Review

Obstructive Sleep Apnea and Chronic Intermittent Hypoxia: A Review

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Abstract

Hypoxia is an important topic both physiologically and clinically. Traditionally, physiology research has been focusing on the effect of acute and chronic sustained hypoxia and human adaptive response to high altitude. In the past 20 years, genetic studies by many have expanded our understanding of hypoxia to the molecular level. However, in contrast to our extensive knowledge about acute and chronic sustained hypoxia, we know relatively little about the effect of chronic intermittent hypoxia (CIH).

In recent years, CIH has attracted more research attention because of the increasing prevalence of obesity and obstructive sleep apnea (OSA) in the western countries. Clinically, CIH is commonly seen in patients with sleep-disordered breathing including OSA, Cheyne-Stokes respiration and nocturnal hypoventilation. It was estimated that for OSA of at least mild severity prevalence estimates range from 3 to 28% in the general population. OSA is characterized by recurrent upper airway collapse during sleep leading to intermittent nocturnal hypoxia and sleep fragmentation. OSA is associated with significant mortality and morbidity including neurocognitive dysfunction, hypertension, many cardiovascular disorders and metabolic disorders such as diabetes and metabolic syndrome.

The intermittent hypoxia in OSA closely mimics what is seen in the ischemia-reperfusion injury. Experimentally, there is no universally accepted definition for CIH. Laboratory protocols vary greatly in duration of hypoxia exposure, numbers of hypoxia episodes per day and the total number of days of exposure. Despite the lack of a uniform definition, recent data suggest that CIH may lead to multiple long-term pathophysiologic consequences similar to what we see in patients with OSA. Recent evidences also demonstrate that there are remarkable differences in the response of the physiologic systems to sustained hypoxia and intermittent hypoxia.

This review is aimed to briefly discuss the clinical significance of sleep-disordered breathing and our current understanding of CIH.

Key Words: chronic intermittent hypoxia, obstructive sleep apnea, sleep fragmentation

Introduction

Hypoxia is an important topic both physiologically and clinically. Traditional hypoxia research focused on the effect of sustained hypoxia and human adaptive response to high altitude. In recent years, there is a striking growth of research interests in intermittent hypoxia due to our increasing awareness of the importance of obstructive sleep apnea (OSA).

Recent data suggest that there are remarkable differences in the response of the physiologic systems to sustained hypoxia and intermittent hypoxia (39).

The fluctuation of oxygen saturation in sleep due to repetitive upper airway obstruction in OSA closely mimics what is seen in the hypoxia-reoxygenation or ischemia-reperfusion injury. The major objectives of this brief review are to [1] address the clinical importance and pathogenesis of OSA, as well as the proposed physiologic mechanisms of the OSA-associated complications, and [2] to review the recent literature that investigates the intermittent hypoxia-mediated mechanisms that lead to cardiovascular, neurocognitive and metabolic derangement.

An Overview of Obstructive Sleep Apnea

Obstructive Sleep Apnea: Clinical Significance

Obstructive sleep apnea, characterized by recurrent upper airway collapse during sleep, can cause intermittent nocturnal hypoxia and sleep fragmentation, and is known to be associated with significant morbidity and mortality (35). In the past few years, the relationship between OSA and cardiovascular disorders has become evident. There is a growing consensus that OSA is an important independent risk factor for hypertension (36). This association between OSA and hypertension appears to be present even at the mild end of the OSA severity spectrum. It also appears that OSA increases other cardiovascular morbidities and mortality as well. Multiple studies have demonstrated that approximately 50% of all congestive heart failure patients have sleep-disordered breathing, including both OSA and Cheyne-Stokes respiration (17, 25). A recent study has also estimated that 50% of the patients with atrial fibrillation may have OSA (19). Furthermore, OSA is associated with coronary artery disease, pulmonary hypertension, stroke, and white matter ischemia (49).

In addition to the cardiovascular morbidities, patients with OSA frequently have impaired neurocognitive function, poor health-related quality of life, and metabolic dysfunction such as insulin resistance, type 2 diabetes, or metabolic syndrome. Clinically, it is also common to see symptoms of other organ systems, including gastroesophageal reflux, headaches, depression, insomnia, psychosomatic complaints, nocturia, and sexual dysfunction in patients with OSA. It has been known for many years that patients with moderate to severe OSA could have up to 7-fold increase of motor vehicle accidents (18). Their spouses or bed partners frequently suffer from snoring-induced environmental insomnia. Table 1 summarizes the common clinical manifestations associated with OSA.

Despite its irrefutable significance, OSA is unfortunately grossly under-appreciated by physicians and patients. It was projected in the early nineties that

Table 1. Common clinical manifestations associated with OSA

Cardiovascular manifestations
- Systemic hypertension
- Congestive Heart Failure (systolic and diastolic dysfunction)
- Coronary Artery Disease
- Arrhythmias
- Pulmonary hypertension
- Stroke

Neuropsychiatric manifestations
- Depression
- Insomnia and/or excessive daytime somnolence
- Cognitive and neurobehavior abnormalities: Impairment of concentration, perception, memory, performance and learning
- Attention deficit hyperactive disorder (ADHD)
- Headaches

Metabolic manifestations
- Glucose intolerance and insulin resistance
- Type 2 Diabetes Mellitus
- Metabolic syndrome

Other manifestations
- Gastroesophageal reflux
- Genitourinary: Nocturia and sexual dysfunction
- Toxemia (preeclampsia/ecclampsia) during pregnancy

up to 85% of the patients with OSA in the United States were undiagnosed and thus untreated (51, 56). Of the adult population in the United States, it was estimated that at least 2 to 5% have OSA associated with significant sleepiness. It was also projected that for OSA of at least mild severity with apnea-hypopnea index (AHI) ≥ 5, prevalence estimates ranged from 3 to 28% in the general population. For OSA of at least moderate severity with AHI ≥ 15, prevalence estimates may be in the range of 1 to 14% (56). The occurrence of OSA appears to increase steadily with age in midlife and is highly prevalent in those over 65 years of age (57). A recent study from China estimated that when AHI ≥ 5 was taken as the cut-point, the prevalence of OSA was 20.4% among Chinese. After excessive daytime sleepiness (defined as Epworth sleepiness scale ≥ 9) was added as part of the criteria for OSA, the conservatively estimated prevalence of OSA was 3.6%. It appears that similar to the western society, OSA is also a great burden to public health among Chinese (22).

The cost implications of OSA when left untreated are immense. These costs include those associated with occupational injuries, motor vehicle crashes,

reduced work productivity and comorbidity (4). Sassani *et al*. have recently assessed the costs associated with OSA-related motor vehicle collisions and concluded that the cost in year 2000 in the United States was approximately $15.9 billion U.S. dollars (48). The economic burden of occupational consequences is currently unknown, but is likely to be substantial as well. Another recent study demonstrates that treatment with continuous positive airway pressure (CPAP) reverses the trend of increasing healthcare utilization seen prior to diagnosis (1).

Obstructive Sleep Apnea: Therapy

Currently, nasal CPAP is considered the therapy of choice in the treatment of moderate to severe OSA (29). CPAP, by applying a positive pressure in the upper airway, provides a "pneumatic splint" to prevent upper airway collapse during sleep. The CPAP level required for treatment of OSA patients typically varies from 5 to 20 cmH$_2$O. Unfortunately, poor compliance to CPAP is not uncommon in patients with OSA. Multiple studies have suggested that long term adherence to CPAP therapy was achieved only in approximately 60% patients.

As long as reasonable CPAP compliance can be attained, CPAP is effective in improving many of the complications associated with OSA, including neurocognitive function, daytime sleepiness, performance, and certain cardiovascular outcomes (3, 5, 7). CPAP therapy has been shown to decrease systemic blood pressure in average by up to 10 mmHg and pulmonary pressure by 5 mmHg (3, 5). CPAP also appears to improve congestive heart failure and arrhythmias. Marin *et al*. recently published their 10-year observation in men with severe OSA and found untreated severe OSA significantly increases the risk of fatal and non-fatal cardiovascular events and CPAP therapy appears to reduce this risk. There are also evidences that CPAP treated subjects may decrease their motor vehicle accidents to normal (32).

However, despite improvement of many outcomes in the majority of patients, some patients continue to have residual sleepiness despite CPAP therapy. The mechanisms of this residual sleepiness in treated sleep apnea are not well-defined, but animal studies suggest that intermittent hypoxia may lead to both neural injury and neurobehavioral impairments (20).

Other treatment options include oral appliances, upper airway surgery, weight loss (in overweight patients) and positional therapy (in patients with predominantly supine-related apnea). Pharmacological therapy has not been successful and is frequently limited by side effects. Mild OSA patients may be treated with oral appliances which reposition and advance the mandible, and thus increase the cross-sectional dimension of the upper airway (16). Upper airway surgery may also be considered in selected OSA patients or in patients with moderate to severe OSA for whom positive airway pressure therapy fails (10).

Obstructive Sleep Apnea: Pathophysiologic Consequences

The recurrent collapse of the upper airway during sleep in OSA patients leads to four major immediate pathophysiological changes, including [1] hypoxia-reoxygenation, [2] hypercapnia, [3] frequent arousals resulting in fragmentation of sleep architecture, and [4] large negative inspiratory deflection of intrathoracic pressure. In very severe OSA cases, respiratory events and arousals can occur at a frequency of over 120 per hour with oxygen desaturation to the range of 50-60%.

The cardiovascular, neurocognitive and metabolic consequences of these changes can be profound. However, since intermittent hypoxia, hypercapnia, exaggerated negative intrathoracic pressure and arousals all occur throughout sleep in patients with OSA, it is difficult to sort out the relative contribution and significance of each component on clinical basis. Table 2 summarizes the pathophysiological consequences observed in human subjects with OSA and animal experiments.

I. Cardiovascular Pathophysiologic Consequences of OSA

The precise mechanisms of cardiovascular complications in OSA have not been well-elucidated, but are certainly complex with involvement of multiple pathophysioliogical pathways (Figure 1) (26). Potential mechanisms may include increased oxidative stress, enhanced systemic inflammation, endothelial dysfunction, sympathoexcitation, renin-angiotensin system activation, and metabolic dysregulation as the results of either CIH or frequent arousals or both. Increased fibrinogen, coagulation, platelet aggregation, blood viscosity, and hematocrit can contribute to atherosclerosis and clot formation in patients with OSA (26, 28).

Studies have consistently shown that patients with OSA have high levels of sympathetic activity. During sleep, intermittent hypoxia, hypercapnia and arousals act through chemoreceptor reflexes and other mechanisms to increase sympathetic drive. This elevated sympathetic activity is present even during daytime wakefulness. It has been shown that hypoxemia is an important stimulus for sympathoexcitation, with larger oxygen desaturation causing greater increase in sympathetic activity. It has also been demonstrated that CPAP therapy decreases muscle sympathetic nerve activity in OSA patients (33). This activation of sympathetic system is believed to be a major link between OSA and cardiovascular morbidities.

Table 2. The pathophysiologic consequences of OSA and/or intermittent hypoxia

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A. Cardiovascular Sequelae
- Increased sympathetic activity
- Increased oxidative stress
- Increased inflammatory response (Elevated CRP, NF-κB, TNF-α , IL-8, IL-6, and EPO)
- Endothelial dysfunction (Increased big ET-1 or ET-1, reduced nitric oxide level, and activation of renin-angiotensin system)
- Increased coagulation (fibrinogen)
- Increased platelet aggregation
- Increased blood viscosity

B. Neurocognitive Sequelae
- Increased oxidative stress
- Increased neuronal apoptosis within the cortex and CA1 region of the hippocampus
- Increased COX-2 protein and gene expression

C. Metabloic Sequelae
- Activation of the sympathetic system
- Increased release of adipocyte-derived inflammatory mediators (IL-6, TNF-α, leptin)
- Activation of hypothalamus-pituitary-adrenal axis (? Increased cortisol)

D. Other Sequelae
- Reduced upper airway muscle endurance and impaired pharyngeal dilator EMG responses to physiological stimulation
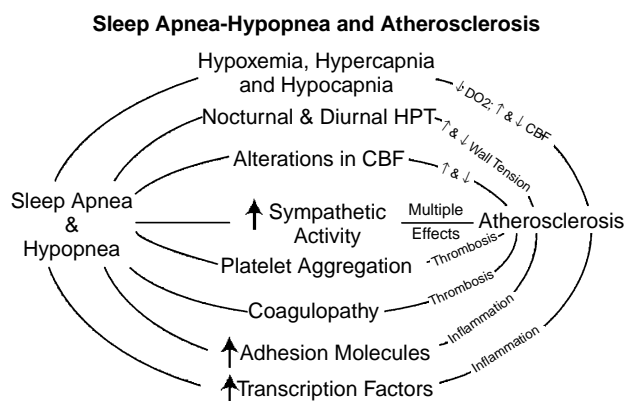

Sleep Apnea-Hypopnea and Atherosclerosis

Fig. 1. Proposed mechanisms by which sleep-disordered breathing may cause or contribute to progression of atherosclerosis. (˙DO2, oxygen delivery; CBF, coronary blood flow.) (Originally published in Javaheri: Heart failure and sleep apnea: Emphasis on practical therapeutic options. *Clin. Chest Med.* 24: 207- 222, 2003, and reproduced by permission from Elsevier.)

In addition to the increased sympathetic tone, recent data demonstrate that OSA is characterized by an inflammatory response. Shamsuzzaman *et al.* found that patients with OSA have elevated levels of plasma C-reactive protein (CRP) which is a clinical marker of inflammation (49). In multivariate analysis, CRP levels were independently associated with OSA severity. Several other studies also confirmed this finding. Both intermittent hypoxia and frequent sleep disruption may contribute to the elevation of CRP (9, 12).

Furthermore, many studies have demonstrated increased TNF-α, interleukin-6 (IL-6), interleukin-8 (IL-8), and intercellular adhesion molecule-1 (ICAM-1) in OSA patients and their fall with CPAP therapy. Ryan *et al.* recently studied circulating Nuclear Factor kappa B (NF-κB) dependent genes in patients with OSA and found that TNF-α levels were higher in OSA patients than controls. They confirmed that CPAP therapy lowered TNF-α levels. Another NF-κB dependent cytokine, IL-8, showed similar changes between groups and after CPAP therapy, but a range of other inflammatory mediators, including IL-1, IL-6, IL-10 and IL-12, showed no differences (47).

Impaired systemic endothelial function has been observed in patients with OSA. Ip *et al.* demonstrated circulating nitric oxide (NO) is suppressed in OSA, and this is promptly reversible with the use of CPAP. The findings offer support for NO being one of the mediators involved in the acute hemodynamic regulation and long-term vascular remodeling in OSA (23). Several studies have assessed plasma endothelin-1 (ET-1) level but revealed conflicting results. A more recent study suggests that the endothelin (ET)

precursor, big ET-1, was considerably elevated in untreated OSA patients and dropped to normal values after long-term CPAP depending on compliance, yet ET-1 concentrations remained within the normal range and did not change with CPAP (27)

II. Neurocognitive Pathophysiologic Consequences of OSA

The clinical neurocognitive manifestations of OSA include excessive daytime sleepiness, personality and psychosocial maladjustment, and impairment of thinking, concentration, perception, performance, memory, communication, or the ability to learn. It has been suggested that reductions in general intellectual measures and executive and psychomotor tasks are primarily attributable to the severity of hypoxemia, whereas other attention and memory deficits may be induced by sleep deprivation and fragmentation (6). Poceta *et al.* demonstrated both respiratory arousals and degree of hypoxemia contribute interactively to the inability to maintain wakefulness in patients with OSA (37).

Beebe and Gozal recently proposed the "Prefrontal Model" which is a conceptual framework for the relationship between sleep disruption and intermittent nocturnal hypoxia and cognitive and neurobehavior dysfunction. This model postulates that OSA-related sleep disruption, intermittent hypoxemia and hypercarbia alter the efficacy of restorative processes occurring during sleep, and disrupt the cellular and chemical homeostasis and neuronal and glial viability within particular brain regions. Subsequent dysfunction of prefrontal cortical regions alters the functional recruitment of more primary cognitive abilities, thereby resulting in maladaptive daytime behaviors (8).

III. Metabolic Pathophysiologic Consequences of OSA

The relationship between sleep-disordered breathing and diabetes is a very complex one. Over the past few years, there is a rapidly growing body of literature that implicates OSA in the pathogenesis of altered glucose metabolism. OSA has been found to be associated with insulin resistance independent of obesity, with greater severity of OSA associated with worse insulin resistance (24, 40). Since insulin resistance is generally considered as a "pre-diabetic state", it was proposed that OSA may predispose to development of type 2 diabetes mellitus independent of obesity. Conversely, diabetes has been suspected as causal in the development of sleep-disordered breathing as well. An analysis found that people with diabetes had more episodes of periodic breathing than those without diabetes (43). It has been proposed that autonomic dysfunction and/or other mechanisms
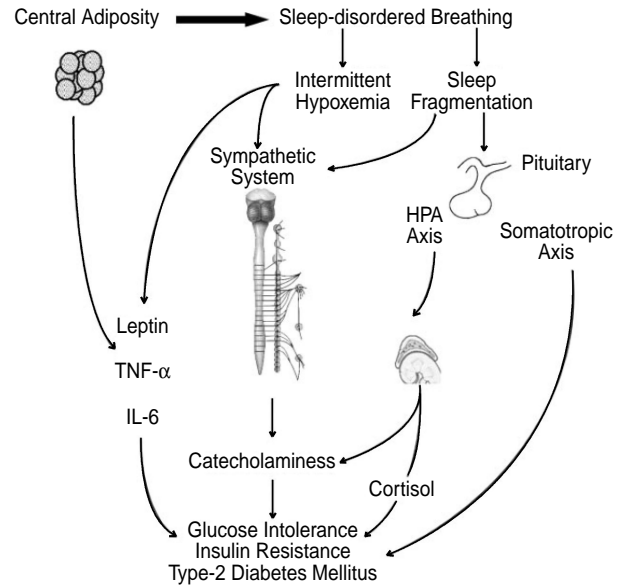
Fig. 2. Intermediate pathways linking sleep apnea, glucose intolerance, insulin resistance, and Type 2 diabetes mellitus. (Originally published in Punjabi and Polotskym: Disorders of glucose metabolism in sleep apnea. *J. Appl. Physiol.* 99: 1998-2007, 2005, and reproduced by permission of the American Physiological Society)

including inflammatory processes can possibly lead to breathing instability seen in sleep-disordered breathing.

Reichmuth *et al.* recently found that there was a greater prevalence of diabetes in subjects with increasing levels of OSA. A total of 14.7% of subjects with an AHI of 15 or more had a diagnosis of diabetes compared with 2.8% of subjects with an AHI of less than 5 (42). On the other hand, using the Berlin questionnaire and oximetry, West and colleagues estimate that OSA is highly prevalent in men with type 2 diabetes and most are undiagnosed (55). Moreover, Coughlin and his associates have demonstrated that OSA is independently associated with an increase in the cardiovascular risk factors that comprise the metabolic syndrome and its overall prevalence (15).

Pathophysiologically, scientific literature suggests intermittent hypoxia and repetitive arousals may trigger a cascade of physiological events through autonomic activation, release of potent adipocyte-derived proinflammatory mediators such as IL-6, TNF-α, and leptin, and possibly alterations in hypothalamus-pituitary-adrenal (HPA) axis (Figure 2) (41). Punjabi and Polotsky recently published an extensive review delineating the pathophysiologic relationship between OSA and altered of glucose metabolism (41).

It is known that activation of the sympathetic system influence glucose homeostasis by increasing muscle glycogenolysis and hepatic gluconeogenesis.

Several studies also demonstrated sympathetic activation promotes lipolysis and release of free fatty acids which can induce insulin resistance. In addition, IL-6, TNF-α, and leptin are three adipocyte-derived factors which contribute to glucose metabolic abnormalities. Recent data suggest TNF-α antagonizes insulin action and contributes to insulin resistance. Serum IL-6 level also correlates with insulin resistance. Leptin level is increased in OSA patients and decreases with CPAP therapy independent of body weight changes. Leptin resistance in OSA may predispose to alternation of glucose metabolism. Lastly, sleep deprivation is known to lead to increase of plasma cortisol level which can cause glucose intolerance. Although sleep fragmentation is physiologically different from sleep deprivation, preliminary evidence seems to suggest sleep fragmentation may lead to increased cortisol and HPA hyperactivity in patients with OSA (41).

Intermittent Hypoxia

Intermittent Hypoxia: Definition

Experimentally, the effect of intermittent hypoxia can be tested. Many animal models have been developed to study the effects of CIH on a variety of outcomes. Currently, there is no universal definition on intermittent hypoxia. Intermittent hypoxia is generally accepted as "repetitive hypoxia interspersed with episodes of normoxia" (34). Laboratory protocols vary greatly in duration of hypoxia exposure, numbers of hypoxia episodes per day and the total number of days of exposure. Although more sophisticated models are available, in the majority of studies utilizing rodent models of intermittent hypoxia expose rodents to hypoxia of fixed duration (typically in the range of 30-120 seconds) throughout the sleeping or light phase and maintain normoxia during the active or dark phase.

Intermittent Hypoxia: Pathophysiologic Mechanisms

Despite the lack of a more precise criterion of CIH, experimental data demonstrate that CIH lead to multiple cardiovascular, neurocognitive, and metabolic pathophysiological abnormalities. In addition, CIH has been shown to cause upper airway muscle dysfunction.

I. Mechanisms of Intermittent Hypoxia-Mediated Cardiovascular Sequelae

Oxidative stress is a well-known mechanism for cell injury. The repetitive hypoxia-reoxygenation in OSA resembles what is seen in the ischemia-reperfusion injury. It has been established that hypoxia-reoxygenation

or ischemia-reperfusion promotes the formation of reactive oxygen species which activate critical redox-sensitive signaling pathways and transcription factors. This facilitates the expression of genes that encode proteins essential for adaptive response to hypoxia and inflammatory pathways. Accordingly, inflammation will lead to activation of endothelial cells, leukocytes and platelets. These activated cells then express adhesion molecules and proinflammatory cytokines that further cause endothelial cell injury and dysfunction (30).

It is known that sustained hypoxia is associated with the activation of a ubiquitous adaptive response mediated by the transcription factor hypoxia-inducible factor-1 (HIF-1). HIF-1 can result in increased expression of a number of genes encoding proteins such as erythropoietin (EPO), vascular endothelial growth factor (VEGF), and inducible nitric oxide synthase (iNOS). Such factors are important in mediating the adaptive response to hypoxia by increasing tissue perfusion and oxygenation and hence overcoming the initial hypoxic insult. However, it was uncertain if hypoxia of intermittent nature brings about similar molecular changes as in sustained hypoxia (46).

Ryan *et al.* recently demonstrated that HeLa cells exposed to intermittent hypoxia demonstrated selective activation of the proinflammatory transcription factor NFκB, whereas the adaptive regulator HIF-1 was not activated. These changes would account for the selective activation of the inflammatory pathway over the adaptive pathway in intermittent hypoxia compared with sustained hypoxia (46). They also showed higher circulating TNF-α levels in OSA patients than in control subjects which normalized with CPAP therapy. In contrast, EPO levels were similar throughout. These data suggest selective activation of inflammatory pathways in intermittent hypoxia and OSA may be very important in the molecular pathogenesis of endothelial dysfunction and cardiovascular diseases (Figure 3). This finding could possibly be extrapolated to other disorders associated with intermittent hypoxia such as Cheyne-Stokes respiration and chronic respiratory disorders including chronic obstructive pulmonary disease. It is certainly plausible that CIH in these disorders may activate the inflammatory pathways and contribute to adverse outcomes.

II. Mechanisms of Intermittent Hypoxia-Mediated Neurocognitive Deficits

The research group of David Gozal has contributed greatly to our understanding of CIH-associated neurocognitive and behavior deficits. Gozal *et al.* demonstrated that intermittent hypoxia is associated with transient disruption of sleep architecture followed by normalization of sleep patterns in rats. However, after 14 days of CIH, learning impairments during
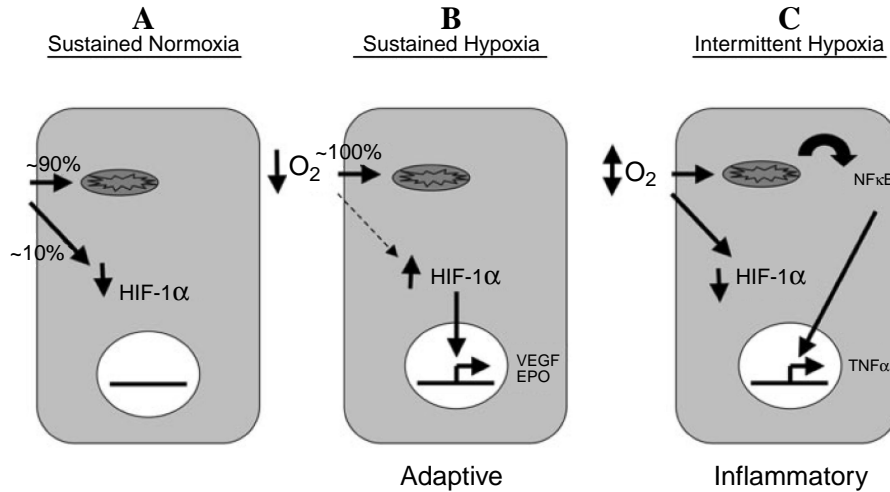
Fig. 3. Molecular responses to normoxia, sustained hypoxia, and intermittent hypoxia. A, In normoxia, about 90% of available oxygen is consumed by mitochondria, leaving sufficient oxygen for HIF-1 degradation. B, In sustained hypoxia, the mitochondria consumes almost all the O_2, and rapid stabilization of HIF-1 occurs, which leads to increased transcription (arrow) of genes such as EPO. C, In intermittent hypoxia, the extent of hypoxia is not sufficient to allow HIF-1 stabilization; however, possibly through mitochondrial stress, it results in the activation of NFκB with the downstream consequences of production of inflammatory mediators such as TNF-α. (Originally published in Ryan, Taylor, and McNicholas: Selective activation of inflammatory pathways by intermittent hypoxia in obstructive sleep apnea syndrome. *Circulation* 112: 2660-2667, 2005, and reproduced by permission)

acquisition of a spatial memory task (Morris water maze experiments) occurred and were only partially reversed after 14 days of recovery. Anatomical correlates for such decreases in behavioral maze performance show time-dependent increases in apoptosis within the cortex and CA1 region of the hippocampus. This study provide support for the concept that intermittent hypoxia during sleep is associated with substantial deterioration of behavioral performance and with parallel disruption of the anatomical substrate (20).

It has been previously shown that brain tissue contains a large amount of polyunsaturated fatty acids and is highly susceptible to oxidative reactions such as lipid peroxidation. In addition, oxidative stress has been associated with aging-related behavioral impairments on spatial learning tasks in the rodent. Gozal and his colleagues thus investigated the molecular mechanisms of CIH-associated neurobehavior deficits and hypothesized that oxidative stress is a significant contributing factor to the behavior impairment and cellular injury associated with intermittent hypoxia. They demonstrated that intermittent hypoxia is associated with significant increases in lipid peroxidation and oxidant stress in brain tissue, and that administration of the antioxidant, PNU-101033E, attenuates the spatial learning deficits associated with exposure to intermittent hypoxia (45). These findings support the postulate that oxidative stress contributes to the cellular damage and consequent behavioral impairments associated with

severe forms of sleep-disordered breathing.

Another hypothesis was that cyclooxygenase-2 (COX-2) induction may be involved in hypoxia-induced neuronal loss. COX-2 is present in selected brain neurons, and its expression is known to be upregulated in neurological diseases, including Alzheimer's disease and ischemic brain injury such as stroke. COX-2 activity also appears to play a critical role in neuronal cell injury and death, and the administration of selective COX-2 inhibitors attenuates ischemic brain injury. Gozal's group thereby investigated the role of COX-2 in CIH-induced learning deficit. They found that intermittent hypoxia was associated with increased COX-2 protein and gene expression from Day 1 to Day 14 of exposure in rats (31). CIH-induced COX-2 upregulation was found to be associated with neuronal apoptosis and neurobehavioral deficits. Administration of NS-398 abolished CIH-induced apoptosis without modifying COX-2 mRNA expression. No changes were found in COX-1 gene expression. It thus seems that COX-2 may play a role in intermittent hypoxia-mediated neurobehavioral deficits.

Zhan *et al*. hypothesized that CIH exposure modeling the oxygenation patterns of moderate-severe OSA in adult mice may result in lasting hypersomnolence and could be associated with nitration and oxidation injuries in specific brain regions. They were able to demonstrate that two weeks after recovery from intermittent hypoxia exposures, wild-type mice showed increased iNOS activity in representative

wake-active regions. Inhibition of iNOS after intermittent hypoxia in wild-type mice was effective in reversing the proinflammatory gene response (58). These data support a critical role for iNOS activity in the development of CIH-related impairments, lipid peroxidation, and proinflammatory responses in wake-active brain regions, and suggest a potential role for inducible NO inhibition in protection from proinflammatory responses, oxidative injury, and residual hypersomnolence in OSA.

The relationship between sleep disorders and attention deficit hyperactivity disorder (ADHD) in children has been extensively studied in recent years (13, 14). Neurocognitive deficits, such as learning impairments and an increased incidence of hyperactivity in children, particularly male children, comprise one of the primary morbidities associated with pediatric OSA (54). Gozal's research team thus hypothesized that exposure to intermittent hypoxia throughout the vulnerable ages would result in increased behavioral impairments in the juvenile rat. Their data suggest rat pups exposed to intermittent hypoxia displayed significant spatial learning impairments, and exposed male rats (but not female rats) displayed increased locomotor activity in the open field. These findings indicate that exposure to intermittent hypoxia during a critical period of neuronal vulnerability at an age that corresponds to the peak incidence of OSA in children induces substantial learning impairment and gender-dependent behavioral hyperactivity in the juvenile rat (21, 44).

III. Mechanism of Intermittent Hypoxia-Mediated Metabolic Abnormalities

Previous studies demonstrated sustained hypoxia exposure did not cause insulin resistance and resulted in a decrease in fasting blood glucose and unchanged glucose tolerance. Polotsky et al. have shown that obese mice exposed to intermittent hypoxia for 12 weeks developed a time-dependent increase in fasting serum insulin levels and worsening glucose tolerance, consistent with an increase in insulin resistance. This response was only evident in the obese leptin-deficient mice suggesting that disruption of leptin pathways may be important for intermittent hypoxia-mediated alterations in glucose metabolism (38). This study suggests that the intermittent nature of hypoxia is critical in the development of insulin resistance.

In the central regulation level, Volgin and Kubin recently tested whether CIH similar to that seen in OSA leads to distinct and relevant for metabolic regulation transcriptional changes in the posterior hypothalamus in a rodent model. They found that rats exposed to CIH for 35 days had twice higher levels of the adrenergic alpha2A receptor mRNA than the

matching sham control. The increases occurred only in the perifornical region. Their results show that, at least at the transcriptional level, CIH exerts a distinct and regionally selective central effect on the expression of selected mRNAs involved in metabolic regulation through adrenergic, leptinergic and inflammatory pathways (53).

IV. Other Intermittent Hypoxia-Mediated Changes: Upper Airway Muscle Dysfunction

It is well known that the repetitive collapse of the upper airway during sleep in patients with OSA is the result of a sleep-related decrement in upper airway muscle activity with consequent failure of the pharyngeal dilator muscles to oppose the collapsing pressure generated by the respiratory muscles during inspiration. Until recently, little is known about the effects of episodic hypoxia on upper airway muscle function.

Bradford et al. recently demonstrated that intermittent hypoxia reduces upper airway muscle endurance and selectively impairs pharyngeal dilator EMG responses to physiological stimulation. They speculate that intermittent hypoxia is responsible for the progression of OSA through impairment of the neural control systems that regulate upper airway patency. A vicious cycle of hypoxic insult and further airway obstruction that chronically exacerbates and perpetuates OSA is then established. Their study provides evidence that chronic intermittent hypoxia contributes to the pathophysiology of sleep-disordered breathing (11).

Summary

Much has been learned about the pathogenesis, pathophysiology, molecular mechanisms, clinical diagnosis and management of OSA over the past decade. We now have clear evidences that OSA is a major and widely prevalent clinical disorder. Given the worsening of obesity pandemic, OSA will only become more important in the foreseeable future. Pathophysiologically, OSA causes intermittent nocturnal hypoxia, hypercarbia, sleep fragmentation and exaggerated negative intrathoracic pressure swing. These physiological changes can further lead to cardiovascular, metabolic and neurocognitive morbidities and mortality.

Intermittent hypoxia apparently plays a major role in causing many of the abnormalities associated with OSA. Intermittent hypoxia-induced systemic and cellular responses are different from what we see in sustained hypoxia. Regrettably, compared with what we know about acute and chronic sustained hypoxia, our understanding about intermittent hypoxia remains

fairly limited. More animal researches are needed to delineate the complex molecular mechanisms involved in intermittent hypoxia and to address many of the unanswered questions.

References

1. Albarrak, M., Banno, K., Sabbagh, A., Delaive, K., Walld, R., Manfreda, J. and Kryger, M.H. Utilization of healthcare resources in obstructive sleep apnea syndrome: a 5-year follow-up study in men using CPAP. *Sleep* 28: 1306-1311, 2005.

2. Ali, N.J., Pitson, D. and Stradling, J.R. Natural history of snoring and related behaviour problems between the ages of 4 and 7 years. *Arch. Dis. Child* 71: 74-76, 1994.

3. Arias, M.A., Garciá-Ro, F., Alonso-Fernandez, A., Martínez, I. and Villamor, J. Pulmonary hypertension in obstructive sleep apnea: Effects of continuous positive airway pressure: A randomized, controlled cross-over study. *Eur. Heart J.* 27: 1106-1113, 2006.

4. Ayas, N. and Marra, C. Continuous positive airway pressure therapy for obstructive sleep apnea syndrome: Do the dollars make sense? *Sleep* 28: 1211-1212, 2005.

5. Becker, H.F., Jerrentrup, A., Ploch, T., Grote, L., Penzel, T., Sullivan, C.E. and Peter, J.H. Effect of nasal continuous positive airway pressure treatment on blood pressure in patients with obstructive sleep apnea. *Circulation* 107: 68-73, 2003.

6. Bedard, M.A., Monplaisir, J., Richer, F., Rouleau, I. and Malo, J. Obstructive sleep apnea syndrome: pathogenesis of neuropsychological deficits. *J. Clin. Exp. Neuropsychol.* 13: 950-964, 1991.

7. Bedard, M.A., Monplaisir, J., Malo, J., Richer, F. and Rouleau, I. Persistent neuropsychological deficits and vigilance impairment in sleep apnea syndrome after treatment with continuous positive airways pressure (CPAP). *J. Clin. Exp. Neuropsychol.* 15: 330-341, 1993.

8. Beebe, D.W. and Gozal, D. Obstructive sleep apnea and the prefrontal cortex: towards a comprehensive model linking nocturnal upper airway obstruction to daytime cognitive and behavioral deficits. *J. Sleep Res.* 11: 1-16, 2002.

9. Boudjeltia, K.Z., Meerhaeghe, A.V., Doumit, S., Guillaume, M., Cauchie, P., Brohee, D., Vanhaeverbeek, M. and Kerkhofs, M. Sleep apnea-hypopnea index is an independent predictor of high-sensitivity C-reactive protein elevation. *Respiration* 73: 243-246, 2006.

10. Boudewyns, A.N. and Van de Heyning, P.H. Surgical treatment of obstructive sleep apnea. In: Sleep Apnea: Current Diagnosis and Treatment, edited by Randerath W.J., Sanner, B.M. and Somers, V.K. Basel, Switzerland: Karger, 2006, pp. 167-173.

11. Bradford, A., McGuire, M. and O'Halloran, K.D. Does episodic hypoxia affect upper airway dilator muscle function? Implications for the pathophysiology of obstructive sleep apnea. *Respir. Physiol. Neurobiol.* 147: 223-234, 2005.

12. Can, M., Acikgoz, S., Mungan, G., Bayraktaroglu, T., Kocak, E., Guven, B. and Demirtas, S. Serum cardiovascular risk factors in obstructive sleep apnea. *Chest* 129: 233-237, 2006.

13. Chervin, R.D. and Archbold, K.H. Hyperactivity and polysomnographic findings in children evaluated for sleep-disordered breathing. *Sleep* 24: 313-320, 2001.

14. Chervin, R.D., Dillon, J.E., Bassetti, C., Ganoczy, D.A. and Pituch, K.J. Symptoms of sleep disorders, inattention, and hyperactivity in children. *Sleep* 20: 1185-1192, 1997.

15. Coughlin, S.R., Mawdsley, L., Mugarza, J.A., Calverley, P.M.A. and Wilding J.P.H. Obstructive sleep apnea is independently associated with an increased prevalence of metabolic syndrome. *Eur. Heart J.* 25: 735-741, 2004.

16. Ferguson, K.A., Cartwright, R., Rogers, R. and Schmidt-Nowara, W. Oral appliances for snoring and obstructive sleep apnea: A Review. *Sleep* 29: 244-262, 2006.

17. Ferrier, K., Campbell, A., Yee, B., Richards, M., O'Meeghan, T., Weatherall, M. and Neill, A. Sleep-disordered breathing occurs frequently in stable outpatients with congestive heart failure. *Chest* 128: 2116-2122, 2005.

18. Findley, L., Unverzagt, M. and Suratt, P.M. Automobile accidents involving patients with obstructive sleep apnea. *Am. Rev. Respir. Dis.* 138: 337-340, 1988.

19. Gami, A., Pressman, G. and Caples, S. Association of atrial fibrillation and obstructive sleep apnea. *Circulation* 110: 364-367, 2004.

20. Gozal, D., Daniel, J.M. and Dohanich, G.P. Behavioral and anatomical correlates of chronic episodic hypoxia during sleep in the rat. *J. Neurosci.* 21: 2442-2450, 2001.

21. Gozal, D., Reeves, S.R., Row, B.W., Neville, J.J., Guo, S.Z. and Lipton A.J. Respiratory effects of gestational intermittent hypoxia in the developing rat. *Am. J. Respir. Crit. Care Med.* 167: 1540-1547, 2003.

22. Huang, S.G. and Li, Q.Y. Sleep respiratory disorder study group respiratory disease branch shanghai medical association. Prevalence of obstructive sleep apnea-hypopnea syndrome in Chinese adults aged over 30 yr in Shanghai. *Zhonghua Jie He He Hu Xi Za Zhi.* 26: 268-272, 2003.

23. Ip, M.S., Lam, B., Chan, L.Y., Zheng, L., Tsang, K.W., Fung, P.C. and Lam, W.K. Circulating nitric oxide is suppressed in obstructive sleep apnea and is reversed by nasal continuous positive airway pressure. *Am. J. Respir. Crit. Care Med.* 162: 2166-71, 2000.

24. Ip, M.S., Lam, B., Ng, M.M., Lam, W.K., Tsang, K.W. and Lam, K.S. Obstructive sleep apnea is independently associated with insulin resistance. *Am. J. Respir. Crit. Care Med.* 165: 670-676, 2002.

25. Javaheri, S, Parker, T.J., Liming, J.D., Corbett,W.S., Nishiyama, H., Wexler, L. and Roselle, G.A. Sleep apnea in 81 ambulatory male patients with stable heart failure. *Circulation* 97: 2154-2159, 1998.

26. Javaheri, S. Heart failure and sleep apnea: emphasis on practical therapeutic options. *Clin. Chest Med.* 24: 207- 222, 2003.

27. Jordan, W., Reinbacher, A., Cohrs, S., Grunewald, R.W., Mayer, G., Ruther, E. and Rodenbeck, A. Obstructive sleep apnea: Plasma endothelin-1 precursor but not endothelin-1 levels are elevated and decline with nasal continuous positive airway pressure. *Peptides* 26: 1654-1660, 2005.

28. Kasasbeh, E., Chi, D.S. and Krishnaswamy, G. Inflammatory aspects of sleep apnea and their cardiovascular consequences. *Southern Med. J.* 99: 58-67, 2006.

29. Kushida, C.A., Littner, M.R. and Hirshkowitz, M., Practice parameters for the use of continuous and bilevel positive airway pressure devices to treat adult patients with sleep-related breathing disorders: An American Academy of Sleep Medicine report. *Sleep* 29: 375-380, 2006.

30. Lavie, L. Obstructive sleep apnea syndrome: An oxidative stress disorder. *Sleep Med.* 7: 35-51, 2003 (Review).

31. Li, R.C., Row, B.W., Gozal, E., Kheirandish, L., Fan, Q., Brittian, K.R., Guo, S.Z., Sachleben, L.R. Jr. and Gozal, D. Cyclooxygenase 2 and intermittent hypoxia-induced spatial deficits in the rat. *Am. J. Respir. Crit. Care Med.* 168: 469-475, 2003.

32. Marin, J.M., Carrizo, S.J., Vicente, E. and Agusti, A.G. Long-term cardiovascular outcomes in men with obstructive sleep apnea-hypopnea with or without treatment with continuous positive airway pressure: an observational study. *Lancet* 365: 1046-1053, 2005.

33. Narkiewicz, K. and Somers, V.K. Sympathetic nerve activity in obstructive sleep apnea. *Acta. Physiol. Scand.* 177: 385-390, 2003.

34. Neubauer, J. Physiological and genomic consequences of intermittent hypoxia. Invited review: Physiological and pathophysiological responses to intermittent hypoxia. *J. Appl. Physiol.* 90: 1593-1599, 2001.

35. Pack, A. Advances in sleep-disordered breathing. *Am. J. Respir.*

Crit. Care Med. 173: 7-15, 2006.

36. Peppard, P., Young, T., Palta, M. and Skatrud, J. Prospective study of the association between sleep-disordered breathing and hypertension. *N. Engl. J. Med.* 342: 1378-84, 2000.

37. Poceta, J.S., Timms, R.M., Jeong, D.U., Ho, S.L., Herman, M.K. and Mitler, M.M. Maintenance of wakefulness test in obstructive sleep apnea syndrome. *Chest* 101: 893-897, 1992.

38. Polotsky, V.Y., Li, J., Punjabi, N.M., Rubin, A.E., Smith, P.L., Schwartz, A.R. and O'Donnell, C.P. Intermittent hypoxia increases insulin resistance in genetically obese mice. *J. Physiol.* 552: 253-264, 2003.

39. Prabhakar, N.R. and Kumar, G.K. Oxidative stress in the systemic and cellular responses to intermittent hypoxia. *Biol. Chem.* 385: 217-221, 2004.

40. Punjabi, N.M., Sorkin, J.D., Katzel, L.I., Goldberg, A.P., Schwartz, A.R. and Smith, P.L. Sleep-disordered breathing and insulin resistance in middle-aged and overweight men. *Am. J. Respir. Crit. Care Med*. 165: 677-82, 2002.

41. Punjabi, N.M. and Polotskym, V.Y. Disorders of glucose metabolism in sleep apnea. *J. Appl. Physiol.* 99:1998-2007, 2005.

42. Reichmuth, K.J., Austin, D., Skatrud, J.B. and Young, T. Association of sleep apnea and type II diabetes: a population-based study. *Am. J. Respir. Crit. Care Med*. 172: 1590-1595, 2005.

43. Resnick, H.E., Redline, S., Shahar, E., Gilpin, A., Newman, A., Walter, R., Ewy, G.A., Howard, B.V. and Punjabi, N.M. Diabetes and sleep disturbances: findings from the sleep heart health study. *Diabetes Care* 26: 702-709, 2003.

44. Row, B.W., Kheirandish, L., Neville, J.J. and Gozal, D. Impaired spatial learning and hyperactivity in developing rats exposed to intermittent hypoxia. *Pediatr. Res.* 52: 449-453, 2002.

45. Row, B.W., Liu, R., Wei, X., Kheirandish, L. and Gozal, D. Intermittent hypoxia is associated with oxidative stress and spatial learning deficits in the rat. *Am. J. Respir. Crit. Care Med*. 167: 1540-1547, 2003.

46. Ryan, S., Taylor, C.T. and McNicholas, W.T. Selective activation of inflammatory pathways by intermittent hypoxia in obstructive sleep apnea syndrome. *Circulation* 112: 2660-2667, 2005.

47. Ryan, S., Taylor, C.T. and McNicholas, W.T. Predictors of elevated nuclear factor kappa B-dependent genes in obstructive sleep apnea syndrome. *Am. J. Respir. Crit. Care Med.* Jul 13; [Epub ahead of print], 2006.

48. Sassani, A., Findley, L.J., Kryger, M., Goldlust, E., George, C. and Davidson, T.M. Reducing motor-vehicle collisions, costs, and fatalities by treating obstructive sleep apnea syndrome. *Sleep* 27: 453-458, 2004.

49. Shahar, E., Whitney, C.W., Redline, S., Lee, E.T., Newman, A.B., Javier Nieto, F., O'Connor, G.T., Boland, L.L., Schwartz, J.E. and Samet, J.M. Sleep-disordered breathing and cardiovascular disease. *Am. J. Respir. Crit. Care Med*. 163: 19-25, 2001.

50. Shamsuzzaman, A.S.M., Winnicki, M., Lanfranchi, P., Wolk, R., Kara, T., Accurso, V. and Somers, V.K. Elevated C-reactive protein in patients with obstructive sleep apnea. *Circulation* 105: 2462-2464, 2002.

51. Strohl, K. and Redline, S. Recognition of obstructive sleep apnea. *Am. J. Respir. Crit. Care Med*. 154: 279-289, 1996.

52. Veasey, S.C., Davis, C., Zhan, G., Hsu, Y.J., Fenik, P., Pratico, D. and Gow, A.J. Long-term intermittent hypoxia in mice: protracted hypersomnolence with oxidative injury to sleep-wake brain regions. *Sleep* 27: 194-201, 2004.

53. Volgin, D.V. and Kubin, L. Chronic intermittent hypoxia alters hypothalamic transcription of genes involved in metabolic regulation. *Auton. Neurosci*. 126-127: 93-99, 2006.

54. Weissbluth, M., Davis, A.T., Poncher, J. and Reiff, J. Signs of airway obstruction during sleep and behavioral, developmental, and academic problems. *J. Dev. Behav. Pediatr*. 4: 119-121, 1993.

55. West, S.D., Nicoll, D.J. and Stradling, J.R. Prevalence of obstructive sleep apnea in men with type 2 diabetes. *Thorax* (published online 23 Aug) 2006.

56. Young, T., Evans, L., Finn, L. and Palta, M. Estimation of the clinically diagnosed proportion of sleep apnea syndrome in middle-aged men and women. *Sleep* 20: 705-706, 1997.

57. Young, T., Peppard, P. and Gottlieb, D. Epidemiology of obstructive sleep apnea: A population health perspective. *Am. J. Respir. Crit. Care Med*. 165: 1217-1239, 2002.

58. Zhan, G., Fenik, P., Pratico, D. and Veasey, S.C. Inducible nitric oxide synthase in long-term intermittent hypoxia hypersomnolence and brain injury. *Am. J. Respir. Crit. Care Med*. 171: 1414-1420, 2005.