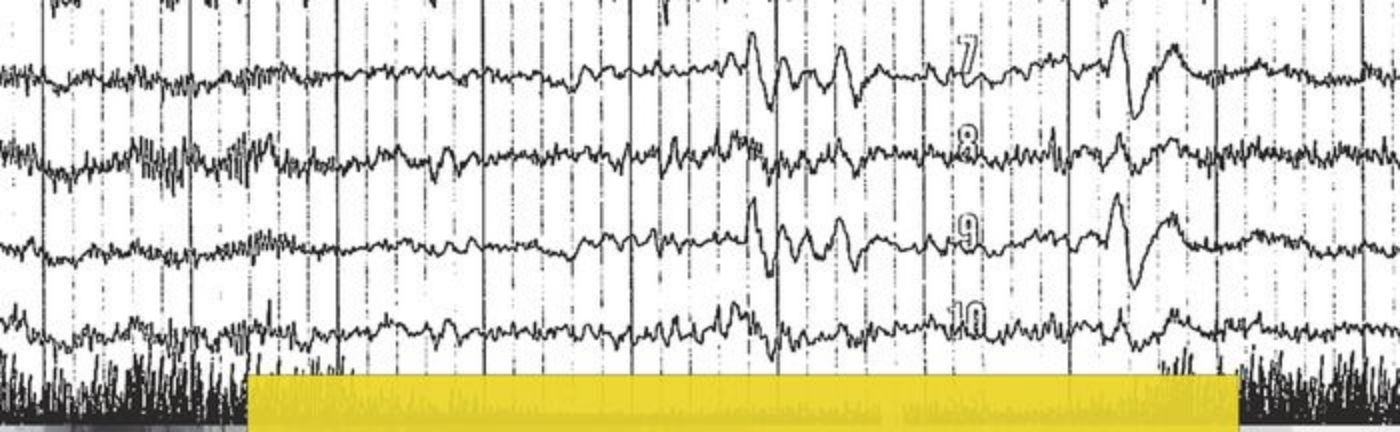

ACUTE AND EMERGENT EVENTS IN SLEEP DISORDERS

Edited by
SUDHANSU CHOKROVERTY
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Preface

In 1999, Frucht and co-workers[1] published a paper on "sleep attacks" in Parkinson's disease (PD) patients on dopamine agonist treatment implying that the treatment itself actually triggered this acute event in these patients. This paper served as a catalyst to awaken the entire movement disorders community about the importance of sleep and sleep dysfunction in PD and other movement disorders and to sensitize the sleep community about acute and emergent events in sleep disorders. It has been known for a long time that sleep deprivation (either resulting from lifestyle factors or sleep pathologies) can lead to fatal and non-fatal accidents at work or on the road. Moreover, sleep deprivation coupled with alcohol consumption is a lethal combination. Every attempt must be made to prevent catastrophic events resulting from sleep deprivation and sleep disorders. Not only lives but billions of dollars are lost from loss of jobs, medical costs and other expenses as a result of acute events derived from sleep deprivation. Unfortunately, the public and profession alike are still not sufficiently cognizant of the fact that a "sleep attack" can be as dangerous as a "heart attack" or "brain attack" (stroke). There is an enormous amount of recent literature on the short-term and long-term adverse effects of sleep restriction and sleep deprivation. Short-term effects include accidents (e.g., falls, fractures, crashes) at work or home, lack of concentration and attention, impaired quality of life and forgetfulness. Long-term effects include hypertension, myocardial infarction, heart failure, cardiac arrhythmias, stroke, obesity, type 2 diabetes mellitus and cognitive impairment. Acute and emergent events may occur without warning in any primary sleep disorder (e.g., obstructive sleep apnea syndrome, narcolepsy, insomnia, circadian rhythm disorders) or comorbid sleep dysfunction associated with medical, psychiatric and neurological disorders, alcohol and medication-related sleep pathologies. There are both anecdotal and case series reports of sudden cardiac arrhythmias and even sudden death associated with severe OSAS and hypoxemia during overnight polysomnographic recordings in

sleep laboratories. In patients with restless legs syndrome (RLS) there are anecdotal or case reports of suicidal thoughts (see Q.80 in Chokroverty[2]), emergency room visits (see Q. 51 in Chokroverty[2]) and injuries related to severe, uncomfortable and unbearable sensory symptoms with an intense urge to move. Many parasomnias, particularly REM behavior disorder (RBD), may be associated with injurious behavior. Although not frequent, it is incumbent upon all sleep professionals and sleep technologists to be vigilant about urgent and acute events occurring in sleep disorders. Regrettably these catastrophic events in sleep medicine are mentioned casually in sleep medicine textbooks without devoting sufficient space to explain in detail the importance of recognizing them so that they can be prevented and treated to minimize morbidity and mortality.

In the last three decades, considerable progress has been made in the field of sleep medicine. Advances in sleep medicine and basic science have brought acute events in sleep disorders to the forefront and have taught us the dangers of sleep deprivation. Through colorful displays of images, special neuroimaging studies have vividly demonstrated activation of the limbic cortex in REM behavior disorder and perhaps even in partial arousal disorders, emphasizing the dangers of such acute events in sleep. Advances in clinical science have clearly demonstrated the impending dangers of sleep apnea, acute insomnia, narcolepsy and other hypersomnias in terms of increasing morbidity and mortality. Advances in laboratory techniques have helped us to identify such acute events (e.g., cardiac arrhythmias, dangerous hypoxemias, ataxic breathing pattern pointing to a destabilized central respiratory controller with impending danger, irresistible hypersomnolence resulting in falls and accidents) so that appropriate measures for prevention and treatment can be readily instituted. Finally, advances in treatment (e.g., positive pressure therapy, pharmacological treatment for narcolepsy and other hypersomnias, insomnia and other sleep disorders) have enabled us to effectively manage the acute and emergent events observed in common sleep disorders.

Therefore, now is the most opportune moment to bring together in this single volume comprising these many acute and urgent events that can occur in almost every sleep disorder listed in the International Classification of Sleep Disorders, edition 2 (ICSD-2).

In this volume, we are fortunate to have some of the World's foremost sleep specialists who agreed to contribute chapters emphasizing the acute events in sleep disorders medicine. We owe these contributions an enormous amount of gratitude and heartfelt thanks. In order to emphasize the urgent events, we asked the authors to prepare the background by briefly outlining the salient features of the disease, and therefore, there are some unavoidable repetitions which, we hope the readers will understand. We tried to cover all aspects but we are certain there are some omissions for which we send our regrets. We will rectify such deficiencies in our future edition should the readers point to us such deficiencies.

This book should be useful to all multidisciplinary sleep specialists including those practicing internal medicine (particularly pulmonary, cardiovascular, gastrointestinal, renal and endocrine medicine), intensive care physicians and surgeons, emergency room physicians, neurologists, psychiatrists, family physicians, pediatricians, otolaryngologists, dentists, psychologists practicing sleep medicine, neurosurgeons as well as sleep and EEG technologists, respiratory therapists, nurses, particularly ICU nurses and other professionals with an interest and curiosity about sleep and sleep disorders. It will also be a handy and useful resource in sleep centers and sleep labs across the world where one may encounter these emergent situations.

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The co-editor (PS) would like to thank Betty March for all her help with sorting the authors' contributions and helping with correspondence. I could not have done it without her help. I would like to thank the senior editor for all his work and lead during this project. I would also like to acknowledge the patience and support of my wife Shaku Sahota, support of my children Sheena and Shawn, and the ever-guiding hand of my parents especially my late father Gurbaksh Singh Sahota whose memory, spirit and sacrifice has guided me all my life.

Finally, we are thankful to all our patients who gave us a chance to learn not only acute and urgent events, but also all aspects of sleep medicine which helped us contribute towards patient care, education and research to the best of our ability.

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Section 1

Emergent Events Related to Sleep Disorders

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Sleep Apnea: Respiratory Issues

Greg Matwiyoff, MD, Sheila Tsai, MD, and Teofilo Lee-Chiong, MD

Relatively few respiratory emergencies occur during polysomnography.[1] Sleep apnea is a chronic problem that in many cases has been present for several years. However, since patients with sleep apnea tend to have more preexisting comorbidities, it is essential to be aware of potential problems and to have an appropriate plan in place to deal with emergencies should they occur. It is also important to keep in mind that polysomnography is often an elective procedure that should be scheduled when the patient is in a chronic, stable state free from acute illness; this usually provides the most valuable and reliable study, and limits the potential for complications related to acute illness. As such, the primary strategy for managing respiratory emergencies during polysomnography is to prevent them from occurring in the first place. Thus, it is imperative to obtain a thorough medical history, including any underlying respiratory disorders, and to assess the patient's current health. The patient should be asked to provide a current and comprehensive list of medications he or she is taking and should be questioned specifically regarding the use of any sleep medications, including hypnotics, narcotics, and benzodiazepines. The technical staff in the laboratory should ensure that the patient has been appropriately screened and has provided the relevant data mentioned above. Furthermore, technicians should verify that the patient being studied is free of acute illness and is behaving appropriately.

Sleep apnea is characterized by the repetitive cessation or reduction of airflow that occurs during sleep. These respiratory events can occur despite the presence of respiratory efforts and can be due to complete or partial upper

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The views expressed in this work are those of the authors and do not necessarily reflect the official policy or position of the Department of the Navy, Department of Defense, nor the U.S. Government.

airway collapse during sleep, as in the case of obstructive sleep apnea. Cessation of airflow can also result from absent respiratory efforts, as in the various forms of central sleep apnea. Apnea in an adult is defined by a cessation of nasal and oral airflow for at least 10 seconds, and is classified as central if respiratory efforts are absent; as an obstructive event if respiratory efforts are present; or as a mixed event if there is an initial central apneic component followed by an obstructive component. A hypopnea, on the other hand, is defined as a reduction in airflow by at least 30% from baseline with a duration of at least 10 seconds associated with an oxygen desaturation of 4% or more.[2]

Obstructive Sleep Apnea

Obstructive sleep apnea is estimated to affect 2% to 4% of adults in industrialized countries.[3] The prevalence is likely to increase as the obesity epidemic continues to worsen throughout the world. It is more common among men than women, with roughly twice the prevalence in men. However, the prevalence in postmenopausal women tends to approach that of men. Other risk factors include obesity, specific craniofacial abnormalities (large neck circumference, enlarged tonsils and adenoids, crowded posterior pharyngeal space, large uvula, macroglossia, and retro- or micrognathia or features of central facial hypoplasia, as seen in trisomy 21).

Evaluation of suspected obstructive sleep apnea should include a thorough clinical history and physical examination. Polysomnography is required for the diagnosis of obstructive sleep apnea since neither clinical nor physical examination features are sufficiently sensitive or specific for this disorder.

Physiology of the Respiratory System During Sleep

It is important to understand the respiratory changes that occur during sleep in order to anticipate problems that may occur during polysomnography. There are several important changes in the control of respiration that occur during both non-rapid eye movement (NREM) and rapid eye movement (REM) sleep; these, in turn, determine the ability to oxygenate and ventilate during sleep. Whereas both metabolic (pH, PaO_2, and $PaCO_2$) and behavioral factors influence respiration during the wake state, during sleep, behavioral input is lost, leaving only metabolic factors to control the frequency and amplitude of respiration. Thus, PaO_2 generally falls by approximately 3 to 9 mmHg and SaO_2 by 2%, and $PaCO_2$ rises by 3 to 8 mmHg during sleep compared to levels during wakefulness.[4,5] These changes occur primarily as a result of reductions in tidal volume resulting in lower overall minute ventilation. Hypoxic and hypercapnic ventilatory responses and activity of accessory muscles of respiration decrease during NREM sleep compared to the awake state.

During REM sleep, respiratory mechanics change even further, with loss of respiratory effort from accessory muscles such as the intercostals and scalenes. Furthermore, in the supine position, abdominal weight creates increased work of breathing and can further decrease ventilation during sleep. Additionally, REM sleep is associated with even more depressed upper airway dilating muscle activity and lower lung volumes.

The upper airway can be conceptualized as a collapsible cylinder, with its patency determined by the balance of factors that either maintain airway opening, with activation of dilator muscles, or promote airway closure, with a reduction in intraluminal extrathoracic airway pressure, with or without accompanying forces external to the airway promoting extrinsic collapse (as is the case with excessive adipose or soft tissue accumulation around upper airway structures). In addition, airway caliber is influenced by lung volume, which decreases during sleep.

Critical closing pressure (P_{CRIT}) is the intraluminal pressure below which the upper airway collapses. Critical closing pressure is progressively less negative among snorers and those with obstructive sleep apnea compared to non-snorers. Activation of the upper airway dilator muscles decreases P_{CRIT}, requiring a larger negative pressure to collapse the airway.

Airflow through the upper airway is dependent upon three principal pressures: upstream (nasal) pressure, downstream (hypopharyngeal) pressure, and the pressure surrounding the vulnerable portions of the upper airway, which tend to promote airway collapse and raise the overall upper airway resistance. Therefore, airflow within the upper airway is greater with higher upstream pressure, lower downstream pressure, and minimal surrounding pressure encroaching on collapsible segments of the upper airway.

In obstructive sleep apnea, the reduced activity of the upper airway dilating muscles during sleep results in repetitive upper airway obstruction. These respiratory events are associated with episodic snoring, oxygen desaturation, and relative bradycardia during airway obstruction. These respiratory events generally terminate with an arousal associated with tachycardia and a transient increase in blood pressure in the immediate post-apneic period.

Nocturnal Hypoxemia in Obstructive Sleep Apnea

Sleep-related hypoxemia is defined by the International Classification of Sleep Disorders, second edition, as oxyhemoglobin saturation during sleep of less than 90% for more than 5 minutes with a nadir of at least 85%, or saturation less than 90% for greater than 30% of the total sleep time[6] in the absence of obstructive, mixed, or central apnea or hypopnea, and inspiratory airflow limitation or snoring.

The degree of oxygen desaturation in persons with obstructive sleep apnea is directly related to the apnea–hypopnea index or AHI (the number of apneas

plus hypopneas per hour of sleep), and worsens depending on the duration of an individual episode of apnea or hypopnea; the percentage of sleep during which apnea or hypopneas are present; and a shorter duration of normal ventilation between periods of apneas and hypopneas. However, there is significant intra- and inter-night variability in AHI in persons with obstructive sleep apnea, as a result of changes in the percentages of supine versus non-supine sleep as well as NREM versus REM sleep. For example, as previously discussed, AHI tends to be higher during REM sleep in the supine position. Alcohol, muscle relaxants, sedatives, and opioids all tend to diminish upper airway muscle tone and can worsen the severity of obstructive sleep apnea, as can changes in nasal resistance brought about by congestion due to allergies or infection. Finally, a change in weight is directly correlated with both the risk and severity of obstructive sleep apnea.

Other factors that increase the severity of oxygen desaturation include levels of awake supine oxygen saturation; baseline sleep oxygen saturation; functional residual capacity and expiratory reserve volume; and the presence of comorbid lung disorders, such as interstitial or chronic obstructive lung disease. The decrease in gas exchange is more obvious in patients with underlying lung diseases and can manifest as more severe hypoxemia and hypercapnia. Oxygen desaturation is also more severe with obstructive rather than central apneas. Finally, respiratory events are generally more frequent, last longer, and are associated with more profound oxygen desaturation during REM sleep compared to NREM sleep.

Differential Diagnosis of Nocturnal Hypoxemia

Aside from obstructive sleep apnea, there are several other disorders that can give rise to oxygen desaturation during sleep. These include central sleep apnea, alveolar hypoventilation syndromes, high altitude, chronic obstructive pulmonary disease, nocturnal asthma, congestive heart failure, neuromuscular diseases, diaphragm paralysis, and restrictive lung disease.

Central Sleep Apnea

In this disorder, repetitive cessation of airflow during sleep is due to a reduction or loss of ventilatory effort. Episodic oxygen desaturation is generally milder than in obstructive sleep apnea. Based on the level of ventilation, central sleep apnea can either be hypercapnic or non-hypercapnic. Hypercapnic central sleep apnea may be seen in neuromuscular disorders or chronic use of long-acting opioids. Examples of non-hypercapnic central sleep apnea include idiopathic central sleep apnea, high-altitude periodic breathing, complex sleep apnea, and central sleep apnea secondary to congestive heart failure.

Cheyne-Stokes respiration is defined by the presence of periodic breathing with recurring episodes of crescendo–decrescendo ventilation separated by central apneas or hypopneas with a cycle time of about 60 to 90 seconds.[7] Central apneas are present during NREM sleep and improve or resolve during REM sleep. Compared to obstructive sleep apnea, in which the nadir of oxygen desaturation typically occurs following termination of apnea, due to the cycle time of these events, patients with Cheyne-Stokes respiration often have a more delayed oxygen desaturation nadir. Also, compared to obstructive sleep apnea, in which the arousals occur at the termination of the apnea, in Cheyne-Stokes respiration, the arousals occur at the peak of the hyperpneic episode.

Alveolar Hypoventilation Syndromes

Sleep-related oxygen desaturation and hypercapnia ($PaCO_2$ during sleep greater than 45 mmHg, or abnormally increased relative to waking levels) are generally present in the various alveolar hypoventilation syndromes. Indicators of hypoventilation include hypoxia, as noted on the pulse oximeter, and hypercapnia, as detected by assessment of end-tidal or transcutaneous monitoring of carbon dioxide, if available. Mechanisms responsible for oxygen desaturation include reductions in tidal volume with a resultant decrease in minute ventilation, abnormal ventilation–perfusion relationships, and diminished ventilatory chemosensitivity and respiratory load responsiveness.

Obesity hypoventilation syndrome is often, but not always, associated with snoring, obstructive sleep apnea, and nocturnal hypoventilation. Other disorders that can cause alveolar hypoventilation include amyotrophic lateral sclerosis, spinal cord injury, and strokes involving the brain stem.

In congenital central alveolar hypoventilation syndrome, failure of automatic control of breathing and markedly diminished responsiveness of central and peripheral chemoreceptors to oxygen and carbon dioxide are first apparent during infancy; patients may present with respiratory failure, cyanosis, apparent life-threatening events (ALTEs), or cor pulmonale. Hypoventilation is worse during sleep than wakefulness and is more severe during NREM than REM sleep. Other common features of this disorder include autonomic dysfunction, gastrointestinal dysmotility disorders, including Hirschsprung's disease, and neural crest tumors. Many cases involve *de novo* mutations of the PHOX2B gene.

High Altitude

Episodes of central apneas and hyperpneas can develop during ascent to high altitude, particularly at elevations above 2,500 meters.[8] The prevalence of high-altitude periodic breathing increases in male subjects with increased

hypoxic ventilatory drive when ascending quickly (24 hours or less) to higher elevations. Hypoxemia is generally more pronounced in those with an underlying cardiovascular or respiratory disorder, particularly if hypoxemia is already present during the awake state at lower elevations. Both periodic breathing and oxygen desaturation occur primarily during NREM sleep, as respirations tend to become more regular during REM sleep.

Chronic Obstructive Pulmonary Disease

Chronic obstructive pulmonary disease is characterized by progressive airflow limitation that is not fully reversible, and consists of emphysema and chronic bronchitis. Nocturnal hypoxemia and hypercapnia can develop in advanced disease, or acutely during disease exacerbations. The likelihood of nocturnal hypoxemia is increased in persons with an FEV_1/FVC of less than 60%, reduced awake oxygen saturation, and comorbid obstructive sleep apnea (overlap syndrome). In the overlap syndrome there is a pre-existing abnormality in gas exchange that is exacerbated during sleep. Mechanisms responsible for sleep-related oxygen desaturation in chronic obstructive pulmonary disease include hypoventilation, ventilation–perfusion mismatching, and decrease in lung volumes.

Nocturnal Asthma

Asthma can present at night with episodic dyspnea, wheezing, or coughing. Both evening peak expiratory flow rate and FEV_1 tend to be lower compared to daytime values, with peak bronchospasticity tending to occur around 4 a.m.[9] Nocturnal hypoxemia can develop during acute exacerbations. In addition, the majority of asthmatic patients experience nocturnal symptoms that may manifest as dyspnea and bronchospasm during the study.[10] Furthermore, reflux may be worse during apneic episodes as a result of the increased thoracic pressure generated by increasing respiratory efforts against a closed glottis. Gastroesophageal reflux, in turn, may contribute to worsening asthma symptoms. Patients who awaken with acute worsening of dyspnea should receive their bronchodilators, if available, especially if severe wheezing and dyspnea are present.

Congestive Heart Failure

Obstructive and central sleep apnea, Cheyne-Stokes respiration, and pulmonary edema complicate the clinical course of congestive heart failure, all of which can give rise to sleep-related oxygen desaturation. The prevalence and severity of respiratory events are correlated with left ventricular function.

Diaphragm Paralysis

Individuals with diaphragm paralysis may develop obstructive or central apneic events during sleep. Because the diaphragm assumes a greater role in respiration during REM sleep due to atonia of the accessory muscles, nocturnal hypoxemia can become particularly severe during this sleep stage.

Restrictive Lung Disease

Diminished lung volumes secondary to disorders involving the lung parenchyma, as in the various forms of interstitial lung disease, pleural or chest wall disorders (e.g., kyphoscoliosis), and morbid obesity, can give rise to transient or sustained sleep-related oxygen desaturation as well as obstructive and central sleep apnea. Lung function may deteriorate acutely during continuous positive airway pressure therapy in persons with kyphoscoliosis. Hypoxemia related to restrictive lung diseases is worse during REM sleep compared to NREM sleep.

Neuromuscular Diseases

Not only are neuromuscular disorders, such as Duchenne muscular dystrophy, myasthenia gravis, post-polio syndrome, and myotonic dystrophy, associated with an increased risk of obstructive sleep apnea, the likelihood of nocturnal hypoventilation is also greater, with oxygen desaturation being most pronounced during REM sleep. Vocal cord abductor paralysis in multiple system atrophy may present with nocturnal stridor, oxygen desaturation, and sudden death during sleep.

Respiratory Distress During Polysomnography

The differential diagnosis of acute respiratory distress during polysomnography includes nocturnal bronchospasm due to asthma or chronic obstructive pulmonary disease, exacerbation of cystic fibrosis, congestive heart failure with paroxysmal nocturnal dyspnea, gastroesophageal reflux and pulmonary aspiration, ischemic cardiac event, pulmonary thromboembolism, sleep-related abnormal swallowing syndrome, sleep-related choking syndrome, and sleep-related laryngospasm.

In sleep-related abnormal swallowing syndrome, arousals from sleep are accompanied by coughing and choking related to pooling of saliva in the oral cavity during sleep. Abnormal swallowing mechanisms and, possibly, excessive production of saliva produce a gurgling sound that can be heard preceding each coughing spell. This appears to be a rare condition, and its clinical course is not well defined.

Patients with the sleep-related choking syndrome present with abrupt awakenings, a choking sensation or inability to breathe, fear, and anxiety. There is no stridor. It is most often encountered during early to middle adulthood and tends to affect women more often than men. Finally, sleep-related laryngospasm is characterized by total or near-total cessation of airflow while asleep, preceding a sudden awakening that is accompanied by an acute onset of dyspnea and inspiratory stridor. Temporary hoarseness can develop, as may cyanosis. Episodes generally last from a few seconds to several minutes. Sleep-related laryngospasm is believed to be due to either vocal cord spasm or tracheal swelling. This condition is more commonly seen in middle-aged adults and is more prevalent among women compared to men.

Therapy of Nocturnal Hypoxemia

Hypoxemia is a common occurrence in the sleep laboratory since many patients presenting for polysomnography have a high pretest probability of having sleep-disordered breathing and resulting hypoxemic states. In addition, the patient being evaluated for sleep-disordered breathing tends to have more pre-existing comorbidities. This poses a considerable dilemma for the sleep physician and technologist because prematurely terminating a study is costly and deprives the patient of a timely diagnosis and potential therapy. On the other hand, serious respiratory conditions often first manifest with tachypnea and hypoxemia, and failure to recognize and respond to severe oxygen desaturation in a timely manner may place the patient in significant danger.

Patients with underlying respiratory disease experience worsened gas exchange during sleep, particularly during REM sleep when muscle atonia is greatest; this may be reflected in desaturations detected on pulse oximetry. Furthermore, the recumbent position also exacerbates gas exchange due to such factors as abdominal weight, which increases the work required for ventilation and associated reduction of functional residual capacity. The risks associated with hypoxemia are greater in this group of patients, in whom progression to respiratory or cardiac arrest may occur. Data suggest that cardiac irritability can result, with an increased propensity for ventricular ectopy occurring at oxygen saturations less than 60% to 80%.[11,12]

Management of Respiratory Emergencies in the Sleep Laboratory

The published medical literature provides few recommendations regarding the management of respiratory emergencies occurring in the sleep laboratory. Acute severe respiratory events are most likely infrequent, with an overall reported rate of adverse outcomes during attended polysomnography of only 0.35%.[1]

Nevertheless, every sleep laboratory should have written protocols for managing acute respiratory failure and other urgent respiratory events, and sleep physicians, technologists, and other ancillary staff should carefully review the written policies and procedures of the laboratory, including emergency protocols. They should receive appropriate training on how to manage medical emergencies. Specific policies regarding the level of emergency response training required of sleep technologists should be set by the medical director of the sleep center. It is highly recommended that all sleep laboratory personnel be trained in the implementation of airway management protocols specified by the American Heart Association's Basic Life Support (BLS).[13] Sleep center accreditation by the American Academy of Sleep Medicine requires that all sleep technologists hold, at a minimum, valid certification in cardiopulmonary resuscitation (CPR), including appropriate skills training.[14] Ideally, an Advanced Cardiac Life Support (ACLS)-certified provider should be available on site should a patient require more aggressive resuscitation.

Finally, proper equipment, including supplemental oxygen delivery devices, should be readily available in all sleep testing facilities. The need for other supplies and medications, such as oral airway devices, and short-acting bronchodilators, such as albuterol, will vary from institution to institution and should be determined in light of the sleep center's proximity to major medical centers.

Assessing the Patient

The basic management strategy of all respiratory emergencies occurring in the sleep center should involve three essential elements: timely recognition of the problem, appropriate patient stabilization, and expedient and safe transport of the patient to a higher level of care if necessary.

When an episode of oxygen desaturation is first noted, there are two questions to answer: whether the pulse oximetry reading is accurate and reliable, and whether a spurious reading is possible. The latter can often be surmised by recognizing the context in which the hypoxemic event occurs. Several factors should be reviewed, including the patient's past medical history and current health status, the altitude at which the study is being conducted, and general trends in oximetry and heart rate readings that have occurred during the study. A rapid physical examination is essential, with particular emphasis on the airway, cardiorespiratory system, hemodynamic parameters, and mental status.

General Measures

Managing a potential respiratory emergency as a result of sleep apnea requires several steps, which must be performed quickly. These include patient assessment to determine stability and initiation of CPR, if necessary. If patients

are stable but have significant oxygen desaturation, treating hypoxemia with supplemental oxygen or initiating positive-pressure therapy may be appropriate.

Once significant sleep-related oxygen desaturation is confirmed, the most important measure is ensuring the safety of the patient. Decisions on whether to terminate the testing or to activate the emergency response system should be made quickly. The on-call physician should also be notified, but care should not be delayed while attempting to contact this person.

If a patient undergoing polysomnography develops significant oxygen desaturation and devices to correct it, such as an oxygen cannula or positive-airway-pressure devices are not immediately available or effective, it may be necessary to wake the patient. This is likely to rapidly reverse hypoxemia that results primarily from sleep-disordered breathing. Patients with severe oxygen desaturation and significant respiratory distress should immediately be evaluated for a life-threatening condition and, if necessary, appropriately stabilized and transported to a higher level of care.

Therapy of Comorbid Disorders

Oxygen desaturation secondary to acute exacerbations of nocturnal asthma or chronic obstructive pulmonary disease may respond to bronchodilator therapy using short-acting beta-agonists such as albuterol. Respiratory depression due to administration of benzodiazepines or opioid narcotics may, in severe cases, require reversal with appropriate agents, but this should be performed only by appropriately guided and qualified personnel. Persons with acute pulmonary edema secondary to congestive heart failure should be assisted and positioned in an upright posture with their legs dangling over the edge of the bed. These patients may likely need transport to another facility for more acute care, depending on the severity of their nocturnal dyspnea and desaturation.

Treatment should be started as soon as possible if there is evidence of cardiac irritability associated with apneic events; this may manifest as sinus pauses greater than 2 seconds, multiple premature ventricular contractions in couplets, or overt ventricular tachycardia. The goal in these cases is vigilant monitoring and timely intervention so as to avoid both short- and long-term complications.

Oxygen Therapy

Although oxygen therapy is not indicated as sole therapy for obstructive sleep apnea, it may be required as a temporary measure to correct hypoxemia either during the baseline portion of diagnostic or split-night polysomnography or early during positive-airway-pressure titration, when lower pressures remain insufficient to reverse upper airway obstruction. Oxygen supplementation may

also be indicated for persons with significant nocturnal hypoxemia due to hypoventilation and obstructive sleep apnea that is not controlled adequately by positive-airway-pressure therapy alone.

In persons with severe oxygen desaturation, it might be more prudent to provide the highest possible level of oxygen supplementation to rapidly achieve an acceptable oxygen saturation and subsequently titrate oxygen levels downward rather than a slow stepwise increase in oxygen titration. Close monitoring is essential: although oxygen supplementation may benefit some persons with obstructive sleep apnea and non-hypercapnic central sleep apnea, it may result in worsening hypercapnia in persons with certain forms of central sleep apnea and chronic obstructive pulmonary disease.

Positive Airway Pressure and Noninvasive Ventilation Therapies

This form of therapy is the treatment of choice for most persons with obstructive sleep apnea. These devices function as pneumatic splints that maintain upper airway patency by increasing intraluminal pressure above the P_{CRIT}. There are several positive airway pressure (PAP) modalities that can be selected to reverse upper airway obstruction and correct any associated oxygen desaturation. Continuous positive airway pressure (CPAP) provides a single constant pressure throughout the respiratory cycle and is sufficient for most patients with obstructive sleep apnea, in whom it effectively decreases the AHI and improves oxygen saturation.

Bi-level positive airway pressure (BPAP) devices provide two pressure levels during the respiratory cycle: a higher level during inspiration (inspiratory positive airway pressure [IPAP]) and a lower pressure during expiration (expiratory positive airway pressure [EPAP]). Bi-level devices may be considered for patients who remain hypoxemic despite CPAP therapy or for those with concurrent hypoventilation syndromes, or obstructive or restrictive lung disease. Bi-level devices may also be required with the addition of a backup rate to assist with ventilation. More complex devices that employ the basic mechanics of bi-level ventilation with the addition of proprietary mechanical algorithms (such as adaptive servo ventilation [ASV]) that regulate and change the inspiratory pressures from breath to breath may also be used to treat patients with Cheyne-Stokes and complex sleep apnea.

Summary

Patients undergoing evaluation in the sleep laboratory present in various states of health and will require varying degrees of attention and focus. Knowledge of the presence of comorbid illness and current health status will enable sleep physicians and technologists to better anticipate problems likely to arise during the sleep study. Many patients presenting for polysomnography

already have a high pretest probability for sleep-disordered breathing and consequent hypoxemia. It is the sleep technologist and physician's job to discriminate between acceptable levels of hypoxemia that are part of the routine diagnosis and treatment process, and life-threatening levels of desaturation that require immediate intervention and termination of the study.

Evaluation of significant desaturations in the sleep laboratory requires at least a basic awareness and understanding of the differential diagnosis of hypoxemia. Management of all respiratory emergencies includes timely recognition of severe hypoxemia, appropriate patient stabilization, and expedient patient transport to a higher level of care, if necessary.

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2

Acute and Emergent Cardiac Events in Obstructive Sleep Apnea

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Introduction

Obstructive sleep apnea (OSA) is prevalent in up to 9% of women and 24% of men.[1] OSA is characterized by recurrent nocturnal apneas that elicit acute hemodynamic and neurohormonal abnormalities during sleep, and it is associated with an increased risk for cardiovascular morbidity and mortality.[2] The majority of OSA patients are undiagnosed and thus untreated, and two population-based studies[3,4] suggest that no more than 18% of prevalent OSA is clinically recognized.

This chapter reviews the cardiovascular physiology of OSA in contrast with normal sleep and summarizes the evidence of the association between OSA and acute cardiac events, including cardiac arrhythmias, myocardial infarction, and sudden cardiac death.

Physiology and Cardiovascular Control During Normal Sleep

Sleep is a dynamic process involving numerous areas of the brain stem and cortex and evokes widespread physiological changes, many of which affect cardiovascular regulation and function.

Respiratory System

During synchronized non-rapid eye movement (NREM) sleep, breathing patterns are regular. Respiration is predominantly under metabolic control during deeper stages of NREM,[5] and minute ventilation is slightly reduced due to the absence of the non-metabolic drive that is present during wakefulness. Hypoxic and hypercapnic ventilatory response is decreased during NREM sleep. Skeletal muscle tone, including the upper airway dilator muscles, is also reduced during sleep; consequently, mild increases in airflow resistance are observed.[6,7]

By contrast, in rapid eye movement (REM) sleep, breathing patterns are quite irregular, due in part to a further increase in airway resistance, particularly in phasic REM. Hypoxic ventilatory drive declines further, and hypercapnic ventilatory response is virtually absent during REM sleep. Due to these physiological changes, a slight decrease in PaO_2 and increase in $PaCO_2$ is observed during sleep; however, oxygen saturation, as determined by pulse oximetry, is stable.[6,8]

Autonomic Control and the Cardiovascular System

During NREM sleep, sympathetic activity gradually decreases, while parasympathetic tone predominates, with resulting decreases in heart rate, cardiac output, systemic vascular resistance, and blood pressure.[9] This relative vagotonia also produces benign nocturnal arrhythmias and conduction disturbances during sleep.[10] The synchronous reduction in heart rate, blood pressure, and sympathetic nerve traffic during NREM sleep is suggestive of a resetting of the arterial baroreflex driven by the central nervous system.[11]

By contrast, during REM sleep heart rate is unstable, with abrupt and marked fluctuations in the RR interval. Sympathetic activation occurs, with associated surges in heart rate and blood pressure to levels similar to wakefulness.[9]

Overall, during sleep, the majority of normotensive subjects have an average decline of 10% to 20% in blood pressure from daytime levels.[12] However, this phenomenon was less evident under conditions that combined strict bed rest with total sleep deprivation.[13]

Coagulability and vascular endothelial function are also influenced by sleep. Tissue-type plasminogen activator (tPA) and its fast-acting inhibitor, plasminogen activator inhibitor-1 (PAI-1), show a marked diurnal variation in plasma. During sleep there is an increase in PAI-1 and a decrease in tPA,[14] with the lowest fibrinolytic activity evident in the morning.[15,16] Platelet aggregation is affected during sleep, and this continues until an upright posture is resumed in the morning.[17] Heightened coagulability and endothelial dysfunction[18] in the early morning hours may provide a potential explanation for the early morning peak in the incidence of cardiovascular events observed in the general population.[19–22]

Respiratory and Cardiovascular Responses During Sleep in Patients with Obstructive Sleep Apnea

The presence of OSA changes cardiovascular physiology and regulation during sleep. OSA patients may have a smaller, more collapsible pharynx that requires relatively high pharyngeal dilator muscle activity to maintain a patent airway. Due to the reduction in the upper airway dilator muscle activity during sleep, these patients experience recurrent complete or partial occlusions of the upper airway, resulting in apneas and hypopneas, despite increased inspiratory effort.[23,24]

During apneas, there can be significant decreases in arterial PO_2, and significant increases in arterial PCO_2, which stimulate the arterial chemoreceptors. Increased arterial chemoreceptor activity results in heightened respiratory drive and inspiratory muscle activity, which exacerbate obstruction of the upper airway.[24] On the other hand, chemoreceptor and possibly mechanoreceptor stimulation in the upper airway lead to arousal from sleep, activating pharyngeal dilator muscles, which results in a nearly immediate decrease in upper airway resistance and restoration of airflow.[25] The increased respiratory drive that occurs during the apneic period may result in a brief period of hyperventilation after airway patency is restored.[26]

Hypoxemia in the absence of lung inflation activates the diving reflex. This reflex produces bradycardia and peripheral vasoconstriction in order to preserve blood flow to the brain and heart vessels, limiting cardiac oxygen demand.[27] However, at the end of apnea, when breathing resumes, lung expansion stimulates pulmonary stretch receptors, which inhibit vagal outflow, followed by sympathetic activation with consequent tachycardia, and surges in blood pressure (Fig. 2–1).[28,29] In summary, in a pattern that recurs cyclically during sleep, the heart rate in OSA patients may decrease at the end of apneas and then increases abruptly immediately post-apnea.[30]

There is some evidence that coagulability may be increased during sleep in OSA patients. Platelet activation is higher during sleep in OSA patients than in the control group.[31] The fibrinolytic system may also be impaired in OSA patients. Recent data suggest that OSA patients have higher levels of PAI-1 than individuals without OSA; PAI-1 levels were even higher in hypertensive OSA patients.[32] However, there are no data comparing the day–night variation of prothrombotic factors in OSA versus non-OSA subjects.

Obstructive Sleep Apnea and Acute Cardiac Events: Potential Mechanisms

Epidemiological studies in the general population have shown that cardiovascular events are more likely to occur in the morning hours after 6 a.m.[19–22] Sympathetic activation is one of the mechanisms proposed to explain this pattern.

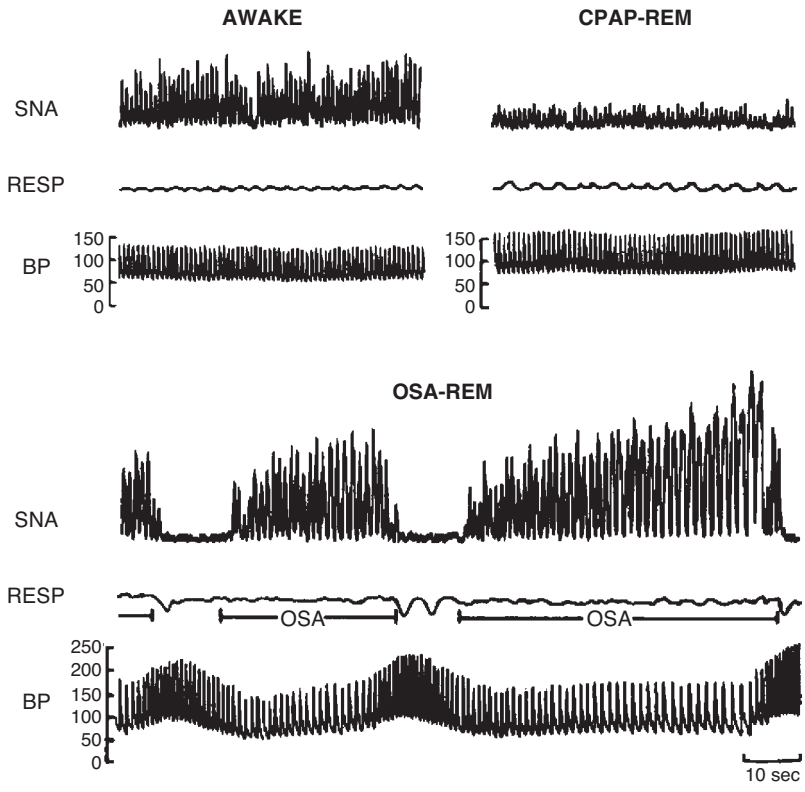

FIGURE 2–1. Recordings of sympathetic activity, respiration, and intra-arterial blood pressure in a patient with sleep apnea on no medications and free of other diseases. Measurements were obtained during wakefulness (*top left*), during obstructive sleep apnea (OSA) in rapid eye movement (REM) sleep (*bottom*), and during REM sleep after treatment of OSA with continuous positive airway pressure (CPAP) (*top right*). During wakefulness, sympathetic activity was high and blood pressure was approximately 130/60 mmHg. During REM sleep, repetitive apnea resulted in hypoxia and chemoreflex stimulation with consequent sympathetic activation. The vasoconstriction resulting from sympathetic activation causes marked surges in blood pressure to levels as high as 250/110 mmHg at the end of apnea, because of increases in cardiac output at termination of apnea. Treatment of sleep apnea and elimination of apneic episodes by CPAP resulted in stabilization and lower levels of both blood pressure and sympathetic activity during REM sleep. (Reprinted with permission from Somers VK, Dyken ME, Clary MP, Abboud FM. Sympathetic neural mechanisms in obstructive sleep apnea. *J Clin Invest*. 1995;96(4):1897–1904.)

Indeed, this hypothesis is supported by the observation of a reduced morning peak in events in patients receiving beta-adrenergic blockade.[33] However, there are still a significant number of events during the nighttime, with 12% to 15% of all cardiac events and almost 36,000 deaths occurring annually occurring during sleep.[19,20] It has been suggested that OSA might play a role in cardiac events occurring at night.[21,22]

OSA elicits hypoxemia followed by sympathetic activation, and a resulting blood pressure and heart rate surge. The tachycardia and an increase in afterload

lead to increased myocardial oxygen demand during hypoxemia and provide a mechanism for increased risk for myocardial ischemia during sleep. The severity of hypoxemia may play a role in nocturnal ventricular arrhythmias.[34] Indeed, epidemiological data from the Sleep Heart Health Study confirm a higher prevalence of ventricular arrhythmias in patients with more severe OSA.[35]

Activation of the diving reflex during apneic events in OSA patients can potentially induce severe bradyarrhythmias, including sinus arrest and AV block. These occur most frequently during REM sleep[36] and can be prevented with OSA treatment.[37]

Associations Between Obstructive Sleep Apnea and Myocardial Ischemia

An association between snoring and ischemic heart disease was first identified more than 20 years ago.[38–40] Some hypothesized that the pathological basis for this association was the presence of OSA.[40] An early demonstration of that association based on polysomnographically proven OSA was an Australian case–control study that found an odds ratio of 23.3 for myocardial infarction (MI) in the upper quartile of OSA severity compared to the lowest quartile after adjustment for known coronary disease risk factors, including body mass index (BMI), hypertension, smoking, and cholesterol.[41] A similar association was identified in a subsequent case–control study involving a broader age range that included subjects as old as 88 years.[42]

In the 1990s there were also several reports[43–45] of ST-segment abnormalities indicating coronary ischemia in association with apneic episodes in subjects with OSA. In a more recent novel approach to the relationship of OSA to MI, it was shown that patients having an MI who were subsequently found to have OSA were more likely to have had onset of their chest pain from midnight to 6 a.m., compared to those without OSA (Fig. 2–2).[22] Together, these findings suggest that the effects of OSA during sleep may precipitate myocardial ischemia and infarction.

The largest study of the association between OSA and prevalent cardiovascular disease (CVD) involved 6,400 patients[46] and was based on the Sleep Heart Health Study, which used unattended polysomnography to identify OSA.[47] The study[46] used any patient self-report of angina, heart attack, heart failure, stroke, or revascularization by coronary bypass grafting or angioplasty as a marker for prevalent CVD. Analysis demonstrated an association of CVD with OSA, with comparison of the highest and lowest quartiles of the apnea–hypopnea index (AHI) producing an odds ratio of 1.42 (95% CI 1.13–1.78) after adjustment for multiple CVD risk factors. Using coronary heart disease alone as the endpoint, the adjusted odds ratio for these risk factors was reduced to 1.27, with statistically significant linear trends across the AHI quartiles.

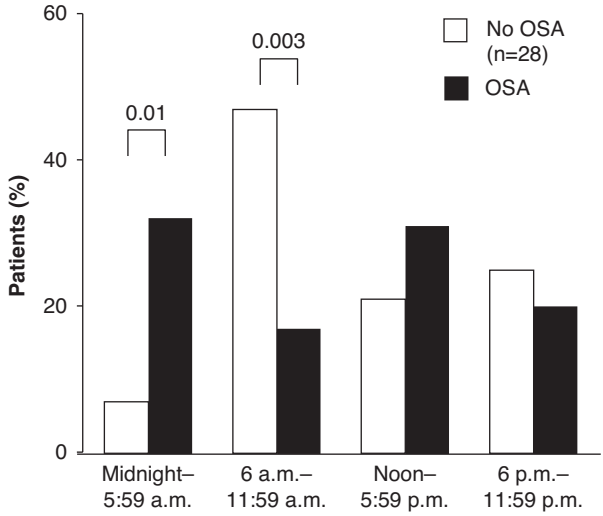

FIGURE 2–2. Day–night pattern of myocardial infarction based on four 6-hour time intervals in patients with (n = 64) or without (n = 28) obstructive sleep apnea. (Reprinted with permission from Kuniyoshi FH, Garcia-Touchard A, Gami AS, Romero-Corral A, van der Walt C, Pusalavidyasagar S, Kara T, Caples SM, Pressman GS, Vasquez EC, Lopez-Jimenez F, Somers VK. Day–night variation of acute myocardial infarction in obstructive sleep apnea. *J Am Coll Cardiol*. 2008;52(5):343–346.)

Several studies evaluated the association of OSA with MI in populations with known coronary artery disease (CAD). In a prospective cohort study of subjects with angiographically demonstrated CAD, sleep-disordered breathing, defined as an oxygen desaturation index of 5 or more, was associated with a composite endpoint including death, cerebrovascular event, and MI with a hazard ratio of 1.59 (95% CI 1.00–2.51) after adjustment for age, sex, BMI, hypertension, diabetes, left ventricular dysfunction, and coronary intervention, at an average 5.1 years of follow-up.[48] Interestingly, in univariate analysis sleep-disordered breathing did not statistically predict MI as a single endpoint, although a combined 77.5% of subjects in both the sleep-disordered breathing and non–sleep-disordered breathing groups had a coronary intervention during follow-up, possibly reducing the prevalence of MI during follow-up in both groups. Thus, here sleep-disordered breathing was associated with increased risk for a composite cardiovascular endpoint, but not specifically MI after risk factor adjustment.

Milleron et al[49] in 2004 studied a cohort of patients with angiographically proven coronary artery stenosis who were subsequently found to have OSA by polysomnography and offered treatment. In a comparison of those treated with those declining OSA treatment, only treatment predicted subsequent composite cardiovascular event-free survival. After adjustment for the risk factors that differed between the cohorts, including hypertension, hypercholesterolemia, age, and AHI, a hazard ratio of 0.24 (95% CI 0.09–0.62) suggested substantial benefit from OSA treatment in preventing subsequent cardiovascular

events, including MI. A similar study of subjects with OSA, including those with and without prior CVD,[50] found an increased risk of cardiovascular events, including death, among those with untreated OSA after adjustment for diabetes and prior CVD, with an average 7.5 years of follow-up.

Recently, two studies evaluated the association of OSA with outcomes in subjects with CAD following percutaneous coronary intervention (PCI).[51,52] In the Japanese study,[51] 89 PCI patients underwent an unattended sleep study within 2 weeks of their PCI. With OSA defined as an AHI of 10 events per hour or greater, OSA was an independent predictor of major adverse cardiac events, including cardiac death, MI, or target vessel revascularization, with a hazard ratio of 11.6 after adjustment for conventional coronary disease risk factors.

The second of these studies[52] evaluated 371 subjects with known OSA based on laboratory polysomnography who subsequently underwent PCI. This study considered the impact of OSA treatment on post-PCI outcomes, including cardiac death, all-cause mortality, and a composite endpoint that included severe angina, MI, PCI, coronary artery bypass grafting, or death. After 5 years of follow-up, OSA treatment provided a significant reduction in cardiac death (3% vs. 10%, $p = 0.027$) and a trend toward reduced all-cause mortality (11% vs. 17%, $p = 0.058$) but no difference in the composite endpoint. The authors suggested that aggressive treatment and risk factor modification in both groups may have attenuated the impact of OSA treatment.

In a study comparing cohorts of men with OSA, both treated and untreated, with simple snoring, and an age- and BMI-matched healthy control group, associations with fatal and nonfatal cardiovascular events after 10 years of follow-up were analyzed.[53] After adjustment for multiple CVD risk factors, the severe untreated OSA patients had an increased risk of cardiovascular death with an odds ratio of 2.87 (95% CI 1.17–7.51), and nonfatal cardiovascular events with an odds ratio of 3.17 (95% CI 1.12–7.52), compared to the healthy controls. The remaining groups, including those with treated severe OSA, those with untreated mild OSA, and simple snorers, had risks that did not differ statistically from the healthy controls.

Three studies examined the association of OSA with incident CVD.[54–56] Two studies were based on longitudinal follow-up of subjects undergoing sleep studies using a limited polysomnographic montage at a Swedish sleep laboratory in 1991.[55,56] In these studies, after 7 years of follow-up, OSA was found to be associated with incident CVD with an odds ratio of 6.7 (95% CI 1.5–28.8) adjusted for age, BMI, and blood pressure.[55] For the more specific outcome of CAD,[56] the odds ratio remained significant at 4.6 (95% CI 1.8–11.6). Both studies also considered the impact of OSA treatment. Subjects meeting the study's criteria for efficient treatment had an adjusted odds ratio for CVD of 0.1 (95% CI 0.0–0.7)[55] and for CAD of 0.3 (95% CI 0.1–0.8),[56] suggesting a reduction of risk with OSA treatment.

The third study of incident CVD[54] was done in the Caerphilly cohort with questionnaire-based OSA identification, a method that has only limited

polysomnography-based validation.[1] After adjustment for age, social class, smoking, alcohol consumption, BMI, and neck circumference, this study showed no significant association (odds ratio 1.21, 95% CI 0.84–1.74) of OSA with incident ischemic events, including nonfatal MI and death attributed to ischemic heart disease. With the limits of the OSA ascertainment method used in this study and the lack of a power analysis, the reliability of this absence of an association between OSA and incident CVD is unclear.

The data described here, taken together, show an association of OSA with both prevalent and incident CVD even after adjustment for confounding factors. In addition, for patients with established CAD, untreated OSA may be a risk factor for further cardiac events, including MI, and OSA treatment may reduce that risk. In these studies, the direct and independent association of OSA with MI alone has not been as strong as the association with a broader CVD composite endpoint. This is probably in part related to advances in the early recognition of myocardial ischemia and its treatment, thus preventing MI.

More than a decade ago, one review[57] stated, "Evidence for a causal association between sleep apnea and other adverse health outcomes is weak" (p. 857). However, in the decade since, much progress has been made in describing the association between OSA and CVD. Therefore, the causal association of OSA for MI and more broadly other CVD markers seems more likely. However, definitive evidence of OSA as a cause of acute cardiac and vascular events, and proof that OSA treatment prevents these events, remains to be obtained; this would require large randomized controlled studies.

Association Between Obstructive Sleep Apnea and Sudden Death

Evidence for an association between sleep breathing disorders and sudden death has been recognized for at least 40 years since the report of a series of five deaths among 22 patients with hospital admissions for what was then known as Pickwickian syndrome.[58] The investigators reported no sudden deaths after 1967 when such patients were kept awake and early mechanical respirator therapy was initiated.

A subsequent study[59] of OSA-associated death while sleeping compared 91 patients with polysomnography-proven OSA, some of whom were treated, with 35 patients referred to a sleep laboratory but found not to have OSA. With an average follow-up of 34 months, no statistical difference in overall mortality was noted. None of the OSA patients died in their sleep, while three of the four deaths among the 35 controls did occur during sleep. However, both the deaths in those with untreated OSA and three of the seven deaths among those with treated OSA were attributed to cardiac causes, while none of the deaths among the controls were thought to be cardiac-related. It is unclear which deaths in either group would fit the contemporary definition of sudden cardiac death, namely "the unexpected natural death from a cardiac

cause within a short time period, generally less than one hour from the onset of symptoms, in a person without any prior condition that would appear fatal."[60] Thus, this reported lack of an association between OSA and sudden cardiac death may be difficult to interpret in light of these definitional issues.

In the early 1990s two studies provided additional evidence suggestive of an association between OSA and sudden cardiac death. A Finnish study of 460 consecutive unexpected deaths in men aged 35 to 76 showed an association between snoring and a cardiovascular cause of death. Among those with cardiovascular causes, there was an association between snoring and death during sleep.[61] A prospective study of 34 obese men, all with OSA, documented a 4-year 15% risk of sudden cardiac death, 300 times higher than the national average for a population of this age.[62]

More recently, three additional studies have provided evidence supporting this association. A study of subjects who had completed polysomnography at one large Minnesota sleep center over a 6-year period identified 112 subjects with sudden cardiac death by death certificate report. An AHI of 5 or more by polysomnography defined OSA. A comparison of the distributions of time of death grouped into 6-hour intervals for those with and without OSA showed a peak occurrence of sudden cardiac death between midnight and 6 a.m. in patients with OSA, while the peak interval for those without OSA was between 6 a.m. and noon. The risk among those without OSA in this study was consistent with the time of highest risk for the general population (Fig. 2–3).[21,63]

The MADIT II trial[64] evaluated implantable cardioverter–defibrillators (ICDs) as primary prevention for life-threatening ventricular arrhythmias and sudden cardiac death and provided a novel opportunity for assessing the relationship of these arrhythmias with obesity.[65] That analysis showed that after adjustment for age, heart failure functional class, and renal function, there was a statistically significant increased risk of ventricular fibrillation, ventricular tachycardia, or sudden cardiac death in those with obesity (defined as a BMI of 30 or more). Among the potential explanations for this obesity-associated risk is the high prevalence of OSA in obese patients,[66] which is further supported by a trend toward more nighttime ICD therapies among the obese in this study population.[65]

The largest population-based study of arrhythmias and sleep-disordered breathing, which was based on the Sleep Heart Health Study,[47] found an association of sleep-disordered breathing, primarily OSA, with nonsustained ventricular tachycardia and complex ventricular ectopy, even after adjusting for age, gender, obesity, and CAD.[35] Although a specific sudden cardiac death endpoint was not assessed, this OSA-associated risk of ventricular arrhythmias is further suggestive of an association between OSA and sudden cardiac death.

Finally, a European study analyzed Holter monitor QT parameters in subjects with OSA before and after continuous positive airway pressure (CPAP)

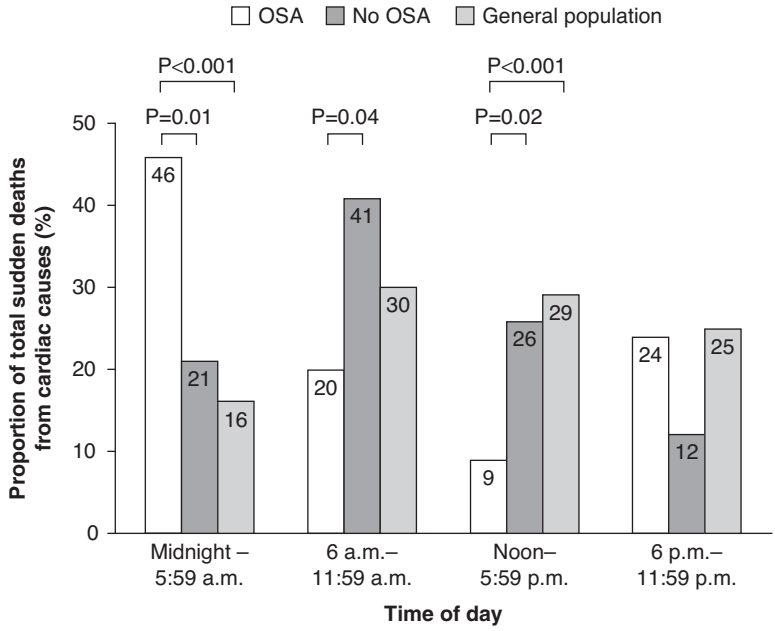

FIGURE 2–3. Day–night pattern of sudden death from cardiac causes in 78 persons with and 34 persons without OSA and in the general population. Data for the general population were derived from Cohen et al.[63] (Reprinted with permission from Gami AS, Howard DE, Olson EJ, Somers VK. Day–night pattern of sudden death in obstructive sleep apnea. *N Engl J Med*. 2005;352(12):1206–1214.)

treatment in comparison to healthy age-matched controls without evidence of OSA or cardiac disease.[67] The study found that CPAP treatment of OSA attenuated the rate dependence of the QT and RT intervals as measured by QT/RR slope or RT/RR slope, which were both significantly higher than controls prior to CPAP treatment. Increased QT rate dependence has been proposed as a marker of vulnerability to ventricular tachycardia in post-MI patients,[68] and as an explanation for the increased risk of sudden cardiac death among diabetics.[69] Thus there is evidence that CPAP treatment in OSA alters electrophysiologic parameters in a manner that has the potential to reduce the risk of ventricular arrhythmias and sudden cardiac death.

Thus, although none of these studies provided direct evidence of an independent association of OSA with sudden cardiac death, especially with a nocturnal predominance, that association is certainly suggested and biologically plausible based on the evidence described above.

Associations Between Obstructive Sleep Apnea and Arrhythmias

A strikingly increased prevalence of rhythm disturbances, including potentially life-threatening brady- and tachy-arrhythmias, among patients with

OSA was first reported more than 30 years ago, and many of those arrhythmias were abolished by OSA treatment with tracheostomy.[70] More recently the Sleep Heart Health Study showed that patients with severe sleep-disordered breathing had two- to four-fold higher odds of atrial fibrillation (AF) and ventricular arrhythmias than those without sleep-disordered breathing, even after adjustment for confounders.[35]

Bradyarrhythmias and Tachyarrhythmias

Roche et al[67] reported an association between OSA and bradyarrhythmia, but other studies failed to show this association.[35,71] Prolonged apnea and hypoxemia in OSA produce vagal activation, which often will elicit bradyarrhythmias such as sinus bradycardia, sinus arrest, and first-, second-, or third-degree AV block, especially during REM sleep.[36,72] Electrophysiological characteristics of the sinus node and atrial conduction system in OSA subjects with nocturnal bradyarrhythmias were nearly normal while awake, and CPAP therapy has been shown to abolish the majority of bradyarrhythmias in OSA patients.[73–75] These findings implicate parasympathetic stimulation in the pathogenesis of the bradyarrhythmias.[70,75–77] Multiple studies have shown successful reduction of these bradyarrhythmias with CPAP treatment.[37,76,78–80] Moreover, Simantirakis et al,[81] using an implantable loop recording device, reported a reduction in the percentage of patients with pauses and bradyarrhythmias after CPAP treatment with at least 16 months of follow up. Thus, CPAP treatment should be considered before implanting a pacemaker in selected OSA patients with bradyarrhythmias.[5,66,80]

Two studies have suggested that there is no significant difference in the frequency of ventricular arrhythmias between patients with and without OSA with normal left ventricular function.[71,82] Subsequently, data from the Sleep Heart Health Study showed that ventricular arrhythmias were more prevalent in OSA patients, even after adjusting for age, sex, BMI, and CAD. Individuals with sleep-disordered breathing had three times the odds of nonsustained ventricular tachycardia and almost two times the odds of complex ventricular ectopy compared to those without sleep disorders of breathing.[35] With the lack of a power analysis and a smaller sample size in two of the studies[71,82], the reliability of the reported lack of an association is uncertain. In addition different AHI cutoffs were used to define the presence of OSA (AHI>10[71], >20[82], and >30[35] events per hour) in these studies with the study showing the association having the most conservative definition and most severe OSA. This may suggest that the severity of OSA plays a role in the development of ventricular arrhythmias in patients with preserved ventricular function.

Ventricular arrhythmias are more common in patients with reduced left ventricular function, and may predict an increased risk of sudden cardiac death.[83,84] Ventricular arrhythmias in OSA patients may appear most often during sleep, with the greatest frequency during apneic periods.[34,79,85]

Ryan et al[86] examined whether treatment of OSA with CPAP in patients with heart failure would reduce the frequency of ventricular premature beats during sleep, and noted a 58% reduction in the frequency of ventricular premature beats during total sleep after 1 month of CPAP treatment.

The mechanisms by which OSA induces ventricular arrhythmias are not completely understood. However, hypoxemia, arousal, and sympathetic activation induced by apneic events may play an important role.[87]

Atrial Fibrillation (AF)

An estimated $6.65 billion (2005 dollars) is spent treating AF annually.[88] Recent estimates have shown that AF prevalence has increased in recent decades and suggest that by 2050 there will be between 7.56 million[89] and 15.9 million[90] persons with AF in the US. Thus identification and subsequent reduction of AF risk factors could have an important impact.

In 1983 Guilleminault et al[72] were among the first to indentify atrial fibrillation during sleep in association with OSA and to show a decline in atrial fibrillation after OSA treatment. More recently Gami et al[91] in comparing patients with AF with other cardiology clinic patients without AF showed an association between OSA and AF with an odds ratio of 2.19 (95% CI 1.4–3.42) after adjusting for BMI, neck circumference, hypertension, and diabetes. In an arrhythmia analysis from the Sleep Heart Health Study comparing those with sleep disordered breathing (defined as an oxygen desaturation index >30) with those without sleep disordered breathing, AF was associated with sleep disordered breathing with an odds ratio of 4.02 (95% CI 1.03–15.74) even after adjusting for age, gender, BMI and CAD in a population with less CAD and heart failure[35] A study of incident AF following OSA determination by diagnostic polysomnography showed that OSA and obesity predicted AF independent of one another in a multiple regression analysis.[92]A 2008 case-control study confirmed the association between AF and SDB with an odds ratio of 3.04 (95% CI 1.24.– 7.46).[93]

Although multiple studies show evidence of an AF – OSA association, there is more limited evidence about the effects of OSA treatment in AF. In the early study treating OSA with tracheostomy no recurrence of AF was noted following treatment.[72] The only study of AF using CPAP for OSA, treatment was associated with a significant reduction in recurrent AF following electrical cardioversion, an association which was independent of age, hypertension, and BMI.[94] This raises the possibility that OSA may be causally related to AF; however, further research is required to definitively demonstrate causality.

CONCLUSIONS

OSA is prevalent in up to 9% of women and 24% of men and is associated with increased morbidity and mortality. However, the majority of people

with OSA are undiagnosed and hence untreated. OSA cyclically disrupts autonomic control of the cardiovascular system during sleep by way of the diving reflex during apneas, producing bradycardia, and immediately post-apnea by vagal outflow inhibition and sympathetic activation, producing tachycardia and blood pressure surges.

Epidemiological studies of the relationship between OSA and a number of cardiovascular endpoints, including myocardial ischemia or infarction, prevalent and incident CVD, arrhythmias, and sudden cardiac death, have generally found an association even after adjustment for known cardiovascular risk factors. There is also observational evidence that OSA treatment may reduce the OSA-associated risk at least for some of these endpoints. A causal relationship between OSA and bradyarrhythmias has been found, and multiple studies have shown a reduction of these arrhythmias with CPAP treatment for OSA. There is also evidence of an association between AF and OSA, with an attenuated risk of AF recurrence with OSA treatment. The association of OSA with ventricular arrhythmias, though, is more variable and may be related to OSA severity.

Thus, disruptions of autonomic control may provide potential mechanistic explanations for the epidemiological association of OSA with CVD and arrhythmias. However, definitive proof that a causal relationship exists, and that OSA treatment reduces these risks, remains to be found.

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3

Acute Issues in Narcolepsy and Hypersomnia

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Introduction

Narcolepsy is a debilitating condition characterized by excessive daytime sleepiness and sleep attacks, as well as cataplexy, hypnagogic and hypnopompic hallucinations, and sleep paralysis. The latter three symptoms are thought to result from an abnormal breach of REM sleep into wakefulness. The International Classification of Sleep Disorders recognizes two types of narcolepsy: narcolepsy with cataplexy and narcolepsy without cataplexy. Cataplexy is thought to be a pathognomonic feature of narcolepsy that is characterized by a sudden loss of muscle tone in response to heightened emotional state, most often laughing or anger.[1,2] Narcolepsy without cataplexy is thought to represent 20% to 50% of cases.[3]

Several studies have found the prevalence of narcolepsy with cataplexy to be around 0.04%; however, significant geographical variation has been observed. Prevalence in Israel, for instance, may be as low as 0.002%,[4] while in Japan, it may be as high as 0.16% to 0.18%.[5,6] Fewer studies exist that investigate the prevalence of narcolepsy without cataplexy. In 2002 a study was published using data from the Rochester Epidemiology Project that found the prevalence of narcolepsy without cataplexy to be 0.021%.[7]

In narcolepsy, a number of acute issues can develop with regard both to symptomatology and treatment, and these acute aspects of its presentation have the potential for accident and injury (e.g., sleep attacks, acute cataplectic events). We shall review the topic of narcolepsy and these aspects will be emphasized in this chapter. The safety of the patients as well as those around them is foremost

among these issues. Excessive daytime sleepiness, sleep attacks, cataplexy, hypnagogic hallucinations, status cataplecticus, and medications used in treatment can all lead to acute situations that must be addressed by the clinician.

ETIOLOGY

The clinical symptomatology of narcolepsy was first described in 1877 by Westphal;[8] it was again described in 1878 by Fisher but was related to a seizure disorder.[9] Only in 1880 were the symptoms characterized together as a syndrome by Gélineau, who was the first to use the diagnostic term *narcolepsy*. The road to the discovery of the pathogenesis of narcolepsy did not begin until almost a century later, with case reports of narcoleptic dogs in the 1970s.[10,11] The breeding of two narcoleptic Doberman pinschers in 1975 would lead to the development of a colony of narcoleptic dogs in which a defect in the hypocretin receptor 2 gene was discovered.[12] Since that time, the narcolepsy phenotype has also been demonstrated in hypocretin-knockout mice.[13]

Hypocretin-1 and hypocretin-2 (also known as orexin-A and orexin-B) are neuropeptides found in cell bodies in the lateral hypothalamus. Projections from these cell bodies have wide distribution in the brain; however, the densest concentration of such neurons outside of the hypothalamus is in the locus ceruleus,[14] suggesting that the hypocretin neuropeptides may have a role in monoaminergic activity over the 24-hour sleep cycle. An upstream player may be the suprachiasmatic nucleus, which sends projections to the hypocretin cell bodies and may, in turn, play a role in regulation of circadian rhythm.

Research in human subjects has suggested that human narcolepsy is more likely caused by a defect in hypocretin neurotransmission secondary to neuronal destruction rather than a gene mutation. Decreased numbers of hypocretin neurons in the lateral hypothalamus have been discovered in human patients with narcolepsy,[15] and low levels of hypocretin-1 in the cerebrospinal fluid (CSF) have been clearly demonstrated in patients with narcolepsy with typical cataplexy.[16] In 2004, researchers used in vivo proton MR spectroscopy to measure *N*-acetylaspartate content in narcoleptic patients' hypothalamuses. *N*-acetylaspartate is a marker that is decreased when neurons are damaged or destroyed. Reduced levels of *N*-acetylaspartate were found in those with narcolepsy; also, subjects with cataplexy had lower levels than those who had narcolepsy without cataplexy.[17] This suggests that the etiology of narcolepsy may lie in the destruction of the hypocretin neurons.

The pathophysiology of cataplexy is incompletely understood but is thought to be an intrusion of the atonia of the REM state onto wakefulness,

and is believed to involve inhibition of the antigravity muscles associated with inhibition of H-reflex and tendon reflexes. During REM sleep there is an active inhibition of muscle tone with monosynaptic reflex (H-reflex) inhibition, leading to the muscle atonia observed during this stage of sleep. The several descending pathways with glycinergic and glutamatergic synapses are thought to be involved in the pathogenesis. In addition, increased amounts of postsynaptic dopamine receptors in the amygdala were discovered in the colony of narcoleptic dogs previously mentioned. These dogs had impaired dopamine release, and it may be that a dysfunctional interaction between dopaminergic and cholinergic neurons could play a role in the underlying process.[18] Canine $alpha_{1b}$ and $alpha_{2}$ receptors also seem to be involved in cataplexy. $Alpha_{1b}$ antagonists cause cataplexy to become more pronounced, while medications that stimulate these receptors decrease cataplexy.[19] $Alpha_{2}$ antagonists decrease cataplexy as well.[20]

Secondary narcolepsy is a well-established albeit rare phenomenon. Many cases of narcolepsy with cataplexy associated with lesions or tumors near the third ventricle have been described.[21–23] Multiple sclerosis, Parkinson's disease, craniopharyngioma, neurocysticercosis, traumatic brain injury, stroke, acute disseminated encephalomyelitis, and others have been implicated in secondary narcolepsy as well.[24–29]

Common Features

The hallmark of narcolepsy is excessive daytime sleepiness leading to unwelcome sleep episodes that can markedly impair daytime functioning. Naps are typically described as refreshing and may be of relatively short duration. Decreased concentration and memory as well as impaired performance in work and school are often reported by patients.

The nocturnal sleep of those with narcolepsy is fragmented and of poor quality. This is a factor that distinguishes narcolepsy from hypersomnia. Patients with narcolepsy wake frequently through the night and may describe nightmares. Sometimes patients may report difficulty with sleep initiation or difficulty falling back asleep after nocturnal awakenings. Periodic limb movements can be observed in this patient population and may contribute to the poor sleep quality.[30]

Cataplexy is thought to be pathognomonic for a diagnosis of narcolepsy, though the degree of muscle weakness and frequency of episodes varies from patient to patient. For example, muscle weakness can range from a mild facial droop to total collapse, and some patients may experience cataplexy only a few times in their lives while others may experience cataplexy several times per day. As patients age cataplexy seems to become less frequent.[30] The episodes are often triggered by emotions, most often laughter and anger. Certainly cataplexy (as well as daytime sleepiness) should be well controlled

if a patient is to have a driver's license or a job in which cataplectic episodes could be particularly dangerous.

In status cataplecticus, a rare phenomenon most often seen with the abrupt withdrawal of anti-cataplectic agents, the cataplectic attack persists for hours, causing severe debilitation.[30] Guilleminault et al[31] described this phenomenon in a young man who despite treatment with imipramine and methylphenidate was effectively house-bound, having on average eight episodes of cataplexy per day when kept without any social interaction and up to 50 daily with social interaction.

Sleep paralysis is a phenomenon commonly associated with narcolepsy. It is often described by patients as a frightening experience. Upon waking, patients have the acute sensation that they are trapped in their bodies and cannot move. They find themselves unable to speak and sometimes even unable to take deep breaths. Visual hallucinations frequently accompany this experience. Sleep paralysis can occur outside of the context of narcolepsy, particularly in those who are sleep-deprived.[32]

Hypnagogic or hypnopompic hallucinations are often reported by those with narcolepsy. Most often these hallucinations take the form of images of simple shapes, although visualizations of animals or people have also been reported. Auditory hallucinations are also known to occur and range from simple sounds to melodies and words. The experiences can seem very real, and patients have been known to call 911 to report intruders in their homes, confusing the hallucination with reality.[30] Olfactory and gustatory hallucinations are not typically reported, though tactile hallucinations, including touch or even levitation, have been described. Just as with sleep paralysis, hypnagogic or hypnopompic hallucinations may occur in those without narcolepsy.[32]

Practitioners, and psychiatrists in particular, should be careful to differentiate the often strange reports by narcoleptics who experience sleep paralysis and hypnagogic hallucinations from psychosis. Those with sleep paralysis and hypnagogic hallucinations have reported alien abductions, demons entering their rooms, and intruders trying to rape or kill them.[33,34] The importance of this distinction is underscored by the difference in treatment appropriate to either diagnosis. There have been reports of hypnagogic hallucinations evolving over time to become well-formed delusions,[35] and certainly psychotic disorders and narcolepsy can co-exist. In addition, there are those who propose that there is a psychotic variant of narcolepsy. This extends from case reports that describe patients who exhibit classic symptoms of narcolepsy concomitant with symptoms of psychosis. These patients experienced no resolution of their psychotic symptoms with traditional antipsychotic medication, but improved with only stimulants.[36]

REM behavior disorder (RBD) can also be associated with narcolepsy. RBD is a syndrome associating dream-related activity without the normal atonia of REM sleep during polysomnography. It is usually seen in patients treated for cataplexy and may be a side effect of medication. A 2005 study found that 68%

of narcoleptic patients who regularly experience cataplexy also experienced symptoms of RBD. This study found equal rates of RBD symptoms occurring in males and females with a mean age of 41 years; this contrasts with epidemiologic data from patients who suffer from RBD alone, in which older males are affected in much higher numbers.[37]

Symptoms of narcolepsy tend to appear first around the time of puberty or young adulthood; however, narcolepsy has been seen in patients as young as 6 months old.[38] A smaller subset of patients is diagnosed much later, typically in the fourth decade of life.[30] Sleep attacks and excessive daytime sleepiness are often the first reported symptoms. Cataplexy may present along with the development of the sleepiness or may present many years later.

Evaluation

The first step in evaluation of the patient with possible narcolepsy is a thorough clinical history and physical examination. Important clinical features to identify include a history of cataplexy, automatic behaviors, sleep paralysis, and hypnagogic hallucinations. The time course of the excessive daytime sleepiness must be ascertained. Information about the use of alcohol, illicit drugs, or sedating medications that could be contributing to or causing symptoms of excessive daytime sleepiness should be gathered. Particular attention should be paid to gathering the history surrounding the presence or absence of cataplexy. As mentioned above, the decrease in muscle tone can be subtle, so much so that the patient may not think to volunteer the information without being asked about it explicitly. On the other hand, the practitioner must be careful not to mistake phenomena such as feeling weakness in one's knees before a performance or a child rolling on the floor laughing from a joke as cataplexy. As previously mentioned, one must also take care to distinguish the hypnagogic or hypnopompic hallucinations from the hallucinations described by acute psychosis.[39]

The next step in making an accurate diagnosis of narcolepsy is to ascertain the presence and degree of daytime sleepiness. The Epworth and Stanford Sleepiness Scales are validated measures of sleepiness completed by the patient.[40] The Multiple Sleep Latency Test (MSLT) is an objective test of daytime sleepiness performed in the sleep laboratory.[41] The test consists of a series of five sequential 20-minute daytime naps in which the patient remains in street clothes in a quiet, dark environment in the absence of alerting environmental stimuli. Polysomnographic EEG data are monitored for the presence of non-REM as well as REM sleep. If a REM episode occurs in the first 15 minutes of a nap it is considered to be a sleep-onset REM episode (SOREM). For patients who have passed puberty, sleep latencies of less than 8 minutes are considered pathological, while sleep latencies greater than 10 minutes are considered normal. Children from the ages of 6 through 11 are considered to be hyperalert, and these criteria do not apply to them.[42]