Handbook of Clinical Neurophysiology

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Volume 6

Clinical Neurophysiology of Sleep Disorders

Volume Editor

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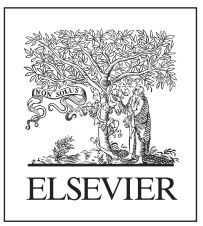

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Note

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Foreword

Clinical neurophysiology encompasses the application of a wide variety of electrophysiologic methods to the analysis of normal function and to the diagnosis and treatment of diseases involving the central nervous system, peripheral nervous system and muscles. The steady increase in growth of subspecialties in neurology has led to a need for a compilation of the whole range of physiologic methods applied in each of the major categories of neurologic disease. While some of these methods are applied to a single category of disease, most are useful in multiple clinical settings.

Each volume will be designed to serve as the ultimate reference source for academic clinical neurophysiologists and as a reference for subspecialists in the area. They will provide the information needed to fully understand the physiology and pathophysiology of disorders in their patients. As such these volumes will also serve as a major teaching text for trainees in that subspecialty.

The Handbook volumes will cover all of the clinical disorders served by clinical neurophysiology, including the epilepsies, autonomic dysfunction, peripheral nerve disease, muscle disease, motor system disorders, somatosensory system disorders, behavioral disorders, visual and auditory system disorders, and monitoring neural function. Each will focus on the advances in one of these major areas of clinical neurophysiology.

Each volume will include critical discussion of new knowledge in basic neurophysiology, approaches to characterization of disease type, localization, severity and prognosis with detailed discussion of advances in techniques to accomplish these. It is recognized that some techniques will be discussed in more than one volume, but with different focuses in each of them.

Each volume will include an overview of the field, followed by a section that includes a detailed description of each of the CNP techniques used in the category of disorders, and a third section discussing electrophysiologic findings in specific diseases. The latter will include how to evaluate each disorder along with a comparison of the relative contribution of each of the methods. A final section will discuss ongoing research studies, and anticipated future advances.

Our recognition of the high prevalence of sleep disorders and our increasing understanding of their variety of presentations make them a particularly appropriate early volume in this series. We are privileged to have one of the world's leaders in the clinical neurophysiology of sleep disorders as the volume editor. He has done a superb job of assembling other world leaders in the description of the neurophysiologic methods of testing and in their application to individual categories of disorders.

This volume defines the role of clinical neurophysiology in the study of disorders of sleep. It includes the physiology of sleep, and the role of clinical neurophysiology in assessing sleep with common and less common methods of testing. The epidemiology of sleep disorders and the wide range of neurophysiologic abnormalities associated with them are described, including disorders associated with other neurologic diseases.

Jasper R Daube
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Series Editors

Preface

Within the past 30 years, sleep medicine has emerged as a new medical discipline. Most of the technology used in sleep medicine is the same as that used by clinical neurophysiologists on a daily basis. The development of the electroencephalogram (EEG) and other polygraphic techniques as the primary descriptor of sleep and wakefulness was extraordinarily important in establishing the field of sleep medicine. These same techniques are used for our own current research.

The many neurons in our brain fire differently; not only during wakefulness compared to sleep but also between the two distinct sleep states (non-rapid eye movement (NREM) and rapid eye movement (REM) sleep). This suggests that what these many and varying neuronal networks control is different during each of these states. It is really important for all of us, particularly physicians, to understand the changes occurring with the different sleep states since the basic nervous system controls of vital functions may vary depending on the physiologic state of the brain. We must have a clear understanding of the normal processes of wakefulness and sleep to be in a better position to assess pathological conditions.

Historically, Henri Pieron's book *Le problème physiologique du sommeil* in 1913 and Nathaniel Kleitman's monograph *Sleep and wakefulness*, which was first published in 1939 and revised in 1963, are the first scholarly and comprehensive works in the field of sleep research. Investigations of pathology linked to sleep came out of two European clinical neurophysiology conferences. The first was under the guidance of Henri Gastaut and the French Society of EEG and Clinical Neurophysiology and resulted in publication of *Le sommeil de nuit normal et pathologique: études électroencéphaologographiques* in 1965. The second conference was the 15th European EEG Society meeting organized in Bologna, Italy by Elio Lugaresi in 1967, which resulted in publication of the book *Abnormalities of sleep in man* in 1968.

These stepping stones led to the recognition of the importance of the dysfunction of sleep states and their impact on our health. We were able to recognize the many negative changes that sleep may bring to a sick patient. The recognition of the dependence of humans on an internal biological clock and awareness of chronopathology generated by modern society has added an important new element in sleep medicine.

The field is now well recognized. Epidemiological studies based on representative samples of the general population from the European and North America communities are available. Asian communities have started similar research. We have deciphered the genetic basis for circadian disorders such as long and short sleepers, and for advanced and delayed sleep phase syndromes. The genetic investigations of canine narcolepsy led to the discovery of a new modulating system distributed throughout the brain: the hypocretin/orexin system. We have progressed in the understanding of sleep in all age groups. The first normative data based on meta-analysis articles on sleep duration were published in 2004. Sleep medicine specialists along with sleep medicine training programs exist in different countries. In addition, clinical neurophysiology training programs in North America and Europe include education of sleep and its disorders.

This book has the problem of all textbooks: it is already outdated compared to the newest research. However, it represents a solid base on which to build. The contributors are internationally recognized specialists that deal on a daily basis with the clinical problems that they address here. We hope that this volume will be helpful not only to clinical neurophysiologists and sleep medicine specialists but also to all individuals who want to have an understanding of the fundamentals of sleep and its pathology.

Christian Guilleminault

Volume Editor

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CHAPTER 1

The physiology of sleep

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1.1. Introduction

1.1.1. Stages of sleep and wakefulness

First and foremost sleep is a brain process. Sleep is often described as a reversible state in which an individual has little or no response to environmental stimuli. Regardless of whether sleep is conceptualized as a process or as a state, it is multidimensional. That is, sleep is not just one process (or state); there are different kinds of sleep. Each type of sleep has its own regulatory mechanisms and presumably different functions. For example, selective deprivation of one type of sleep leads to preferential recovery of that type of sleep when sleep is permitted. The different types of sleep can be thought of as different overall organizational states of the nervous system, some involving increased brain activity and some involving decreased brain activity. While this may sound like neo-dualism, we are not implying that sleep is unimportant to the body. Some bodily processes depend completely on the brain entering one state of sleep or another. Moreover, as the nervous system's organizational state changes during the different states of sleep, concomitant physiological changes occur in the body. In the present chapter we will first describe alterations in brain activity associated with sleep. This will be followed by a description of physiological alterations in various organ systems associated with the different types of sleep.

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1.1.2. Regulation of sleep

There are three basic mechanisms coordinating and governing sleep and wakefulness: (1) autonomic nervous system balance, (2) homeostatic sleep drive, and (3) circadian rhythms. These mechanisms maintain sleep and wakefulness in a dynamic balance. This active equilibrium provides the system with some extent of flexibility. Thus when the balance is upset, these mechanisms provide an avenue for the system to adjust and recover. This arrangement of regulatory mechanisms also provides a means by which an individual can adapt to sudden shifts in the time and duration of sleep.

1.1.3. Difference from stupor, coma and delirium

Like sleep, coma may result from diminished arousal and impairment of cognitive functions. Coma is the result of passive loss of function and metabolic depression in brain stem and cerebral cortex. Ironically, early theories of sleep postulated this process as responsible for sleep. We now know that sleep is an active process involving the interaction of brainstem and cerebral cortex characterized by continued brain oxygen utilization. Notably, sleep can be distinguished from coma by the rapid and complete reversal of any awareness deficit or consciousness impairment when the individual awakens.

Stupor is a state in which consciousness is diminished. It is now realized that alterations in consciousness may involve level, content, or both. Delerium represents a change in the content of consciousness whereas stupor usually involves reduced level of consciousness. The continuum for level of consciousness runs from wakefulness to drowsiness to stupor and finally to coma. Changes in content characteristically arise from diffuse cortical dysfunction; for example,

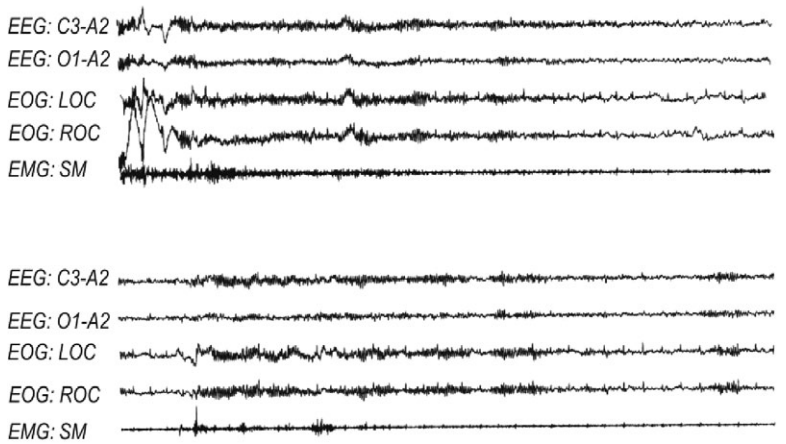

Fig. 1.1. Sleep-onset. Two examples of 30-second epochs showing sleep onset (at approximately three-quarters of the way through the tracing). Electroencephalogram (EEG) is shown from central monopolar mastoid-referenced (C3–A2) and occipital monopolar mastoid referenced (O1–A2) derivations. Electro-oculogram (EOG) is shown from left outer canthus (LOC) and right outer canthus (ROC) derivations. Electromyogram (EMG) from submentalis is also shown (SM).

metabolic encephalopathies. By contrast, changes in the level of consciousness can arise from brainstem lesions.

1.2. Central nervous system

1.2.1. Sleep vs wakefulness

1.2.1.1. EEG correlates

Before brain-recording techniques became available, sleep was mainly discussed in scientific and theoretical texts in terms of behavior. Generally, sleep was associated with rest and wakefulness with activity and these two states alternated. This theoretical construct was formalized by Kleitman as the Basic Rest Activity Cycle (BRAC) and continued as a fundamental construct even long after brain activity recording techniques developed. However, as soon as brain activity recording became possible, sleep was described in electroencephalographic terms by none other than Hans Berger (1930). He noted alpha rhythm disappearance when his test subject fell asleep. The operational definition for sleep-onset remains unchanged to this day: alpha EEG disappearance, generally recorded from an occipital derivation, defines the transition from wakefulness to sleep in a person whose eyes are closed and who is not engaged in challenging mental activity. Thus, the waking brain can be distinguished from the sleeping brain. This differential electroencephalographic (and presumably brain activity) correlate of sleep and wakefulness sets up the basic paradigm for studying human sleep and sleep disorders.

It was, however, noted early on that some individuals do not have clear alpha EEG activity. This makes determining sleep-onset more difficult. In such cases, other correlated electrophysiological activity must be used, including: EEG slowing, occurrence of a vertex sharp wave, cessation of blinking, presence of slow rolling eye movements, and/or diminution of submentalis electromyogram (EMG). Figure 1.1 shows examples of sleep-onset. Overall, regardless of the preceding activity, sleep-onset is marked by sustained low-voltage, mixed frequency EEG activity which is classified as Stage 1 sleep.

1.2.1.2. Neurophysiologic regulation

Hypothalamically generated motivation directs behavioral systems to perform actions designed to reduce drive. In this manner, homeostatic regulation of sleepiness parallels that for thirst, hunger and sex. Thus, sleepiness increases as a function of the duration of prior wakefulness (sometimes called process S) (Borbely, 1994). In general, the longer an individual remains awake, the sleepier he or she becomes. Prolonged wakefulness eventually makes sleep irresistible. The specific site underlying sleep's homeostatic process has not been identified; however, many models have been proposed. Kleitman, the dean of American sleep research, proposed that there was a build-up of neurotoxins during wakefulness that were removed by sleep. The complementary model was that neurotransmitters are used up during wakefulness and must be replenished by sleep, an idea harkening back to Shakespeare's notion of sleep 'knitting up the raveled sleeves

of care'. Of course, the battery is a popular metaphor with sleep playing the role of a recharging process.

Modern scientific investigation of specific models began with Bremer (1935) demonstrating sleep in response to lesioning cortical inputs. This 'deafferentation' model stood for 15 years until the Reticular Activation System (RAS) was described. The RAS's key maintenance of wakefulness role was demonstrated (Moruzzi and Magoun, 1949). These researchers also showed that RAS could promote wakefulness even without cortical inputs, thereby refuting the 'deafferentation' model. Subsequent work mapped out collateral sensory pathways providing RAS input and two main pathways through which the RAS activation is transmitted to forebrain and cortex. The first pathway is the nonspecific thalmocortical projection system, the second is the subthalamus, hypothalamus and basal forebrain route. The first pathway begins dorsally in medulla and connects locus coeruleus (LC) (noradrenergically mediated) to substantia nigra and then (dopaminergically mediated) to the ventral tegmental area and then (serotinergically mediated) to dorsal and median raphe. Projections continue to the laterodorsal tegmentum (LDT) and pedunculopontine tegmentum (PPT) via cholinergic neurons. This pathway continues to nonspecific thalamic nuclei and diffusely to cortex. The second pathway begins ventrally in medulla, connecting to midbrain, subthalamus and hypothalamus and then continues on to basal forebrain, preoptic area and finally cerebral cortex.

Von Economo (1931) observed patients with 'encephalitis lethargica' and severe insomnia had extensive anterior hypothalamic lesions. Subsequent electrical stimulation and ablation studies identified anterior hypothalamus and the hypothalamic preoptic area as sleep-promoting and autonomic (parasympathetic) areas. The GABAergic VLPO connects with the histaminergic TMN (Sherin et al., 1998). Activity in the TMN also inhibits VLPO neuronal firing.

Most people pulling 'all nighters' (i.e., staying awake all night) describe a surge of energy at daybreak. This common experience violates the homeostatic principle that sleepiness increases as a function of prior wakefulness duration. Specifically, when staying awake all night, at 8:00 a.m. a person has been awake longer than they were at 4:30 a.m.; nonetheless, they feel less sleepy. This reveals another factor governing sleep and wakefulness: the circadian rhythm (sometimes called process C) (Borbely and Acherman, 1992). The circadian rhythm is an approximate daylong rhythm (from the root 'circa' + 'dias' [approximately a day]). The circadian pacemaker controlling the sleep–wake cycle is located in the suprachiasmatic nucleus (SCN). Because the core body temperature cycle is usually entrained to this sleep–wake oscillator, temperature is often used as a surrogate marker for circadian phase. Usually maximum alertness occurs at temperature peak with ensuing drowsiness as temperature begins falling. When temperature reaches its nadir, sleepiness can be overwhelming. Alertness improves as temperature starts rising. The cycle begins anew upon temperature reaching its peak (Ashcroft, 1965; Moore-Ede et al., 1982).

1.2.1.3. Neurobehavioral and neurocognitive correlates

Wakefulness is normally marked by responsiveness to the environment, consciousness, and the full array of cognitive abilities. Posture can be recumbent, seated, or erect and mobility is normal. Eyes can be open or closed. Perceived sensorium is a representation of the external reality. During sleep an individual has reduced or absent responsiveness to environmental stimuli. However, if a stimulus is of sufficient magnitude or if it is meaningful to the sleeper, it will likely provoke arousal and subsequent return to wakefulness. However, during sleep there may also be some responsiveness even below the arousal threshold. Consciousness and self-awareness are generally suspended during sleep; however, anxiety level can alter sleep-state perception. Posture during normal sleep is recumbent and eyes are closed. Perceived sensoriums vary greatly depending on what stage of sleep is occurring.

Sleep deprivation studies attempt to explore sleep's function by examining deficits produced by its loss. Not surprisingly, sleep loss increases sleepiness. Sleep loss also seems to diminish coping. Sleep-deprived individuals are notoriously irritable and easily frustrated. Sleep deprivation also adversely affects attention and leads to performance lapses (Dinges, 1992). Very prolonged sleep deprivation can, on rare occasion, produce seizures and may be associated with hallucinations, paranoia and mood swings. Because sleep deprivation is stressful, catecholamine turnover increases and cortisol level rises (Horne, 1988).

1.2.1.4. Neuropharmacology

The regulation of sleep and wakefulness can be viewed as a dynamic balance between alertness-promoting and sleep-promoting neurochemical systems. Two well-established hypothalamically based path-

ways underlying wakefulness promotion involve histaminergic and orexinergic (hypocretin) neurones. Tubulomammillary nucleus histaminergic neurons and lateral hypothalamus perifornical area orexinergic neurons have ascending projections to cortex, basal forebrain and midline thalamus (Vanni-Mercier et al., 1984; Lin et al., 1999; Xi et al., 2001). Descending pathways, especially from orexin neurons, connect to noradrenergic LC, serotinergic raphe and cholinergic LDT and PPT areas (Peyron et al., 1998).

The critical RAS ascending pathways to thalamus, hypothalamus and basal forebrain involve cholinergic, noradrenergic, dopaminergic, and histaminergic neurons. The LDT and PPT cholinergic cells fire at their highest rate during wakefulness. Dopaminergic neurons, especially in the forebrain bundle, appear to increase alertness. Overall, dopamine agonists (especially reuptake inhibitors) are somnolytic. By contrast, GABAergic cell complexes promote sedation and sleep. By contrast, GABA-A receptor agonists are generally somnogenic.

1.2.1.5. Imaging

Overall, imaging studies verify decreased cerebral blood flow, diminished brain oxygen consumption, and lower glucose metabolism associated with sleep onset compared to wakefulness. Brain metabolism on average declines 20–35% during nonrapid-eye-movement sleep. Sleep-related brain reduction in oxygen consumption far exceeds that in the rest of the body (by a factor of 5 : 1).

1.2.2. Sleep stage differences

1.2.2.1. EEG correlates

The human sleep pattern based on all-night, continuous electrophysiological recordings was first described in 1937 by Loomis, Harvey and Hobart (1937). The technological feat of recording all-night sleep EEG was accomplished using a specially designed 8-foot-long drum polygraph. To summarize miles of paper tracings these researchers created a data-reduction scheme called sleep staging. The sleep stage classification system (stages A, B, C, D and E) was largely based on predominant EEG activity within a fixed time domain, or epoch. EEG activity includes beta activity (>13 Hz), sleep spindles (12–15 Hz bursts), alpha rhythm (8–13 Hz, sometimes slower), theta rhythm (4–7 Hz, more common in adolescents than adults), saw-tooth theta waves (4–7 Hz, with notched appearance), delta rhythm (<4 Hz), and slow waves (<2 Hz). As polygraph technology improved and scoring systems evolved, many variations of the 'Loomis system' were developed. The current Standardized System was developed by an ad hoc committee that included a veritable pantheon of prominent sleep researchers under the chairmanships of Drs Allan Rechtschaffen and Anthony Kales (1968). For the most part, the rules for scoring already existed as the Dement–Kleitman system and the Williams–Karacan system. Modifications simplified recording and improved scoring reliability. In the end, however, the critical ingredient was consensus.

In the Standardized System, EEG activity is recorded from central (C3 or C4) derivations, EOG activity from right and left eye (recorded from the outer canthi), and EMG from submentalis. In standard practice, each 30 seconds of recording is considered as 1 epoch. Often, occipital (O3 or O4) is added to the recording montage. The Standardized System defines stage 1 sleep as an epoch containing low-voltage mixed-frequency EEG with no K complexes, spindles or rapid eye movements. It is a non-alpha, state with EEG activity that is deltaless and spindleless; however, vertex sharp waves may be present. Stage 2 sleep is characterized by sleep spindles or K-complexes but high-amplitude (75 micro-volts, or greater) delta EEG activity may be present but for less than 20% of the epoch. Stage 3 is scored when 20–50% of an epoch has high-amplitude delta EEG (or slow-wave activity). Stage 4 is defined by predominant delta EEG (or slow-wave) activity, occupying 50%, or more, of an epoch (see Figure 1.3).

Eugene Aserinsky (1953), while working in Nathaniel Kleitman's laboratory in the early 1950s, noticed EOG activity suggesting rapid, jerky eye movements occurring during stage 1 when it naturally recurred after 90–100 minutes of sleep. Initially, this EOG finding was dismissed as recording artifact; however, continued efforts verified that actual eye movements were occurring. These jerky eye movements (JEMs, as Aserinsky called them) eventually became known as REMs (rapid eye movements) and lent its name to a unique sleep state. REM sleep is scored when rapid eye movements and muscle atonia accompanying a stage 1 EEG pattern. In addition to REMs, other electrophysiological correlates associated with REM sleep include saw-tooth theta EEG, middle ear muscle activity (MEMA), periorbital integrated potentials (PIPs) and sleep-related erections (SREs). Some REM sleep epochs have intense eye movement activity; at other times, few or no eye

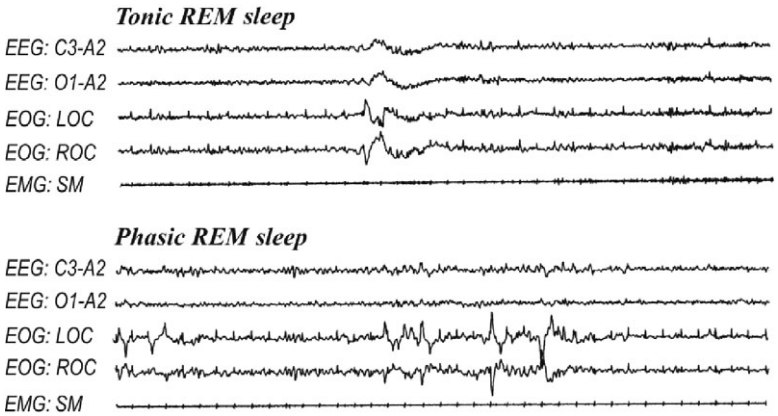

Fig. 1.2. Rapid eye movement (REM) sleep. An example of one 30-second epoch for tonic REM sleep and for phasic REM sleep. Electroencephalogram (EEG) is shown from central monopolar mastoid-referenced (C3–A2) and occipital monopolar mastoid referenced (O1–A2) derivations. Electrooculogram (EOG) is shown from left outer canthus (LOC) and right outer canthus (ROC) derivations. Electromyogram (EMG) from submentalis is also shown (SM).

movements occur. These two faces of REM sleep are called phasic REM sleep and tonic REM sleep (see Figure 1.2).

Sleep stage scoring involves dividing the recording into epochs and classifying each as wake or sleep stage 1, 2, 3, 4 or REM. Epoch length is a convention left over from procedures developed for paper polysomnographic tracings. These tracings were usually recorded at a chart speed of 10 mm s; therefore, each resulting polygraph page was 30 s in duration. Because each polygraph page is numbered, it was a matter of convenience to summarize sleep state for each 30-s page. Notwithstanding the ability of computerized polysomnographic systems to easily resize pages and alter temporal resolution, the 30-s epoch remains.

Stages 1, 2, 3 and 4 are sometimes collectively referred to as NREM or non-REM sleep. Stages 1 and 2 are sometimes referred to as light sleep (LS) while stages 3 and 4 are often combined and called slow-wave sleep (SWS) or deep sleep (see Figure 1.3). Table 1.1 summarizes EEG–EOG–EMG characteristics for wakefulness and the different sleep stages.

A healthy young adult sleeper will have a 90–95% sleep efficiency; that is, 5–10% or less of the total time in bed will be spent awake. Sleep onset should occur swiftly (less than 15 minutes) and nocturnal awakenings should be few and brief. Stage 2 sleep usually accounts for approximately half the night's sleep and REM sleep will account for another 20–25%. A nightly total of 1–5% of stage 1 sleep will be distributed at the wakefulness–sleep transition and at light sleep transitions. The remaining sleep will be distributed between slow-wave sleep stages 3 and 4. Only minor differences are found for sleep stage distributions between young adult men and women. Figure 1.4 shows the nightly percentages for each stage.

The normal pattern involves repeated 90–120-minute-long cycles of NREM and REM sleep. With each cycle reoccurrence, systematic alterations in cycle properties occur. The progression and continuity of sleep through the sleep cycles on a given night is called sleep architecture. Figure 1.5 shows a typical night with normal sleep architecture in a healthy young adult. In general, (1) adult sleep begins with NREM sleep, (2) NREM and REM sleep alternate approximately every 90–120 minutes, (3) slow-wave sleep predominates in the first third of the night, (4) REM sleep predominates in the last third of the night, and (5) REM sleep occurs in 4–6 discrete episodes each night with episodes generally lengthening as sleep period progresses.

Sleep pattern changes as a function of aging. Total sleep time gradually declines over the lifespan. REM sleep percentage (of total sleep time) decreases from more than 50% at birth to 20–25% at adolescence. REM sleep then stabilizes; additional decline may occur after age 65 years. By contrast, slow-wave sleep begins declining post-adolescence and continues declining as a function of age, disappearing completely in some elderly individuals. Greater wakefulness intermixed with sleep (fragmentation) increases with age and the elderly spend more time in bed but less time sleeping than younger subjects. Some of the sleep disturbances associated with aging are pro-

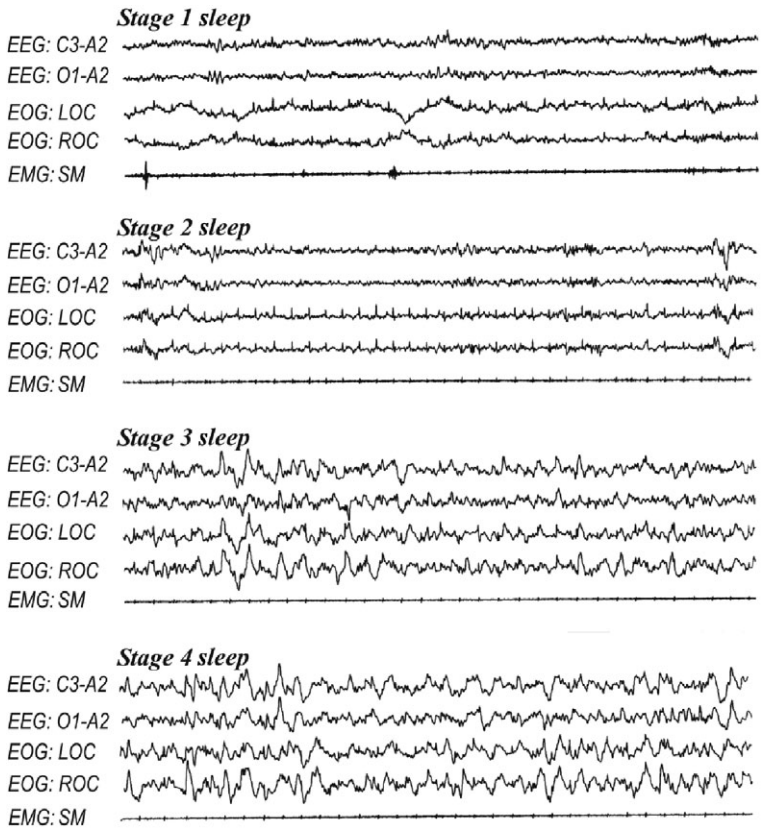

Fig. 1.3. NREM sleep. An example of one 30-second epoch for each NREM sleep stage (stage 1, stage 2, stage 3 and stage 4). Electroencephalogram (EEG) is shown from central monopolar mastoid-referenced (C3–A2) and occipital monopolar mastoid referenced (O1–A2) derivations. Electrooculogram (EOG) is shown from left outer canthus (LOC) and right outer canthus (ROC) derivations. Electromyogram (EMG) from submentalis is also shown (SM).

Table 1.1

EEG-EOG-EMG characteristics of sleep and wakefulness.

State or stage	Beta EEG	Alpha EEG	Spindle Activity	Delta EEG	Other EEG features	EOG	EMG muscle activity
Wakefulness	+	>50% of epoch	–	–		Slow and rapid	High
Stage 1 sleep	–	–	–	–	Vertex sharp waves	Slow	Decreased from W
Stage 2 sleep	–	–	+	<20% of epoch	K complexes	None	Decreased from W
Stage 3 sleep	–	–	+	20–50% of epoch		None	Decreased from W
Stage 4 sleep	–	–	+	>50% of epoch		None	Decreased from W
REM	+	+ bursts	–	–	saw-tooth theta waves	Rapid	Nearly absent

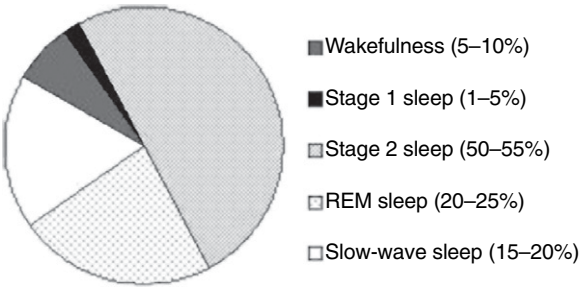

Fig. 1.4. Sleep stage percentages in a healthy young adult.

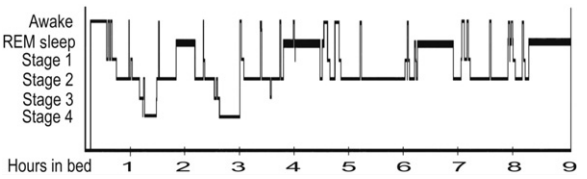

Fig. 1.5. Sleep stage histogram for a healthy young adult.

duced by increasing sleep-related pathophysiology (for example, arousals from sleep apnea). However, some proportion of age-associated sleep deterioration may directly relate to neurophysiological processes and not to secondary factors compromising sleep.

1.2.2.2. Neurophysiologic regulation

Sleep spindles, delta waves and slow cortical waves are the three waveforms characteristic of NREM sleep. Sleep spindles appear to be generated by GABAergic reticulothalamic neurons that create inhibitory postsynaptic potentials on thalamocortical neurons. By contrast, delta waves are cortically generated with input from thalamus. During NREM sleep RAS activation diminishes in response to thalamocortical hyperpolarization. Thus, NREM is marked by functional deafferentation produced by thalamocortical inhibition. Slow waves arise from cortical cells after prolonged depolarization and hyperpolarization and are prominent in frontoparietal regions (McCarley, 1994).

Jouvet and colleagues' transection studies demarcated REM-generating neurons as located in the pons. Through a series of brain-slicing studies it was concluded that the pons is sufficient and necesary to generate all signs of REM sleep (Jouvet et al., 1959; Siegel, 2000). Subsequent work discovered REM-on neurons in LDT and PPT (Mitani et al., 1988). LDT and PPT project to areas involved in PGO (pontine–lateral geniculate–occipital cortex) spike generation (related to eye movment activity during REM sleep) (McCarley and Ito, 1983) and to thalamic, basal forebrain and cortical areas thought to produce REM-related EEG desynchronization.

1.2.2.3. Neurobehavioral and neurocognitive correlates

Slow-wave sleep is marked by very low responsiveness to the environment and very little consciousness. In all stages of sleep, posture is recumbent and eyes are closed. NREM sleep sensorium is fairly impoverished, except at the sleep–wake transition when elaborate hypnagogic or hypnapompic images may be present. At other times, simple images or shapes may appear.

During REM sleep, dreaming occurs. When referring to dreams here we mean visualized or narrated stories with characters, actions and plot. When REM sleep was first discovered, awakenings from REM sleep revealed dreaming on 20 of the 27 trials (Aserinsky and Kleitman, 1953). And thus, the EEG correlates of dreaming were established, arming researchers with a laboratory tool to unlock the mysteries Freud had called the 'the royal road to the unconscious', or so it was thought.

After many hundreds of studies attempted to exploit the REM-dreaming paradigm; no unified 'dream theory' emerged. Some Freudian concepts were verified (e.g., daytime residue) while others were not. The major competing modern theories are (1) the neurophysiologically based activation-synthesis hypothesis and (2) cognitive dream theory. The activation-synthesis hypothesis considers dreaming epiphenomenologic, created by a cortex trying its best to interpret incoming random subcortical activity. By contrast, the cognitive theories consider dreaming an extension of daytime thought albeit governed by different grammar and looser rules (Hobson and McCarley, 1977; Foulkes, 1982).

Jouvet introduced the concept that REM sleep was an important third state of nervous system organization and not just another component of the basic rest activity cycle (BRAC). During wakefulness the nervous system supports an active brain in an active body. Under normal circumstances, an individual is conscious of the surroundings and responsive to the environment. During sleep, for the most part, we lose our environmental responsiveness and become unconscious. Therefore, sleep was traditionally regarded as a deactivated (or inactive) brain in an inactive body. With the discovery of REM sleep muscle atonia (presumably accompanying dreaming), another organiza-

tional state could be postulated: an active brain in an inactive body.

1.2.2.4. Neuropharmacology

LDT/PPT neurons are cholinergic and act as REM-on cells. Serotinergic dorsal raphe nuclei and noradrenergic locus ceruleus (LC) neurons act as REM-off controllers. REM sleep atonia is mediated by the release of glycine which inhibits alpha motor neurons. PRF 'REM-on' neurones slowly activate 'REM-off' cells of the dorsal raphe (serotonergic), LC (aminergic) that then inhibit REM-on cells, thus producing the cyclical REM sleep pattern (McCarley, 1994). Orexin knockout mice and dogs manifest narcolepsy. Orexin neurons project to VLPO which may coordinated REM–NREM transitions.

At a cerebrocortical level, aminergic activity is high during wakefulness, decreases during NREM sleep, and reaches a very low level during REM sleep. In contrast to this stepwise reduction in activity from wakefulness to NREM to REM sleep, cholinergic activity is high during wakefulness and during REM sleep. It reaches its low point during NREM sleep.

1.2.2.5. Imaging

In general, cerebral blood flow, whole brain absolute CGMR, and oxygen consumption are lower during NREM sleep compared to wakefulness or REM sleep. Imaging also shows a correlation between increasing EEG slow-wave activity and brain metabolic rate. The largest decreases in brain activity during NREM sleep occur in frontal cortex, thalamus, brainstem reticular formation and cingulate gyrus.

Although whole brain metabolism for wakefulness and REM sleep are similar, localized patterns differ. Interestingly, REM sleep is associated with greater activity (compared to wakefulness) in limbic structures (especially cingulate and amygdala) and less activity in prefrontal cortex. Finally, cerebral glucose metabolism in oculomotor systems correlates with REM activity.

1.3. Autonomic Nervous System (ANS)

1.3.1. Sleep vs wakefulness

The solitary tract nucleus (NTS) arising from dorsolateral medullary reticular formation and projecting to limbic forebrain structures is thought to modulate ANS activity during sleep. In general, sleep requires decreased sympathetic activation and increased parasympathetic balance. Consequently, anything that increases sympathetic outflow can disturb sleep. The net effect is the same regardless of whether the sympathetic activation originates endogenously or exogenously (Hirshkowitz et al., 1997). That is, sleeplessness can result from drinking coffee at bedtime (exogenous) or anxious rumination (endogenous). This feature of autonomic regulation has survival value. When emergencies occur in the middle of the night, there needs to be a mechanism to promote quick response and sustained alerting. The survival value may be why autonomic activations commence rapidly but dissipates slowly. Unfortunately this mechanism may go awry and contribute to insomnia. If an individual gets 'worked up' about something right before bedtime, they may toss and turn for hours. 'Winding down' rituals can promote progressive relaxation with gradual reorientation away from daytime stressors. In children that sleep well, elaborate pre-sleep rituals are common. The ritual may include a bedtime story, a light snack, teeth brushing, prayers and having a favorite stuffed animal toy, pillow and blanket. The toy animal, pillow and blanket also provide stimulus cues for sleep-onset and likely facilitate conditioning. As an autonomic process, sleep-onset is amenable to classical conditioning. Pavlov was able to condition a dog to salivate by repeatedly pairing a ringing bell with food presentation (canines automatically salivate when food is present). Conditioning sleep-onset to the bed, pillow, blanket (or stuffed animal toy for children) occurs. However, in some cases a bedroom stimulus will cue an alerting response (producing psychophysiological insomnia). Similarly, if a parent becomes the child's stimulus cue for sleep-onset, the parent may have to rock the baby back to sleep at any and all times of the night.

1.3.2. Sleep stage differences

If we consider sympathetic and parasympathetic activity balance during the wake state, sleep-onset is marked by increasing parasympathetic tone. The overall autonomic tone increases parasympathetically as NREM sleep progresses. This process continues through tonic-REM sleep. By contrast, during phasic REM sleep, intermittent bursts of sympathetic activation occur, producing swings in blood pressure, irregular breathing, and overall cardiovascular instability. The progressive increase in parasympathetic activation can be observed using surrogate measures, such as pupillary constriction. During phasic REM sleep,

the transient sympathetic bursts are associated with pupillary dilation. Interestingly, direct measurement of sympathetic motor neurons reveal REM-related increased sympathetic activation. By contrast, skin sympathetic activation using electrodermal activity reveals activation during slow-wave sleep with a complete cessation during REM.

1.4. Endocrine

Endocrine function has been extensively studied during wakefulness and sleep. Endocrine function is affected both by the circadian and homeostatic mechanisms (Van Cauter, 2000). The following section summarizes endocrine changes during sleep.

1.4.1. Corticotrophin axis

ACTH and cortisol regulation is under circadian control. Cortisol's highest levels occur in early morning hours. During the day, cortisol levels remain low with the minimum level occurring in late evening and during the early part of sleep. This overall corticotropic axis activity pattern is not affected by the presence or absence of sleep; however, the sleep–wake homeostatic mechanism can change the amplitude of the activity by 15% (Van Cauter, 2000). Initiation of sleep can elongate the nadir period while awakening at the end of sleep period may increase the amplitude of the peak cortisol level (Weitzman et al., 1983). Therefore, a reverse effect is expected and seen during sleep deprivation. That is, sleep deprivation delays the return of corticotropic activity to its nadir and results in higher than baseline corticotropic activity the following night. Furthermore, sleep fragmentation and awakenings interrupting sleep are associated with corticotropic activity.

1.4.2. Growth hormone (GH)

GH secretion is stimulated by GH-releasing hormone (GHRH) and suppressed by somatostatin. Therefore, the balance between these two hormones determines the GH release. The GH secretion pattern is characterized by a low baseline level with abrupt pulses. GH regulation is primarily sleep-dependent. Sleep onset is associated with a GH secretion pulse regardless of its time of occurrence (Van Cauter and Plat, 1996). GH level and amount of slow-wave sleep correlate strongly. GH release, like slow-wave sleep, diminishes with advancing age (Mullington et al., 1996; Van Cauter and Plat, 1996; Van Cauter, 2000). Furthermore, because GH is strongly sleep-dependent, awakenings and sleep fragmentation inhibit GH secretion. Nonetheless, circadian oscillation can affect GH secretion. GH secretion is higher during the early evening, even before sleep onset. This elevation reflects GHRH and somatostatin balance (Jaffe et al., 1995).

1.4.3. Thyroid function

Thyroid hormone secretion is controlled by thyrotropin (TSH). TSH secretion is under both circadian and sleep–wake homeostatic control (Brabant et al., 1990). TSH level is low during the day and it gradually rises in the evening and at the beginning of sleep (Chokroverty, 1999; Van Cauter, 2000). Afterwards it declines, returning to its low daytime level. In response to sleep deprivation, night-time TSH rises above the normal level suggesting that sleep suppresses TSH level; however, this effect is not sleep stage dependent (Chokroverty, 1999).

1.4.4. Prolactin secretion

Prolactin is regulated through a dopaminergic system, has sleep-dependent secretion, reaches its highest level during the sleep, and is lowest during the wake hours. Prolactin level begins rising after sleep onset and peaks in the early morning hours (5:00–7:00 a.m.). Prolactin secretion is temporally related to delta wave sleep. Morning awakening and sleep interruption during the night is accompanied by prolactin inhibition. Circadian oscillation also affects prolactin levels, albeit to a much lesser degree than sleep (Partsch et al., 1995). Circadian oscillation presents as the progressive prolactin level increases during the late afternoon and before sleep onset and is more pronounced in females than males (Desir et al., 1982; Waldstreicher et al., 1996). Maximal prolactin secretion occurs when the sleep and circadian effects are superimposed.

1.4.5. Glucose regulation

Sleep in humans represents a relatively long period of fasting, however, blood glucose level is usually maintained (Van Cauter, 2000). Studies of glucose regulation during sleep show a marked decrease in glucose tolerance during nocturnal sleep. With initiation of sleep, this tolerance decreases and reaches minimum level around the middle of the sleep period. After reaching minimum, glucose tolerance gradually increases

towards the awake level (Simon et al., 1987; Van Cauter et al., 1989). Decreased brain and peripheral glucose uptake is the main reason for the altered glucose tolerance (Boyle et al., 1994). Restoration of glucose tolerance in the second half of the sleep period is due to increased REM sleep (therefore increased glucose uptake by brain) and increased insulin sensitivity (resulting from low cortisol level) (Van Cauter, 2000).

1.4.6. Other hormones

A clear relationship between sex hormones and the sleep–wake cycle has not been found, however, gonadotropin levels rise during sleep in prepuberty and puberty stages (Wu et al., 1996). Testosterone's pulsatile release appears to have peaks near the NREM–REM transition. Parathyroid secretion is linked with cycles of slow-wave sleep and with peak occurrence every 100 minutes (Kripke et al., 1978). Hormones involved in salt and water metabolism include aldesterone, vasopressin and the renin–angiotensin system. Aldesterone level rises before awakening but vasopressin secretion appears unrelated to the sleep–wake cycle. By contrast, plasma renin level increases with slow-wave sleep.

1.5. The Respiratory System During Sleep

1.5.1. Overview

The major functions of respiratory system are to provide the body with the required oxygen and remove carbon dioxide produced during metabolism. In addition, the respiratory system is involved in acid–base regulation. Because O_2 and CO_2 are critical for survival, levels of these two gases are closely regulated. This regulation operates through a negative feedback loop. For example, elevated CO_2 increases ventilation, while hypocapnia decreases ventilation. The loop consists of gas exchange units (lungs), a pump (respiratory muscles including diaphragm, upper airway muscles and intercostal muscles), a controller (central nervous system), and the sensory and afferent elements relaying information from the respiratory system and blood to the controller.

Sensory elements of the respiratory system are divided to chemoreceptors and non-chemoreceptor components. The chemoreceptor component consists of peripheral and central chemoreceptors. The peripheral chemoreceptors in human are located in the carotid body that responds to changes in O_2 and CO_2 level in the blood. An estimated 30% of CO_2 chemosensitivity is provided by the peripheral chemoreceptors (Honda and Tani, 1999). The carotid body response to change in arterial pressure of CO_2 ($PaCO_2$) is linear. With hypercapnia, the firing rate of the carotid body increases. In contrast, the peripheral chemoreceptor provides 90–95% of hypoxic chemosensitivity (Honda and Tani, 1999). The carotid body response to reduction of arterial pressure of O_2 (PaO_2) is not linear. Instead, it responds linearly to arterial blood oxygen saturation. Concomitant hypercapnia and hypoxia have an additive effect on carotid body response. Furthermore, acidosis can stimulate the carotid body and augment the effect of hypercapnia and/or hypoxia on the carotid chemosensor.

The carbon dioxide level is mainly regulated by central chemoreceptors. These are located in the superficial layers of the ventral medulla (Mitchell, 1969). Furthermore, other deeper areas responsible for CO_2 chemosensitivity have been considered. The central chemoreceptor areas are sensitive to changes in H^+ concentration in the cerebrospinal fluid (CSF) and the medullary interstitial tissue. Carbon dioxide is a lipid-soluble gas and can pass through the blood–brain barrier. In CSF CO_2 reacts with H_2O to produce H^+ and HCO_3^-. Carbonic anhydrase accelerates this reaction. Change in the CO_2 concentration in blood affects the CSF H^+ concentration and through that stimulates or suppresses the respiratory generator. Therefore, by increasing the H^+ concentration in CSF, hypercapnia increases the rate and depth of breathing. The opposite effect is produced by hypocapnia.

The rhythmogenicity of the central respiratory controller is not known and is out of the scope of this chapter (Remmer, 1999). However, extensive research localizes the respiratory controller in the medulla oblongata and pons (Berger et al., 1977a, 1977b, 1977c; Mitchell and Berger, 1977; Von Euler, 1986). The rhythmic respiratory activity is generated by the central pattern generator (CPG) in the medulla. The CPG is defined as a neural circuit that generates a periodic rhythm with defined spatiotemporal characteristics in the absence of phasic sensory input. The medullary respiratory area consists of (1) the dorsal respiratory group (ventrolateral nucleus of tractus solitarius (NTS)) (Berger et al., 1977b, 1977c), and (2) the ventral respiratory group. The NTS is mainly involved with inspiration and its activity increases during inspiration. The ventral respiratory group consists of a group of neurons with inspiratory or expiratory activity. For example, nucleus ambiguus

innervates the muscles of upper airway. The pontine respiratory group is not necessary for generating respiration; however, it is involved in processing of vagal afferent and upper brain inputs (e.g., hypothalamus and cerebral cortex) (Von Euler, 1986). These inputs are integrated in the pontine respiratory group and then relayed to medullary centers.

Finally, the efferent arm of the feedback loop consists of motor output to the upper airway (especially the pharyngeal area), diaphragm, intercostal and abdominal muscles through phrenic and intercostal nerves. In summary, the respiratory system under control of the CPG in the medulla oblongata sustains ventilation and maintains O_2 and CO_2 within a normal range in the blood and tissue environment. The central controller through chemoreceptor and non-chemoreceptor sensors monitors O_2, CO_2 and H^+ concentration in blood. Alterations in the level of these gases adjust ventilatory output. In situations with increased O_2, CO_2 or H^+ demand, the respiratory controller increases ventilation. This in turn will restore the normal level of these gases. This negative feedback loop is the basis for automatic control of respiratory activity. The automatic control of ventilation is maintained regardless of the sleep or awake state of the animal. However, the respiratory controller activity can be affected by behavioral and voluntary input from a higher area of the brain, like cortex during the awake state and possibly rapid eye movement (REM) of sleep.

Activity of the respiratory controller differs in wakefulness and different stages of sleep. It is also affected by different disease conditions like cardiovascular or respiratory disorders. In the following sections we will review changes in respiratory system function with sleep.

1.5.2. Wakefulness vs NREM and REM sleep

With transition from wakefulness to NREM and REM sleep, alveolar ventilation and therefore, CO_2 and O_2 concentrations change. Ventilation is under automatic control during sleep. With initiation of sleep minute ventilation falls about 0.5–1.5 liters per minute (Hudgel et al., 1984; Chokroverty, 1999). The minute ventilation change with sleep is due to reduced CO_2 production and O_2 uptake, absence of wakefulness stimulus, reduced chemosensitivity and increased upper airway resistance. A similar reduction in minute ventilation is reported in REM sleep. The reduction of minute ventilation results in a 2–8 mmHg elevation of partial pressure of carbon dioxide ($PaCO_2$) up to 10 mmHg reduction in partial pressure of oxygen (PaO2); and less than 2% reduction of oxygen saturation (Douglas et al., 1982; Chokroverty, 1999).

1.5.2.1. Upper airway

Upper airway patency depends on multiple factors, including anatomical characteristics, tonic and phasic upper airway muscle activity (Kuna and Remmers, 2000), and thoracic volume (Begle et al., 1990). Phasic upper airway muscle activity is regulated by the respiratory center. By contrast, tonic activity is independent of the respiratory center, depending instead on the general muscle tone (Krieger, 2000). With transition from wakefulness to NREM and from NREM to REM sleep, upper airway resistance increases. This increase is mainly in the palatal or hypopharyngeal areas (Lopes et al., 1983; Hudgel and Hendricks, 1988), is greater in snorers and obese subjects (Skatrud and Dempsey, 1985; Dempsey et al., 1996), is highest during REM sleep (Orem and Lydic, 1978), and is induced by diminished upper airway muscle phasic activity and loss of upper airway protective reflexes (Dempsey et al., 1996; Krieger, 2000). With transition into REM sleep, the tonic activity of the upper airway muscles diminishes further. Hence, upper airway occlusion is usually more prominent in REM sleep. In addition to reduced upper airway muscle activity, there is a breath-to-breath variation in the upper airway resistance during sleep. This variation is mainly due to change in sleep state and lung volume with sleep (Dempsey et al., 1997).

1.5.2.2. Lower airway

Lower airway resistance shows a circadian variation, especially in patients with asthma. In these patients, mild bronchoconstriction during sleep is reported (Kerr, 1973). Cough due to stimulation of airways is suppressed with sleep and only occurs with arousals (Douglas, 2000).

1.5.2.3. Respiratory pump

Input to respiratory muscles is controlled by the respiratory center in the brain stem through phrenic and intercostal nerves. The phasic activity of the respiratory pump is state dependent and therefore diminishes with initiation of sleep; however, phasic activity of the diaphragm is maintained. With progression of sleep into REM, the tonic component of the respiratory muscle pump decreases. The changes in muscle activity result in increased upper airway resistance and decreased minute ventilation.

1.5.2.4. Chemoreceptors
The hypoxic ventilatory response diminishes during sleep (Hedemark and Kronenberg, 1982). In NREM sleep, men show more reduction from wakefulness than women (White et al., 1982). This difference is mainly due to higher ventilatory drive during wakefulness in men. With progression to REM sleep, the hypoxic ventilatory drive further falls in both men and women (Douglas, 2000).

The hypercapnic ventilatory response diminishes about 50% with the transition from wakefulness to NREM sleep (Bulow, 1963; Douglas et al., 1982; Douglas, 2000). In REM sleep the ventilatory response falls even further; therefore, the lowest ventilatory response to hypercapnia occurs during REM sleep (Douglas et al., 1982).

Overall, with transition from wakefulness to NREM sleep, the wakefulness stimulus and voluntary control of ventilation are lost, leaving automatic control to prevail. In addition, CO_2 production and O_2 uptake diminish, upper airway resistance increases, chemoreceptor response to hypercapnia and hypoxia falls, and operating lung volume decreases. Subsequently, $PaCO_2$ rises and PaO_2 falls. Combination of these changes can produce respiratory instability and predispose to periodic breathing and obstruction of the upper airway during sleep. Loss of muscle tone with REM makes the upper airway more prone to obstruction.

1.6. The Cardiovascular System During Sleep

1.6.1. Overview

The cardiovascular system is closely regulated by the autonomic nervous system (ANS). The sympathetic nervous system (SNS) innervates atria, ventricles, sinoatrial and atrioventricular nodes and vasculature. SNS increases the heart rate, the ventricular contractility, and the peripheral vascular resistance, and reduces the atrioventricular conduction delay. The overall effect of the SNS is tachycardia, increased cardiac output, and increased systemic blood pressure. The parasympathetic (vagal) nervous system mostly innervates the atrium, and sinoatrial and atrioventricular nodes. Therefore, vagal stimulation reduces the heart rate, prolongs atrioventricular conduction, but does not have an appreciable effect on ventricular contractility or peripheral vascular resistance. The effect of the autonomic nervous system on cardiovascular function is the net balance of the two components of ANS (Schlant et al., 1998). Changes in the cardiovascular system during sleep therefore, are mostly subsequent to alterations in ANS activity.

1.6.2. Wakefulness vs NREM vs REM sleep

1.6.2.1. Cardiac changes
With transition from wakefulness to NREM sleep, the SNS activity diminishes and parasympathetic (vagal) nervous system predominates (Mancia, 1993; Somers et al., 1993; Cherniak, 1999). As sleep deepens the vagal dominance increases.

1.6.2.2. Rhythm changes
NREM sleep is characterized by heart rate reduction due to vagal predominance (Khatri and Freis, 1967). The lowest heart rate occurs during the deepest stages of NREM sleep (slow-wave sleep). In contrast to NREM, REM sleep is characterized by episodic increases in heart rate due to heightened SNS activity on a backdrop of vagal predominance (Verrier et al., 2000). Additionally, during tonic REM, episodes of heart rate deceleration due to episodic increased vagal activity are seen. Arrhythmias observed during normal sleep include sinus pauses longer than 2 seconds (in 4–10%), sinus bradycardia with heart rate less than 40 (in 24%), first-degree atrioventricular block (in 8–12%), and Wenckebach second-degree AV block (in 6–11%) (Brodsky et al., 1977).

1.6.2.3. Pump changes
Cardiac output decreases at sleep-onset in normal sleep and continues to drop as sleep deepens. This reduction is mainly due to slowing of heart rate rather than any appreciable change in stroke volume (Khatri and Freis, 1967). However, during REM sleep with episodic changes in SNS, cardiac output varies.

1.6.2.4. Vascular changes
The vascular bed, and therefore regional perfusion, is under autonomic and local control. Mean arterial pressure, the driving force moving the blood in the circulation, is determined by cardiac output and peripheral vascular resistance. Both cardiac output and peripheral vascular resistance are tightly controlled by the ANS. The peripheral vascular bed receives innervations from SNS. Various vascular beds respond differently to changes in SNS. Blood flow change in different organs is dependent on sleep state change while the cerebral blood flow changes are tied to its various functions during different sleep states (flow-metabolism coupling) (Franzini, 2000).