetic tone. A disturbance in any part of the hierarchy of factors that regulate the circadian rhythm of sympathetic neural tone, such as the waking-sleep cycle, seems to disturb the circadian blood pressure rhythm (259). In patients with OSA, the normal circadian blood pressure rhythm appears to be eliminated or reversed (259). It was noticed in OSA that the normal nocturnal dip in catecholamine levels was absent (228, 260). It was also noticed that the prevalence of non-dippers is significantly higher in OSA hypertensives than in essential hypertensives (261).

Arousal increases sympathetic activity during sleep in normal subjects (262). Incresed sleep efficiency is associated with decreased urinary norepinephrine levels and percent time awake in bed is associated with increased urinary epinephrine levels (263). In subjects with OSA, movement arousals influenced daytime sympathetic tone and blood pressure independent of respiratory events and hypoxia (264).

SUBJECTS AND METHODS

POPULATION

COHORT

In 1984, there was a total of 35,779 men aged 30-69 years registered in the city of Uppsala, Sweden. With systematic random sampling of approximately every ninth man, a sample of 4,021 men was identified. A questionnaire was posted to all of them in 1984 with two reminding letters sent to the non-responders. A total of 3,201 men responded (response rate = 79.6%); their age distribution was almost the same as that of the target population (23, 28). Of these 3,201 subjects, 226 had died before 1994. To the remaining 2,975, a new questionnaire was sent in 1994. Again, after two reminding letters to the non-responders, a total of 2,668 subjects responded (response rate = 89.7%) (24, 133).

We investigated the data for those 2,668 who answered the two questionnaires. In 1984, 46 subjects did not answer the direct question "Do you have diabetes?". Of the remaining 2,622, 118 did not answer the same question in 1994. Thus, the analysis was based on the questionnaires of 2,504 subjects who answered the question on diabetes in both 1984 and 1994. Those who answered “yes” in 1994 after “no” in 1984 were defined as the new diabetics. Those who answered “no” both times were defined as non-diabetics.

HYPERTENSIVE SAMPLE

From March 1996 to February 1998 a case-control study was conducted with the main purpose of studying the relationship between sleep disordered breathing and hypertension (265). Based on the 1994 questionnaire responses, there was a total of 392/2,668 (14.7%) hypertensive subjects with the following age distribution: 21.7% aged 40 - 49 yrs, 27.8% aged 50 - 59 yrs, 28.3% aged 60 -

69 yrs, and 22.2% aged 70 - 79. To avoid a skewed age distribution, the 392 subjects were stratified with 10 year age strata, and hypertensive cases were included randomly within each age stratum. There were 116 subjects involved in the study with the following age distribution: 21.6% aged 40 - 49 yrs, 33.6% aged 50 - 59 yrs, 26.7% aged 60 - 69 yrs, and 18.1% aged 70 - 79. An age and BMI matched control group of 117 non-hypertensive men was selected from the same cohort.

We investigated the 116 hypertensive subjects, whereas the 117 controls were not considered as they did not represent a random sample of the non-hypertensive population in the original cohort.

SLEEPY SNORER SAMPLE

Based on the reported snoring and EDS in the 1984 questionnaire, a group of 166 men was defined as strongly suspected of having OSAHS (28). A sample of 61 was studied using a whole night polysomnography in 1985 (28). In 1995, seven of the 61 studied men had died. Of the remaining 54 who were invited to take part in the follow-up study, 38 (70.4%) participated in this investigation.

QUESTIONNAIRES

QUESTIONNAIRES 1984 AND 1994: DEFINITIONS

The 1984 questionnaire consisted of 15 questions about nighttime and daytime sleep related complaints and 9 questions about somatic diseases (23, 266). There were direct questions concerning hypertension, cardiac disease, psychiatric disorder, diabetes mellitus, chronic airway disease, and asthma. Other questions concerned regular medical check-ups, medications, and previous hospital admissions because of medical disorders.

A "yes" answer to the direct question "Do you have diabetes?" was defined as indicating diabetes mellitus.

Thirteen of the questions about sleep-related complaints were of the multiple-choice type. The subjects were asked to state how often they had specific symptoms by choosing one score on a 5-point scale. Snoring was investigated by asking the subjects how often they snored loudly and disturbingly. The scores were: 1 (never), 2 (seldom), 3 (sometimes), 4 (often) and 5 (very often). In the subsequent analyses, scores 4 and 5 were defined as habitual snoring.

In the questionnaire used in 1994, the first part was identical with that used in 1984. In the second part, 45 new questions were added, including questions concerning current and past smoking habits, alcohol consumption, physical activity, and work and traffic accidents (24, 133).

Based on the answers of the 1994 questionnaire, hypertension was defined as reporting regular medical check-ups for hypertension and/or answering "yes" to the question "Do you have high blood pressure?" and also being on antihypertensive medication(s).

Based on the new questions added in the 1994 questionnaire, smoking was assessed by six questions about regular smoking for at least 6 months at any time, whether the respondent was an ex-smoker or current smoker, the number of cigarettes per day and the age of starting and quitting smoking . Subsequently, it was possible to establish whether the subject had been a smoker in 1984.

Alcohol dependence was investigated only in the 1994 questionnaire using the cut-down, annoyed by criticism, guilty about drinking, eye-opener drinks (CAGE) questionnaire. Alcohol dependence was defined as answering "yes" for at least two of the four questions (267, 268).

For the level of physical activity, four categories with an increasing level of physical activity during leisure time were used (269, 270). Physical inactivity was defined as category 1; spending most time in front of the television, reading and other sedentary activity. Categories 2, 3 and 4 were considered as physically active involving activities as riding a bicycle to work, walking, fishing or bowling for at least 4 h a week or participation in more vigorous activities on a weekly basis.

NEW QUESTIONNAIRE FOR HYPERTENSIVE MEN

A structured interview-based questionnaire was answered by the 116 hypertensive subjects to confirm the regular medical check-ups for hypertension, the duration of being diagnosed as hypertensive, the duration of being treated with antihypertensive medication(s), and the type of antihypertensive medication(s). According to the number of drugs received, subjects were categorized as being treated with one drug, two drugs, or more than two drugs.

The participants were also asked if they ever had been referred to hospital or had attended regular medical controls for angina pectoris, myocardial infarction, heart failure and/or stroke. Cardiovascular disease (CVD) was defined as answering "yes" to at least one of these questions.

Parameters of severity of hypertension were defined as the duration of hypertension, the number of antihypertensive drugs received, and having had one or more CVD.

INTERVIEW BY TELEPHONE FOR SLEEPY SNORERS

A structured interview was performed by telephone on the 38 sleepy snorers before the follow-up polysomnography in 1995. The subjects were asked about their health, medications, medical check-ups, and hospital admissions because of CVD. They were asked to state whether their symptoms of snoring and EDS had decreased, increased, or been stable during the 10-year period. They were also asked whether they had ever sought medical advice because of any of these symptoms and, if so, which kind of investigation and/or treatment they had been offered. Medical records were obtained from the relevant departments.

SLEEP STUDY AT HOME

EDEN TEC

Whole night respiratory monitoring was performed on the 116 hypertensive subjects using the Eden Trace II multichannel recording system (model 3711 Eden Tec corporation, Eden Prairie Minnesota, USA) (67). The system includes a microphone, applied on the neck at the level of the thyroid cartilage to record the snoring sounds, a thermistor to record the oronasal airflow, a thoracic belt to record the thoraco-abdominal impedance, a sensor cable to record the body position, and an oxygen transducer applied to the index finger to record oxygen saturation. The subject was given the Eden Tec with detailed instructions for use. At night, the Eden Tec was applied by the subject himself at home.

All respiratory events were automatically scored (ETS 2.0 E INFINITI Medical, Täby, Sweden) and manually edited by one physician who was blinded to the actual patient identity. Total sleep time (TST) was estimated by visual assessment of the overnight tracing in conjunction with use of the subject's diary. To accept the record, TST must have totalled at least four hours. Thus, 14 recordings were rejected the first time but accepted after a second night study. A desaturation event was defined as a drop in oxygen saturation of ≥ 4%. An apnea was defined as a cessation of oronasal airflow for at least 10 seconds. A hypopnea was defined as a decline in oronasal airflow of ≥ 50% of the average peak airflow during the last two minutes for at least 10 seconds followed by a desaturation and/or an increase in thoraco-abdominal impedance of ≥ 50%. The apnea-hypopnea index (AHI) and desaturation index (DI) were calculated as the total number of such events divided by TST. Average oxygen saturation (average SaO2) and minimum oxygen saturation (Min SaO2) were determined. Snoring sounds were scored automatically and snoring index was defined as the % of TST with sounds ≥ 90 dB (271).

OSA was defined as AHI ≥ 10/h of TST whilest Severe OSA was defined as AHI ≥ 20/h.

ANTHROPOMORPHIC MEASUREMENTS

OBESITY AND CENTRAL OBESITY

Both in 1984 and in 1994 questionnaires, weight and height were reported by the subjects. For the 116 hypertensive subjects, weight, height, waist and hip circumferences were measured by the research nurse. Waist circumference was measured midway between the lower rib margin and the anterior superior iliac spine and hip circumference was measured at the widest circumference over the great trochanters. For the 38 sleepy snorers, weight and height were measured both in 1985 and in 1995 and a physical examination was performed in the Sleep Laboratory at the Department of Psychiatry.

Subsequently the body mass index (BMI) was calculated as Quetelet´s index (weight in kg / (height in m)2) (272). Those men with BMI of > 27 kg/m2 were considered as obese (155). The waist to hip circumference ratio (WHR) was calculated and central obesity was defined as WHR ≥ 1.0 (155).

BLOOD ANALYSIS

DIABETES

The hypertensive subjects returned to the clinic the following morning directly after the Eden Tec sleep recording and after at least 8 hours of overnight fasting. A fasting venous blood sample was taken for blood glucose (FBG), serum insulin (FSI) and glycated hemoglobin (HbA1c). The reference ranges for FBG, FSI and HbA1c were 3.3-5.6 mmol/l, 5-20 mU/l and 3.8-5.2%, respectively, according to our laboratory methods.

An FBG concentration of ≥6.1 mmol/l was used for the diagnosis of diabetes mellitus (DM) and blood glucose ≥5.6 to <6.1 mmol/l was defined as impaired fasting glucose (IFG) (182, 184). Thus, we defined DM, for the hypertensive subjects, as reporting regular medical controls for diabetes or previously undiagnosed diabetes with FBG ≥ 6.1 mmol/l.

URINE ANALYSIS

CATECHOLAMINES

The hypertensive subjects were instructed to void urine before going to bed for the night of the Eden Tec sleep recording and then to collect all the urine during the night and the next morning in a clean flask. The following morning, directly after the sleep recording, the urine flask was delivered to the research nurse. HCl (15 ml of 6 mol*L-1) was added to the clean flask before urine collection. After homogenization aliquots of 100 ml were transferred to clean test tubes and frozen at -20 C°.

The urine samples were analysed for catecholamines using High Performance Liquid Chromotography (HPLC) with electrochemical detection (273). Analysed catecholamines and metabolites were noradrenaline, normetadrenaline, metadrenaline, mettyramine and 3-methoxy 4-hydroxy mandelic acid (MHMA). The results were expressed in µmol per mol of creatinine except for MHMA (mmol per mol of creatinine). In the subsequent statistics, the 75th percentile (75th%) was used as a cut-off point to define subjects with high levels (≥ 75th%) and subjects with low levels (< 75th%) of catecholamines.

POLYSOMNOGRAPHY

For the sleepy snorers, the one-night polysomnography in 1995 was performed with the same method as in 1985. A 16-channel polygraph (Nihon Koden) was used. The paper size was 300 mm per page with a paper speed was 10 mm/s, resulting in epoch duration of 30 sec. Recording involved 2-channel-electroencephalogram (EEG, C4/A1 and C3/A2), 2-channel-electrooculogram (EOG, E1/A1 and E2/A1), submental electromyogram (EMG), nasal and oral airflow, thoracic and abdominal respiratory movements, static charge sensitive bed (Biorec OY), movement sensors (Siemens, 230), snoring sound, and electrocardiogram (ECG). Oxygen saturation was recorded using a pulse oximeter (BIOX III).

All the scoring procedures were performed manually by one investigator. An epoch-by-epoch approach was applied in the scoring procedures for sleep stages (274). An apnea was defined as complete cessation of oronasal airflow for at least 10 s and hypopnea as marked decrease in airflow for at least 10 s, followed by a desaturation of at least 4% from the baseline and/or an arousal. AHI was calculated as the total number of such events divided by hours of sleep. Δ AHI was calculated as AHI 1995 - AHI 1985. OSA was defined, in this study, as AHI ≥ 5/h.

STATISTICAL METHODS

Statistical analysis was performed using the StatView SE+Graphics™ (Abacus Concepts, Inc. Berkeley, CA, USA) and StatView 5.0 (SAS Institute Inc. Cary, NC, USA). For comparison of continuous variables, the unpaired t-test and ANOVA test were used while the chi-square test was used for comparison of proportions. To achieve normal distributions, all continuous variables were log transformed. Linear regression analysis was used to calculate correlations between continuous variables and the results were presented as a standard coefficient of regression (r) while Spearman Rank correlation was used for nominal variables and the results were presented as the Rho value. For simultaneous evaluation of more than two variables, multiple logistic regression analysis was

performed and the results are presented as the adjusted odds ratio (OR) with 95% confidence intervals (95% CI). A p-value of less than 0.05 was regarded as statistically significant.

ETHICAL ASPECTS

All the study protocols were approved by the Ethics Committee of the Medical Faculty at Uppsala University and all the participants gave their informed consent.

RESULTS

HABITUAL SNORING AND DIABETES

In 1984, 393 men reported habitual snoring (14.7%). The incidence of new diabetes during the 10 years was higher among the habitual snorers than among the non-habitual snorers (5.4 vs 2.4%, $p < 0.001$). The habitual snorers were older, with a higher BMI and with a higher prevalence of smoking in comparison to the non-habitual snorers.

Of the non-diabetics in 1984, 69 reported diabetes in 1994 (new diabetics) while 2,390 were still non-diabetics. Of the 69 new diabetics, 47 reported that they were receiving oral hypoglycemic drugs and only two that they were receiving insulin together with an oral hypoglycemic drug. Compared to the non-diabetics, the new diabetics were older, more obese but with less weight gain over the ten years and were more often habitual snorers at baseline.

As shown in Fig. 3, we divided the whole population into four subgroups, based on the presence or absence of obesity and the presence or absence of habitual snoring in 1984. In the snorer obese subgroup the incidence of new diabetes was higher than in the non-snorer non-obese and the snorer non-obese subgroups ($p < 0.0001$). The incidence of diabetes among the snorer obese subgroup was higher, although not significantly, in comparison with the obese non-snorer subgroup (13.5 vs 8.6%, $p = 0.17$) (Fig. 3). There was no significant difference in BMI between the snorer obese and obese non-snorer subgroups (29.3 ± 2.4 vs 29 ± 1.8, $p = 0.6$). Similar results were found when we divided the subjects into two age groups (young: 30-49 yrs and old: 50-69 yrs).

In a logistic regression model with the non-snorer non-obese subgroup as the reference group, the OR (95% CI) for development of diabetes was higher in snorer obese group [7.0 (2.9-16.9)] than obese non-snorers [5.1 (2.7-9.5)] after adjustment for age, Δ BMI, smoking, alcohol dependence and physical inactivity. Similar results were found when we divided the subjects into two age groups (young: 30-49 yrs and old: 50-69 yrs).

OSA AND DIABETES IN HYPERTENSION

Of the 116 hypertensive subjects, 25 (21.5%) had DM, 8 (7%) had IFG and 83 (71.5%) were normoglycemic. Among the 25 subjects with DM, 16 (64%) were obese and 21 (84%) had central obesity, compared to 31 (37%) obese and 53 (64%) with central obesity among the 83 normoglycemic subjects. There were no significant differences in the use of any major type of antihypertensive drugs (beta blockers, ACE inhibitors, and calcium-channel antagonists) between the diabetic patients and the normoglycemic subjects, and all five subjects on thiazide diuretics were normoglycemic subjects.

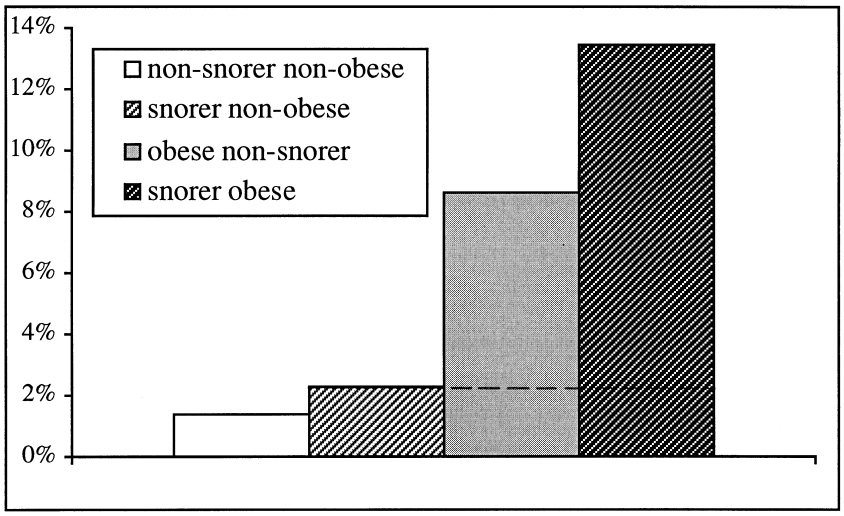

Fig. 3: Incidence of new diabetics, from 1984 to 1994, in four sub-populations based on combinations of habitual snoring and obesity.

Subjects with DM had a higher mean BMI and a higher mean WHR compared to normoglycemic men. There was a trend, although not significant, of an increasing snoring index, AHI and DI from normoglycemic subjects to IFG subjects to DM subjects, while the Min SaO2 was decreasing in the same direction, e.g., AHI and DI were higher in the DM group compared to the normoglycemic group (p=0.06 and 0.08, respectively). The prevalence of severe OSA increased significantly from 14.5% in normoglycemic subjects and 12.5% in IFG subjects to 36% in DM subjects ($p<0.05$).

First, we divided the 116 subjects into four subgroups based on the presence or absence of severe OSA, (AHI $\geq$ 20/h) and the presence or absence of central obesity (WHR$\geq$1.0). The prevalence of DM was significantly higher in the group of OSA WHR$\geq$1.0 in comparison to the control group (non-OSA, WHR<1.0) ($p < 0.01$) (Fig. 4[A]). The WHR did not significantly differ between the two groups with central obesity (1.02 ± 0.02 vs 1.03 ± 0.03, p=0.1). We then performed the same calculations replacing central obesity with obesity (BMI > 27 kg*m-2). In comparison to the non-OSA non-obese group, the prevalence of DM was significantly higher in the OSA obese group ($p < 0.01$) (Fig. 4[B]). BMI did not significantly differ between the two obese groups (30.7 ± 3.6 vs 32.3 ± 4.2, p=0.14).

In a multiple logistic regression model with the same subgrouping as above, the OR (95% CI) for the presence of DM in the OSA WHR$\geq$1.0 subgroup [11.8 (2.0-69.8)] was higher than in the non-OSA WHR$\geq$1.0 [3.6 (0.9-14.8)] after adjustment for age, current smoking, alcohol dependence, physical inactivity and different types of antihypertensive drugs. Similar results were obtained when replacing central obesity with obesity; the adjusted OR (95% CI) for the presence of DM was higher in the OSA obese subgroup [7.8 (1.8-34.9)] in comparison to the non-OSA obese subgroup [3.0 (0.93-9.9)].

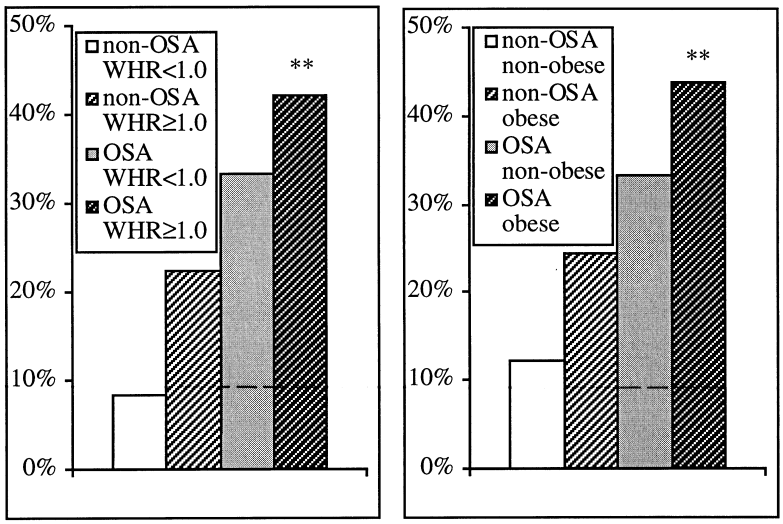

Fig. 4: Prevalence of DM in four subgroups based on combinations of central obesity [A] or obesity [B] with severe OSA. **: p<0.01 in comparison to non-OSA non-obese subgroup.

Moreover, in a multiple linear regression model, after adjustment for age, WHR and different types of antihypertensive drugs, the Min SaO2 was significantly correlated with FSI (r=-0.36, p<0.001), FBG (r=-0.22, p<0.05) and HbA1c (r=-0.25, p<0.01). DI was significantly correlated with FSI (r=0.3, P<0.01), FBG (r=0.2, p<0.05) and HbA1c (r=0.18, p<0.05), while AHI was significantly correlated with FSI (r=0.25, p<0.05) and FBG (r=0.19, p<0.05). The snoring index was significantly correlated with FSI (r=0.35, p<0.001). However, these independent associations between variables of sleep disordered breathing and variables of glucose metabolism were no longer significant when we replaced WHR by BMI in this multivariate model.

OSA AND CATECHOLAMINES IN HYPERTENSION

In this group of hypertensive subjects, 58 subjects were receiving one antihypertensive drug, 40 were receiving two drugs, and 11 were receiving more than two drugs. Twenty-six subjects reported having had 39 CVD events, 20 angina pectoris, 11 myocardial infarction, 4 heart failure, and 4 stroke. Those with reported CVD (n=26) had significantly higher concentrations of normetadrenaline (181±60 vs 149±49 µmol/mol, p<0.01) and metadrenaline (80±36 vs 60±24, p<0.01) in comparison to subjects without CVD (n=90).

OSA subjects (AHI ≥ 10/h) were older, more obese, and with significantly more prevalent CVD in comparison to non-OSA subjects. Urine catecholamines were generally higher in the OSA subjects and significance was reached for normetadrenaline (182 ± 57 vs 141 ± 45, p<0.001) and metadrenaline (70 ± 28 vs 61 ± 28, p<0.05) in comparison to non-OSA subjects.

The relationship between variables of sleep disordered breathing and urinary catecholamines was investigated in a multivariate regression model, after adjustment for age, BMI and parameters

of severity of hypertension. In this model, normetadrenaline was significantly associated with AHI, DI, and Min SaO2, and metadrenaline was significantly associated with AHI and DI.

EVOLUTION OF OSA IN SLEEPY SNORERS

Of the 61 subjects who participated in the polysomnography study in 1985, seven had died, 13 did not wish to participate in the 10-year follow-up, and three did not answer the invitation or the reminding letters. No significant difference was found between the 38 participants and the 23 non-participants in the follow-up in terms of age, BMI, AHI, or sleep architecture at baseline. The non-participants were, however, more often smokers (71% vs 32%, $p<0.01$) and had a higher prevalence of hypertension at baseline (35% vs 10%, $p<0.05$).

During the 10-year period, a total of nine subjects had been treated for OSA or snoring by surgery and/or CPAP. Compared to the 29 untreated subjects, the treated group had a higher AHI at baseline (11.8±7.7 vs 2.1±4.2, $p<0.001$). All nine men who had been treated were excluded from the following analyses.

Among the 29 untreated subjects, four had OSA and 10 years later all of them still fulfilled the criterion of AHI ≥ 5/h. In addition, nine subjects had developed OSA at the follow-up. The AHI for the group as a whole increased significantly from 2.1±4.2 to 6.8±7.2 ($P<0.01$). No significant associations were found between Δ AHI and age or BMI at baseline, weight gain, smoking, alcohol dependence, or physical inactivity in 1994.

In the interview by telephone, nine of the 29 untreated men reported that they had experienced increasing EDS during the 10-year period. The mean Δ AHI of these nine men was significantly higher than that for the other 20 men with unchanged or decreasing EDS (10.3 ± 9.7 vs 2.2 ± 5.1, $p = 0.01$). Four men reported that they suffered from an increase in snoring at the follow-up. They had a somewhat higher mean Δ AHI compared to the 25 who reported less or unchanged snoring (8.8 ± 9.9 vs 4.1 ± 7.3, ns).

DISCUSSION

SLEEP DISORDERED BREATHING AND DIABETES

HABITUAL SNORING AND DIABETES

The main finding in our first study is that men with habitual snoring have a more than two-fold higher incidence of diabetes than non-habitual snorers in the same age group. Although the increased risk of developing diabetes in habitual snorers is largely attributable to obesity it should be noted that odds ratio for development of diabetes was higher in obese snorers than obese non-snorers. As far as we know, this is the first general population-based prospective study concerning the relationship between snoring and diabetes.

A difficulty in this study was to assess specificity and sensitivity of the question "How often do you complain of loud and disturbing snoring?" as there is no standardized method for measuring or analyzing the sound signals. Using the Eden Tec equipment in a sample of 231 men from the population, we found that the sensitivity was low (38%) while the specificity was high (84%) (271). This could mean an underreporting of the snoring problem in this study which might underestimate the relationship between snoring and diabetes.

Another difficulty was to assess the specificity and sensitivity of the question "do you have diabetes?". Of the 69 subjects identified in this manner as having new diabetes, 54 also reported regular medical check-ups for diabetes and 49 reported regular hypoglycemic medication. This indicates that our method had a high specificity. The sensitivity was, however, probably lower as studies based on data from medical records revealed only 50% of subjects with diabetes compared to studies based on active investigation methods (183, 190, 275). Although there were only a few diabetics in this study, the incidence was similar to other Swedish epidemiological surveys. We had 69 new diabetics during the 10 year period (mean annual incidence = 2.81/1000). In the age group 51 to 67 yrs, the mean annual incidence was 4.8/1000, similar to annual incidence reported in Göteborg, Sweden (4.3/1000 and 4.9/1000 for men aged 51 to 60 yrs and for men aged 60 to 67 yrs, respectively) (276).

OSA AND DIABETES IN HYPERTENSION

The main result of the second study is that in hypertensive men, despite the fact that obesity is strongly associated with diabetes, severe OSA seems to add significantly to this association. Our study also shows that the concentrations of FSI, FBG, and HbA1c are associated with parameters of sleep disordered breathing (AHI, DI, Min SaO2, and snoring index) after adjustment for age and central obesity. As far as we know, this is the first general population-based cross-sectional study concerning the relationship between OSA and diabetes.

In the 1984 questionnaire, we did not measure WHR and we relied upon BMI as the only measurement of obesity. In contrast, in the second study, we performed all the calculations twice, once for the WHR and again for the BMI. The rationale is that the BMI estimates the total amount of adipose tissue while the WHR estimates the relative distribution of adipose tissue (193). Besides, central obesity may be considered as a better predictor for type 2 diabetes and morbid obesity, compared to overall obesity (155, 34).

The relationship between parameters of sleep disordered breathing and FSI, FBG, and HbA1c were weak after adjusting for the BMI. A possible explanation is that BMI but not WHR was strongly correlated with sleep breathing disorders in the present study, in accordance with previous results (168. 169).

In contrast to the results of the multiple linear regression analysis, the results of the multiple logistic regression for the defined diabetes did not differ significantly when adjusting for BMI or WHR. It is possible that the severity of OSA must reach a certain threshold (AHI≥20) to be able to predict diabetes or to share in the causation of diabetes.

OSA AND CATECHOLAMINES IN HYPERTENSION

The important finding of the third study is that in a population-based sample of hypertensive men, disordered breathing during sleep was associated with higher urinary excretion of the extraneuronal metabolites, normetadrenaline and metadrenaline, independent of factors known to affect the metabolism of catecholamines. The finding suggests an increased release of noradrenaline from sympathetic neurones and also an increased release of noradrenaline and adrenaline within the

adrenal glands. As far as we know, this is the first general population-based study with objective recording of OSA and metabolites of catecholamines.

It seems that OSA is not only associated with increased sympathoadrenal activity, but also with specific pattern of metabolism of catecholamines. Normetadrenaline is the metabolic product of noradrenaline by catechol-O-methyltransferase (COMT) activity in the synaptic cleft of the sympathetic nerve terminals (277). An increased normetadrenaline concentration indicates an increase in noradrenaline release at the synaptic cleft independent of increased noradrenaline release into the circulation and independent of increased MHMA concentrations (278). The latter is the metabolic product of noradrenaline by monoamine oxidase (MAO) activity within the sympathetic nerve terminals (277). An estimated 48% contribution of the adrenal glands to normetadrenaline production together with the independent association between sleep disordered breathing and metadrenaline indicate increased activity of the adrenal glands with OSA. Metadrenaline is the O-methylated product of adrenaline by COMT activity almost exclusively within the adrenal glands (278). Almost 90% of metadrenaline concentration is independent of adrenaline release into the circulation (278), and this might explain that most of the previous reports did not find a significant relationship between adrenaline and OSA (68, 232).

Although CVD was only defined by questionnaire-based data the significant association between CVD and OSA as well as between CVD and normetadrenaline and metadrenaline, suggest that OSA mediated sympathoexcitation may not only be an important mechanism for hypertension development but also behind increased CVD morbidity in general.

In accordance with other studies, different indices of hypoxia appeared to be strong stimuli for sympathoadrenal excitation in OSA (231, 241). Other components such as arousals and sleep fragmentation may also have played a role (240, 264). As polysomnography was not applied in this study, the potential influence of these components remains unknown.

EVOLUTION OF OSA IN SLEEPY SNORERS

The main finding of the last study is that among sleepy snorer men, sleep disordered breathing became worse over the 10-year period. As far as we know this is the first general population-based study and the follow-up period is longer than previous reports in the literature (127-129).

Reporting an increase in EDS at the follow-up was highly associated with the progression of sleep disordered breathing. However, the definition of EDS as becoming worse over time was based on retrospective recall of symptoms declared during the interview in 1995, which prevents us from drawing definite conclusions. From the data obtained at baseline, it was not possible to predict who was at risk of deteriorating during the following 10 years.

GENERAL DISCUSSION AND FUTURE PERSPECTIVES

This thesis indicates a relationship between sleep disordered breathing and insulin resistance and type 2 diabetes. Previous investigations in this topic have been small and reported conflicting results (228). An independent association was reported in subjects with OSA, as well as in the elderly and the obese subjects (132, 210, 212), but not in healthy subjects (207). A combination of obesity and OSA represents a particular high risk factor for the development of cardiovascular disease and

impaired glucose tolerance (178). Recently, Wilcox et al. suggested that there is an effect of OSA on insulin resistance (and its consequent type 2 diabetes) apart from the effects of co-existent central obesity (167). Strohl suggested that OSA events trigger different, perhaps unique, adaptations in metabolic processes involving insulin action and glucose regulation (208).

Apart from the fact that obesity and/or central obesity may play a major role in the pathogenesis of insulin resistance and type 2 diabetes in subjects with sleep disordered breathing, other possible mechanisms could be:

1- Sleep fragmentation: as sleep quality markedly influences nocturnal brain and peripheral tissue glucose utilization, sleep fragmentation may be associated with disturbances of glucose metabolism (226). Moreover, diurnal variations in glucose tolerance result from the alteration between wake and sleep states (226).

2- Oxygen desaturation: It is well known that hypoxia induces hyperglycemia and elevates plasma insulin in animals (223, 225). In humans, hypoxia induces an enhanced activation of the sympathoadrenergic system and increased plasma insulin with or without elevated plasma glucose concentrations (257, 258, 279).

3- Increased sympathetic activity which has been reported to occur in OSA (167).

4- Increased catecholamines, cortisol, or other counter-regulatory hormones and non-hormonal insulin antagonists (280).

The role of these mechanisms in sleep disordered breathing should be explored further in experimental and prospective studies. We believe that patients with OSA are a good model for studying the metabolic consequences of sleep fragmentation or chronic sleep deprivation. They are also a good model for studying the metabolic consequences of this unique form of hypoxia in OSA in which there is a nocturnal intermittent or remittent hypoxia followed by a daytime normoxia.

A Unifying Model

Based on our results, we present a possible model of the relationships between sleep disordered breathing and other known risk factors for cardiovascular diseases, such as insulin resistance and obesity (Fig. 5). This model is developed from a model originally presented by Strohl et al. 1993 (280).

CONCLUSIONS

We concluded that:

In men aged 30-69 years, habitual snoring was associated with an increased incidence of diabetes within a 10-year period. Although obesity is the main risk factor for developing diabetes, coexistent habitual snoring may add to this risk.

In hypertensive men aged over 40 years old, although obesity is a main risk factor for the presence of diabetes, coexistent severe obstructive sleep apnea may add to this risk. Independent of central obesity, sleep disordered breathing may influence fasting levels of insulin, glucose and glycated hemoglobin.

In hypertensive men over 40 years old, obstructive sleep apnea was associated with increased concentrations of the extraneuronal metabolites of catecholamines, metnoradrenaline and

metadrenaline, independent of recognized confounding factors. This may indicate an increased sympathoadrenal activity and may explain the increased cardiovascular morbidity with obstructive sleep apnea.

In middle-aged men with snoring and daytime sleepiness, sleep disordered breathing significantly deteriorated over a 10-year period. This deterioration was independent of age, obesity, weight gain and smoking. This deterioration should be suspected if worsening of daytime sleepiness is claimed by the subject.

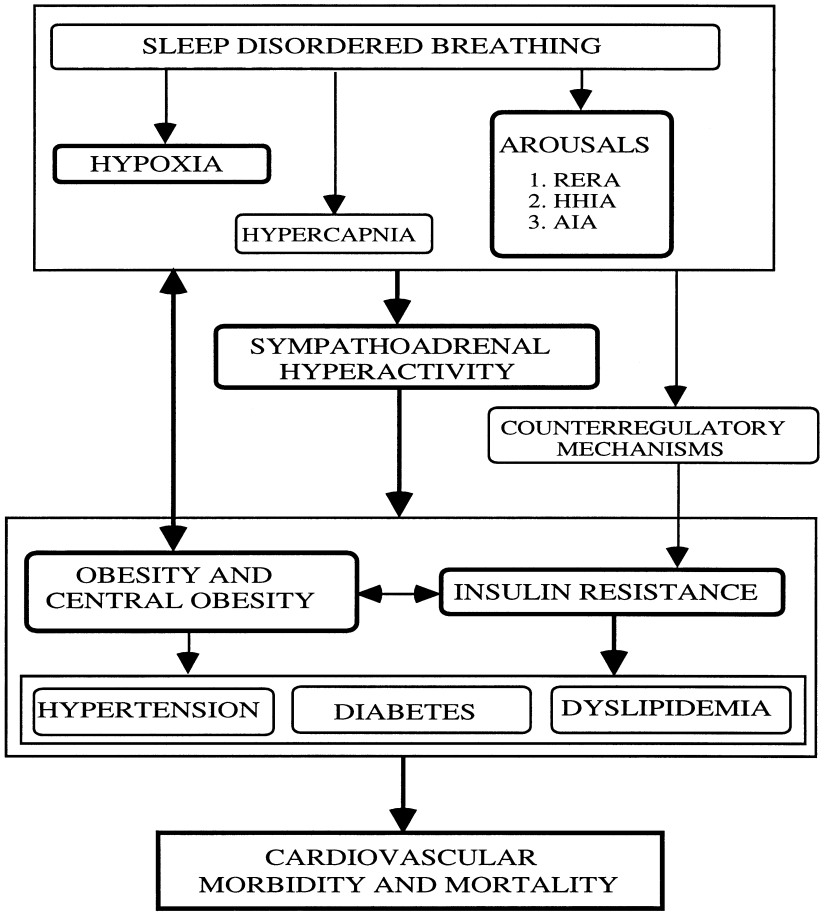

Fig. 5: A model for the possible role of sleep disordered breathing in the insulin resistance syndrome. Modified after Strohl et al. 1993 (280). RERA = respiratory effort related arousals, HHIA = hypoxia-hypercapnia induced arousals, AIA = acoustically (snoring) induced arousals

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