Chapter 24
Hypoxia: Introduction of Mechanisms and Consequences

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Oxygen (O_2) is an important chemical element that represents approximately 21 % of the Earth's atmosphere. Until the end of the 1800s, science has known little about the effects of O_2 depletion in the body. This prompted researchers of the late nineteenth century to investigate the physiological effects of high altitude. In 1878, French physiologist Paul Bert provided the first scientific evidence that the lack of O_2 (hypoxia) caused an incomplete saturation of the blood leading to "undue hyperpnea with exercise, nausea, headaches, and great depression". Since that time, research and clinical observations have demonstrated that hypoxia, whether acute or chronic, causes certain predictable physiologic responses. These occur irrespective of whether hypoxia is induced by a pathological disease or by the environment, such as by exposure to high altitude.

Research into hypoxic mechanisms gained momentum in the early 1900s. Between 1921 and 1922, Joseph Barcroft led an expedition into the Andes to systematically collect and analyze data describing acute and chronic responses occurring during travel to high altitudes. During this expedition, at different altitudes, his group monitored alterations in ventilation, values of arterial carbon dioxide ($PaCO_2$), and arterial oxygenation (PaO_2). From these data, Barcroft observed that, at 14,000 ft, increased respiratory rate raised alveolar O_2 pressures 12–15 mm higher than would otherwise be expected.

In addition to respiratory parameters, the hematological response to high altitude hypoxia was also observed. Specifically, Barcroft and the other investigators were

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Table 24.1 The relationship of gas values in arterial blood during acute vs. chronic hypoxia in humans

	Baseline	Acute hypoxia	Chronic hypoxia vompensated blood gas
pH	~7.4	>7.5	~7.5
PaO_2	>85 mmHg	<70 mmHg	~80 mmHg
$PaCO_2$	~40–45 mmHg	<35 mmHg	~32 mmHg
SaO_2	>93 %	<80 %	90 %
HCO_3^-	22–24 mEq/L	>22–24 mEq/L	16 mEq/L

PaO_2 partial oxygen pressure in arterial blood, *$PaCO_2$* partial carbon dioxide pressure in arterial blood, *SaO_2* arterial oxyhemoglobin saturation, *HCO_{3-}* arterial bicarbonate

subjected to blood analysis before departure from their homeland at sea level (baseline), then repeatedly during their exposure to progressively higher altitudes, and finally, during a gradual descent back to sea level. Of the analyses performed, the most intriguing was related to reticular cell counts. Barcroft reported that in contrast to high altitude natives, all members of the expedition exhibited an increase in reticular cells, blood cell precursors. The counts peaked in the first week of the subjects being at 14,000 ft and remained above normal during the entire stay. However, upon return to sea level, the number of reticular cells fell below baseline values. Barcroft showed that the number of these cells changes at different altitudes, and the cells were characterized as having a "blood breathing function" (Barcroft et al. 1923). Later, hemoglobin molecules were considered to be responsible for O_2 transportation.

In the decades following Barcroft's high altitude expedition through the Andes, much emphasis was placed on describing the respiratory and hematological responses of individuals and populations exposed to high altitude hypoxia. An early study demonstrated that acute exposure to high altitude hypoxia leads to hemoglobin O_2 desaturation, hyperventilation and decreased arterial carbon dioxide (CO_2) concentrations. Table 24.1 highlights general alterations in gas values of arterial blood induced by acute and chronic high altitude hypoxia.

In contrast with environmentally induced hypoxia, disease processes lead to a slightly different profile of arterial blood gas. The diagnosis and treatment of hypoxia are based on identifying the nature and frequency of gas exchange impairment (chronic vs. intermittent, induced either environmentally or pathologically). Some diseases lead to inadequate ventilation while others induce impairment of gas diffusion through the alveoli, resulting in reduced gas transport from the lungs to the tissues (Table 24.2). Insufficient oxygenation results in a reduction of O_2 concentration in the blood and a consequent deficiency of O_2 in the tissues. Thus, hypoxia is characterized by a reduction of O_2 concentration in arterial blood, a condition that greatly stresses all organs.

Table 24.2 Definitions for most commonly encountered types of hypoxia and clinical examples

Causes of hypoxia	Definitions	Clinical example
Hypoxemic hypoxia	Low concentrations of atmospheric O_2 (reduction in arterial pO_2)	High altitude travel
Anemic hypoxia	Low effective hemoglobin concentration	Blood loss, anemia
Shunt hypoxia	Reduction of ventilation-perfusion and gas diffusion in the alveoli	Arteriovenous malformation
		Hepatopulmonary syndrome
Cardiogenic hypoxia	Inadequate transport of O_2 by blood to the tissues due to a decrease in cardiac output	Congestive heart failure
Histotoxic hypoxia	Incapacity of the tissues to make use of O_2 (inhibition of cellular enzyme activity)	Arsenic
Hypermetabolic hypoxia	Increased ATP requirement or energy metabolism (hyperthermia)	High fever

pO_2 arterial pressure of oxygen, *ATP* Adenosine 5′-triphosphate

Hypoxia Induced by Sleep-Related Breathing Disorders in Humans

Obstructive Sleep Apnea

Sleep and breathing disorders are now seen as a major public health problem. Obstructive sleep apnea (OSA) affects 2–4 % of the adult population (i.e., apnea-hypopnea index >5 or more episodes per hour[1] and daytime sleepiness). Considering the apnea-hipopnea index 24 % of middle age males and 9 % of females have apneas during sleep. Additionally, a Brazilian community-based survey study used a probabilistic three-stage cluster sample of São Paulo has shown a high prevalence of sleep apnea.[2] OSA was observed in 32.8 % of the participants. This study is the first apnea survey of a large metropolitan area in South America, identifying a higher prevalence of OSA than previous epidemiological studies. This can be explained by the use of current techniques and clinical criteria, inclusion of older groups, and the higher prevalence of obesity in the studied population. As shown in Fig. 24.1, OSA is characterized by repetitive complete (apnea) or partial (hypopnea) obstruction of the upper airways resulting in pauses in breathing and subsequent O_2 desaturation. OSA is associated with adverse clinical consequences such as excessive daytime sleepiness, coronary artery disease, increased risk for stroke, diabetes, glucose intolerance, and academic and social under-achievements. The classic daytime manifestation of apnea is excessive sleepiness, but other symptoms such as cognitive

[1] In clinical practice, the severity of apnea is associated to the apnea-hypopnea index, defined by the number of such episodes per hour of sleep. The task force suggested apnea hypopnea index (AHI) cutpoints of 5, 15, and 30 events/hour to indicate mild, moderate, and severe levels of (Young et al. 2002).

[2] Tufik et al. (2010).

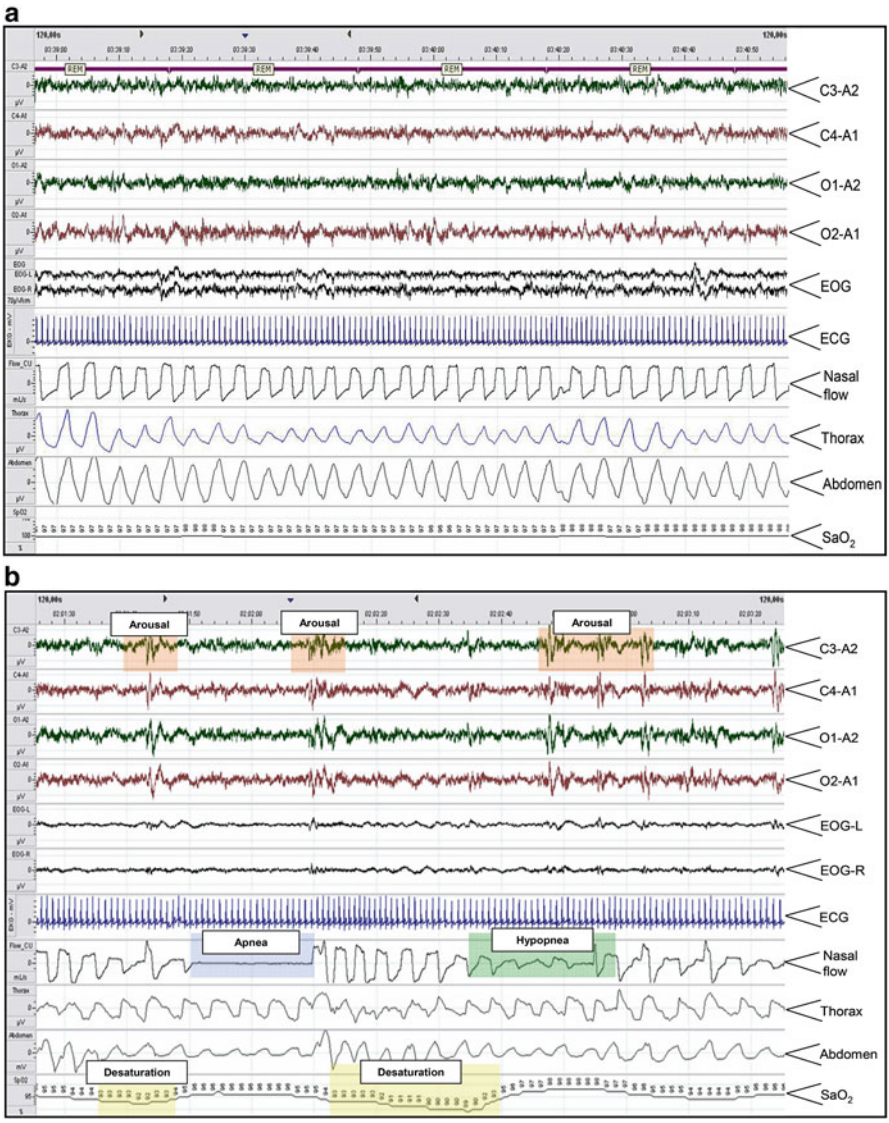

Fig. 24.1 Polysomnography in a normal subject (**a**) and an apneic patient (**b**) during 120 s. Episode of obstructive apnea and hypopnea occurring during REM sleep is demonstrated. Note the increasing ventilatory effort across the episode indicating its obstructive nature, arousal and desaturation. Definition of abbreviations: EEG (C3-A2; C4-A1; O1-A2; O2-A1): eletroencephalogram; *EOG* eletrooculogram, *ECG* eletrocardiogram, *SaO2* arterial oxyhemoglobin saturation. *Illustration*: Sleep Institute-AFIP

deficits and fatigue are commonly reported. Several neurobehavioral morbidities that greatly impact public health and the economy can be traced to obstructive sleep apnea. More direct effects of excessive daytime sleepiness are the accidents involving vehicles and labor. The situation is even more serious due to the high

prevalence of obstructive sleep apnea among adults, who accounted for 800,000 obstructive sleep apnea-related motor-vehicle collisions that incurred an estimated cost of 3.4 billion dollars and claimed 1,400 lives in the year 2000 alone.[3]

The diagnosis of OSA is based on the combination of characteristic clinical features in addition to compatible findings on instrumental tests in which multiple physiologic signals are monitored simultaneously during a night of sleep. A full night polysomnography, conducted by a technologist in a sleep laboratory, is the gold standard for the diagnosis of suspected OSA. The polysomnography apparatus allows the simultaneous recording of neurophysiological and cardiorespiratory variables reflecting the quantity and quality of sleep achieved (Fig. 24.1).

Chronic Obstructive Pulmonary Disease

In Chronic Obstructive Pulmonary Disease (COPD) destruction of lung tissue leads to reduced alveolar gas exchange. COPD is characterized by extreme reduction of exhaling flow. This results in the inability to move O_2 from the environment into the blood as well as a reduction in the flow of CO_2 from the blood back into the environment. Unlike sleep apnea, hypoxia induced by lung disease leads to consistently high blood levels of CO_2 and acidosis. Hypoventilation causes the most important gas-exchange alteration in COPD patients, leading to hypercapnia (Box 1) and hypoxemia, especially during rapid-eye-movement sleep (REM), when marked respiratory muscle atonia occurs. OSA and COPD lead to the blood gas values depicted in Table 24.3.

Table 24.3 Comparative arterial blood gas values during OSA vs. COPD

	Baseline	During OSA event	COPD
pH	~7.40	<7.29	~7.32
PaO_2	>85 mmHg	<60 mmHg	55 mmHg
$PaCO_2$	~40–45 mmHg	>45 mmHg	70 mmHg
SaO_2	>93 %	<80 %	85 %
HCO_3^-	22–24 mEq/L	22–26 mEq/L	30 mEq/L

PaO_2 partial oxygen pressure in arterial blood, *$PaCO_2$* partial carbon dioxide pressure in arterial blood, *SaO_2* arterial oxyhemoglobin saturation, *HCO_{3-}* arterial bicarbonate

Hypercapnia is an excess of CO_2 in the blood. Carbon dioxide is a gaseous product of the body's metabolism and is normally expelled through the lungs. Upon first examination, it would seem that any respiratory condition that causes hypoxia would also cause hypercapnia. But hypercapnia in general only occurs in association with hypoventilation or by circulatory insufficiency.

[3] Sassani et al. (2004).

Animal Models

The use of animal models in the study of human conditions requires validation of the behavioral manifestation and an association with the major characteristics observed in the human situation. Mammalian models (e.g., the dog, pig, baboon and lamb) have been used to determine the effects of hypoxia. These models, however, have ethical limitations and incur high costs over time. Among the animal models proposed to investigate the effects of hypoxia, rodents are of particular interest. Rats and mice make for more than adequate subjects as their response to hypoxia parallels that seen in humans.

Anoxia: O_2 supply to the cell is assumed to be practically zero.
Ischemic-hypoxia: blood hypoperfusion or loss of blood flow to tissue (decrease in cardiac output) and a consequent reduction of O_2 supply to the cells.
Hypoxia: reduction in arterial pO_2 and a consequent deficiency of O_2 in the tissues.
Hypoxemia: reduction of O_2 specifically in the blood.
Hyperoxia: condition opposite to hypoxia, in which there is an excess of O_2 in body tissues or a higher than normal partial pressure of O_2.

Models of Anoxia

Approximately 2.9–9.0 infants per each 1,000 delivered experience some degree of ischemic-anoxic or prolonged anoxic insult. Perinatal brain damage is usually brought about by intrauterine asphyxia following an acute reduction of the uterine or umbilical circulation. The areas most heavily affected are the cerebral cortex and the basal ganglia. The fetus reacts to a severe lack of O_2 with activation of the sympathetic-adrenergic nervous system and a redistribution of cardiac output in favor of the central organs (brain, heart and adrenals). If the asphyxic insult persists, the fetus is unable to maintain circulatory centralization, and the cardiac output and extent of cerebral perfusion plunge.

Unlike hypoxia, which is a reduction in O_2, anoxia is defined as a complete absence of O_2. To induce perinatal anoxia in rodents, on the day of parturition, the dams are anesthetized and hysterectomized, and the isolated intact uterus is immediately immersed in a 37 °C saline bath for some minutes to induce anoxia. Following anoxia, the uterus horns are rapidly opened and the pups removed and stimulated to breathe. A variation to this approach requires that cesarean delivered pups are immediately placed for 15–20 min into a sealed chamber infused with 100 % nitrogen. In this model, the rodents are first submitted to hypoxia and later to anoxia.

Models of Ischemic-Hypoxia

In humans, disturbance of brain perfusion and oxygenation is a leading cause of perinatal brain damage. Ischemic-hypoxia insult during early fetal or neonatal stages leads to the damaging of immature neurons, resulting in behavioral and psychological dysfunctions, such as motor or learning disabilities, cerebral palsy or epilepsy. Ischemic-hypoxia models assess hypoxia associated with a reduction in blood flow (hypoperfusion). An example of such a model is the clamping of the umbilical cord in which the blood and O_2 supply are blocked in the near-term rat fetuses. One of the most frequently employed protocols combines ischemia, induced via unilateral carotid ligation, with exposure to hypoxia (<11 % atmospheric O_2) for a duration of several minutes to hours. The ischemia-hypoxia protocol described by Levine[4] and modified by Rice[5] and colleagues determines that the insult should be induced on the 7th–8th postnatal day in the pups. The animals are anesthetized and submitted to a unilateral carotid clamping. After recovery, the rats are exposed to 8 % O_2 in a humidified chamber at 36 °C for 1 or 2 h. Brain damage, seen histologically, is generally confined to the cerebral hemisphere ipsilateral to the arterial occlusion, and consists of selective neuronal death or infarction, depending on the duration of the systemic hypoxia. Unilateral ischemia-anoxia induces severe neuropathology, such as gross atrophy of the sensorimotor cortex, hippocampus, striatum, and thalamus.

Models of Hypoxia

Hypoxia Perinatal in Rodents

As a major cause of fetal brain damage with long lasting behavioral implications, hypoxia and hypoxia-ischemia have been comprehensively studied since the 1950s. In the development of an animal model of prenatal hypoxia in humans, the selection of the age at which the injury takes place is critical, as the susceptibility of neurons and glia changes considerably in the fetus and newborn.

In one experimental protocol,[6] postnatal rat pups were randomly assigned to either a (1) intermittent hypoxia-inducing chamber; (2) a normoxic chamber—exposed to only compressed air, or; (3) non-handled pups were left undisturbed with the dam. Once inside their respective chambers, rat pups were exposed to either intermittent hypoxia or normoxia during the subsequent 2 h. Rat pups were then removed from the chambers and returned to the dam, for 45 min. Pups were then returned to their

[4] Levine (1960).

[5] Rice et al. (1981).

[6] Decker et al. (2003, 2005).

Fig. 24.2 Intermittent hypoxia insult (10 % O_2) induced on the 7th–11th postnatal day in the C57BL/6 J mice

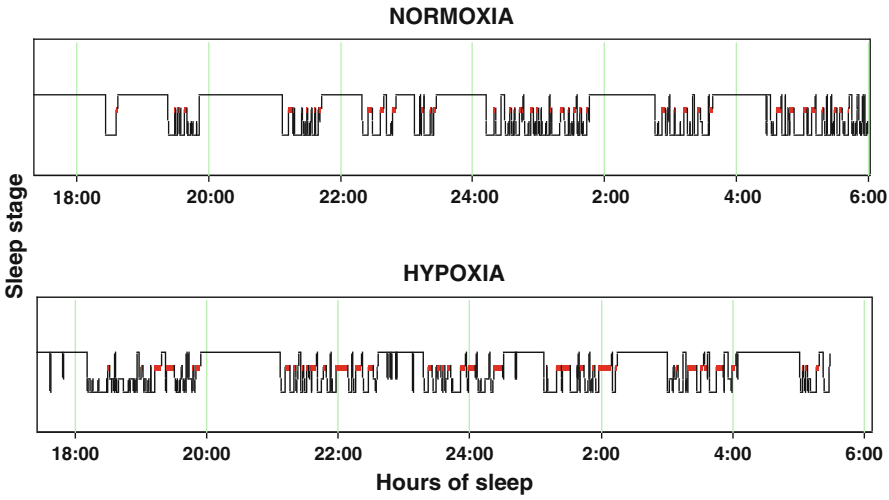

Fig. 24.3 The histograms show the sleep-wake architecture of post-hypoxia juvenile rats compared with normoxia. Neonatal hypoxia stimuli led to increased paradoxical sleep (*red*) and decreased wakefulness in juvenile rats measured during the dark phase of the circadian cycle periods (18:00–6:00)

respective chambers and again exposed to intermittent hypoxia or normoxia for an additional 2 h. Between postnatal 8 and 11 days, hypoxic pups were exposed to 2 h of intermittent hypoxic (or normoxic), followed by a 45 min feeding and grooming session, repeated three times each day (Fig. 24.2).

Behavioral consequences of neonatal intermittent hypoxia are impaired working memory, locomotor hyperactivity, and diminished levels of arousal. Post-hypoxic rats exhibited reductions in wakefulness and increased paradoxical sleep during the lights-off portion of the circadian cycle, as depicted in Fig. 24.3. Neurochemical consequences include reduced dopamine levels and hippocampal cell death.

Hypoxia in the Adult Rodent

Hypoxia is characterized by a reduction of O_2 concentration in arterial blood and a consequent deficiency of O_2 in the tissues. Sustained hypoxia protocols reproduce high altitude or chronic lung disease. The model that is commonly used to mimic sleep apnea is intermittent hypoxia. In this model, hypoxia insults lasting 10–90 s are alternated with similar periods of normoxia (Fig. 24.4).

Hypoxia is performed in a specially built chamber connected to a supply of O_2 and N_2 gas (Fig. 24.5). Inflow of O_2 and N_2 into the chamber is controlled by a computer program to produce sustained hypoxia (5–10 %) or intermittent hypoxia (cycles of room air to 5–10 % O_2).

Chronic sustained hypoxia increases wakefulness, reduces paradoxical sleep and induces slow wave sleep fragmentation. The sleep-wake architecture of rats under the influence of 15.5 % O_2 content was unchanged, compared with that of normoxic controls. One consequence of sustained hypoxia (10 % O_2) is reduced amplitude of the electrocardiogram and low percentages of slow wave and paradoxical sleep in rats. There is partial recovery of both slow wave and paradoxical sleep after 1–2 weeks of hypoxia, although none of the hypoxia values equal control values obtained before the exposure to low O_2. Studies using milder intermittent hypoxia insults have proven to be less disruptive to the sleep architecture. In contrast, the more severe intermittent hypoxia (5 % O_2) induced a subtle modification of slow wave sleep and severe and sustained paradoxical sleep deprivation during the light phase

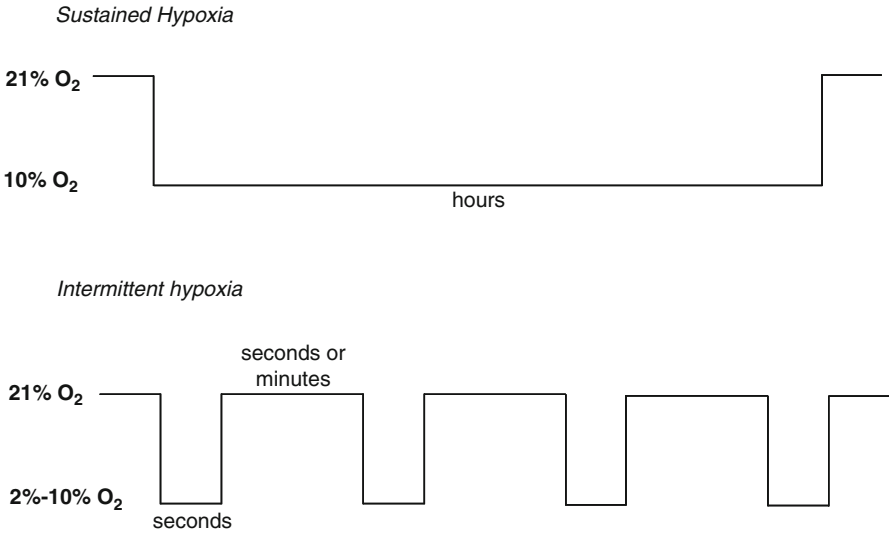

Fig. 24.4 Schematic design of sustained hypoxia and intermittent hypoxia protocols. In the sustained hypoxia episode the O_2 concentration was kept constant for a period of several hours, whereas the duration of each intermittent hypoxic episode lasted between 10 and 40 s, depending on the length of apneas, which are interspersed with normoxic periods that last several seconds or minutes

Fig. 24.5 Hypoxia chamber. Intermittent hypoxia is induced in a specially built chamber (30×20×20 in., Oxycycler model A44X0, Biospherix, Redfield, NY, USA) connected to a supply of O_2 and N_2 gas. Sensors measured O_2 concentration, CO_2 concentration (<0.01 %), humidity (40–50 %) and temperature (22–24 °C). Inflow of O_2 and N_2 into the chamber are controlled by a computer programmed to produce cycles of minutes room air to seconds 2–10 % O_2

and a substantial paradoxical sleep rebound during the dark phase in C57BL/6 J mice. The most sophisticated models have utilized either airway obstruction or the delivery of hypoxic gases with the onset of sleep and subsequent removal of the stimulus when arousal or wakefulness occurs. With hypoxia stimuli, wakefulness episodes were longer and more frequent, and paradoxical sleep was decreased and slow wave sleep episodes were shorter and more frequent. An important outcome in the comparison of sleep-wake patterns in sustained hypoxia vs. intermittent hypoxia stimuli during sleep is that the effects of both conditions on sleep were qualitatively similar. However, the effects of sustained hypoxia were of larger magnitude in slow wave sleep.

It has been proposed that hypoxia and sleep fragmentation are implicated in cardiovascular risk associated to OSA. Animal models have revealed that intermittent hypoxia is the critical stimulus underlying development of increased sympathetic activity and hypertension. These alterations can be related to several different components including augmented sympathetic nerve activity, altered function of arterial chemoreceptors, and elevated norepinephrine and dopamine concentrations.

The brain is particularly vulnerable to the effects of hypoxia, which produces extensive neuronal damage in selected regions. Intermittent hypoxia may cause an

extensive lesion to susceptible brain neurons that does not always result in neuronal death, but rather is followed by a marked impairment of brain functioning, e.g., various behaviors, stress response, learning and memory. When intermittent hypoxia occurs during a critical period of brain development, it disrupts the functional integrity of the dopaminergic system and induces substantial cognitive and behavioral alterations. In adult rats, exposure to intermittent hypoxia has been associated with alterations of monoamine concentrations in the brain. Hypoxia can reduce cerebral perfusion and damage specific subsets of neurons in the cortex, basal ganglia and hipoccampus. This occurs through neurophysiological alterations in the function of ion channels, O_2 sensors, signaling pathways, neuromodulators, induction of apoptosis, or oxidative stress. In general, most neurons respond to hypoxia by decreasing their metabolic demand. Because the brain has limited O_2 reserves and a limited ability to utilize anaerobic processes, most neurons reduce their metabolic requirements by decreasing their activity.

The Canine Model

Basic research on sleep apnea using experimental animals may help to further the understanding and prevention of OSA. To establish a natural model of sleep-disordered breathing, Hendricks and colleagues[7] investigated respiration during wakefulness and sleep in the English bulldog. This breed is characterized by an abnormal upper airway anatomy, with enlargement of the soft palate and narrowing of the oropharynx. During sleep, the animals had disordered respiration and episodes of O_2 desaturation (<90 % for prolonged durations). In REM sleep, the bulldogs had episodes of both central and obstructive apnea, the latter being associated with REM movements of the rib cage and abdomen. During wakefulness, the bulldogs were hypersomnolent as evidenced by shortened sleep latency.

Yet another canine OSA model was described by Kimoff and colleagues.[8] Healthy adult dogs were prepared with a tracheostomy and with implanted electroencephalographic and nuchal electromyographic recording electrodes. A silent occlusion valve was attached to the outer end of the endotracheal tube. The electroencephalogram and electromyogram were monitored continuously by a computer that determined the leep-wake state. At a predetermined time after each sleep onset, a signal was transmitted from the computer to the valve controller, resulting in airway occlusion. When the dog aroused from sleep, the occlusion was released. The telemetry unit, measurements of ventilatory and arousal responses were obtained during daytime sleep. This canine model has been shown to reproduce the characteristic apnoea and hypersomnolence of human OSA. The advantage of this model is that sleep during long-term OSA can be compared with both normal sleep before OSA and recovery sleep after OSA.

[7] Hendricks et al. (1987).

[8] Kimoff et al. (1994).

Potential Pitfalls

Isocapnic and Arterial Blood Acidosis

The methodology employed in several reports utilizes an isocapnic, hypoxia inducing gas mixture of 10 % O_2, 3–5 % CO_2, and balance nitrogen. Some authors add CO_2 to maintain an atmospheric CO_2 pressure near 38 Torr,[9] approximating that of the arterial blood. Thus, during exposure to the isocapnic hypoxic gas mixture, as the rodent becomes hypoxemic and increases minute ventilation, the addition of CO_2 to the gas mixture sustains arterial CO_2 concentrations within the normative range of 35–45 Torr. The net result is a relatively pure hypoxic insult without corresponding hypo- or hypercapnic-induced derangement in acid–base physiology. During an apneic event, cessation of ventilation results in decreased alveolar ventilation. This increases arterial CO_2 levels and induces arterial blood acidosis. While isocapnic hypoxia minimizes potential physiologic confounds induced by altered blood CO_2 levels, it does not induce the same derangement in acid–base physiology that typically accompanies apneic events. Thus, isocapnic hypoxia has the advantage of providing insight into the pathogenic effect of hypoxia alone.

Hypocapnic and Arterial Blood Alkalosis

During the first hours of exposure to low O_2 (10 %) without a CO_2 mixture there are increases in respiration rate and pH, O_2 saturation falls to about 50 %, and decreases of pCO_2 occur, as shown in Fig. 24.6. Hypocapnia is a state in which the level of CO_2 in the

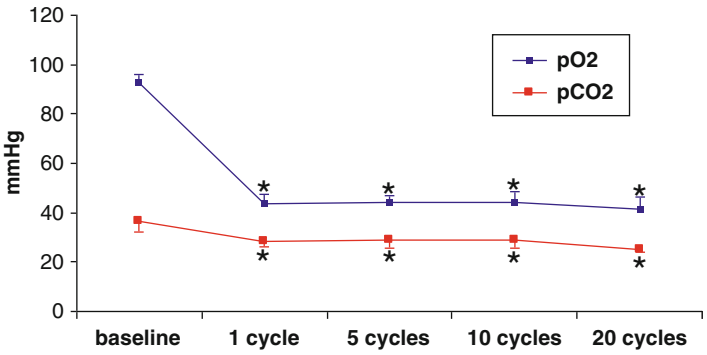

Fig. 24.6 Mean of pO_2 and pCO_2 (mmHg) in arterial blood samples collected before intermittent hypoxia and at the end of the 1st, 5th, 10th and 20th cycle of hypoxia in rats. Each cycle consisted of 2 min with 10 % O_2 followed by 2 min with 20.8 % O_2. One way ANOVA with repeated measurement followed post hoc Newman-Keuls test. *$p<0.05$. (Perry et al. 2007)

[9]The symbol Torr is a non-international system of units of pressure (1 Torr = 1 mmHg = 9.337×10^{-3} psi).

blood is lower than normal. This can result from deep or rapid breathing, known as hyperventilation. The hyperventilation of pure hypoxia (without a CO_2 mixture) is accompanied by respiratory alkalosis. The effects of hypoxia on sleep are linked to O_2 pressure rather than to secondary effects related to hypoxia and respiratory alkalosis. Furthermore, the increase of blood pressure in response to 30 days of intermittent hypoxia is most likely due to hypoxia per se rather than the addition of CO_2. However, following several weeks of chronic hypoxic exposure, the hyperventilation gradually diminishes and CO_2 levels stabilize, as was first described by Barcroft in 1921.

Future Directions

Obstructive sleep apnea is associated with fragmentation of sleep due to the repeated occurrence of end-apneic arousal throughout the night. Arousals are provoked by stimuli generated during upper airway obstruction. Mechanoreceptor stimuli produced during obstructed inspiratory efforts appear to play a major role in mediating the end-apneic arousal response. The sleep disruption resulting from repeated arousals plays a major role in the pathogenesis of most of the consequences of OSA (i.e., neuropsychiatric, respiratory, and cardiovascular) and may contribute to the progression of OSA severity. However, further studies are required to elucidate the relative contribution of sleep fragmentation versus hypoxia in producing these complications and the precise mechanisms involved. Isolated effects of hypoxia and sleep fragmentation in the animal models have been subject to extensive research. Investigating whether associations between hypoxia and sleep fragmentation exert any influence on cognitive function, or on neurochemical and cardiovascular alterations, may be useful in the construction of a more complete model to assess the prevalent syndrome in humans.

Final Considerations

Most sleep disorders result from complex interactions between genes and the environment. Modern molecular techniques are increasingly applied to determine the contribution of genes to sleep and its disorders. Studies proposed in this application will also advance our understanding of the extent to which phenotype and genotype predetermine susceptibility to intermittent apneas and hypoxia-induced cardiovascular and cognitive morbidity. Investigation of the impact produced by hypoxia in animals models contributes to the knowledge of how poorly oxygenated tissue affects the systems. Despite such effects, the cells and tissue may harbor the capacity to adapt to a limited O_2 supply and to unleash a variety of mechanisms to maintain brain integrity and functions under pathophysiological conditions. Knowledge of factors like underlying genotypic traits is necessary to not only confer vulnerability or resistance to intermittent hypoxia, but also to modulate responsiveness to therapeutic interventions aimed at restoring respiratory, cardiovascular, cognitive and metabolic dysfunction following intermittent hypoxic insults.

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