Control of Breathing During Sleep and Wakefulness in the Fetus, Newborn, and Child

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Introduction

The main functions of the respiratory control system are to keep adequate tissue oxygenation and insure excretion of CO_2. To fulfill this, the system is able to respond to a variety of stimuli and modify the breathing pattern (amplitude and frequency of breathing), matching respiration with the metabolic needs. In addition to the sensors responding to increased muscular activity during exercise, or the intricate relations between the respiratory and the sleep/wake neuronal networks, a particular aspect of this system is that there is a constant monitoring of arterial blood gas levels by the peripheral and central chemoreceptors. Peripheral chemoreceptors are located at the bifurcations of the carotid arteries, while central chemoreceptors are found within the brainstem, and are respectively responding to low O_2 (hypoxia) and high CO_2 levels (hypercapnia). These sensors are constantly providing a "drive" to the groups of neurons that generate the respiratory rhythm; the intensity of this drive varies with the arterial pressures of O_2 (PaO_2) and CO_2 ($PaCO_2$). In a laboratory setting, it is possible to evaluate the intensity of these drives, or the chemoreflex functions, by different approaches that alter the levels of arterial blood gases. The typical responses to hypoxia or hypercapnia are an increased neuronal activity of the respiratory control system that is transferred to the spinal motoneurons of the phrenic nerve, thereby increasing minute ventilation in an attempt to restore the levels of arterial blood gases toward normal values. See Figs. 2.1, 2.2, and 2.3 for a simplified model of this system. One particular aspect of this system for sleep medicine emerges from the powerful drive provided by CO_2: if for any reason the $PaCO_2$ falls below a determined level (called the "apneic threshold"), breathing stops, and it is noteworthy that the difference between the eupneic and apneic CO_2 levels (also called the "CO_2 reserve") varies with age, being much smaller in newborns than in adults [1] (Fig. 2.3b). Hypoxic or hypercapnic exposures also result in activation of the sympathetic nervous system and might induce wakefulness when occurring during sleep.

When considering the physiology of this system for sleep medicine in a pediatric population, it is necessary to account for the interactions between sleep and breathing, and the developmental pattern of the respiratory control system. This developmental pattern can conveniently be separated in three main periods: fetal life, the early postnatal period (including the case of preterm birth, up to 1 year of age), and children. This chapter will briefly review the influence of sleep on the respiratory control system in the fetus and newborn, and how sleep exacerbates respiratory instabilities and apneas. We will then describe our current knowledge on the development of the respiratory control system during sleep based on studies from developing human and animal models. The influence of sex as a factor that modulates the regulation of breathing is also briefly discussed. Finally, we will describe respiratory control and the influence of sleep across the ages from early childhood through adolescence.

Influence of Sleep on the Respiratory Control System

The influence of sleep on the respiratory control system is a rich and fascinating field of research, tied to clinical and fundamental issues. It is clearly beyond the objectives of this chapter to provide a full overview. Several excellent reviews have been published over the years [2–4]. We will simply highlight the key elements that are pertinent to understand

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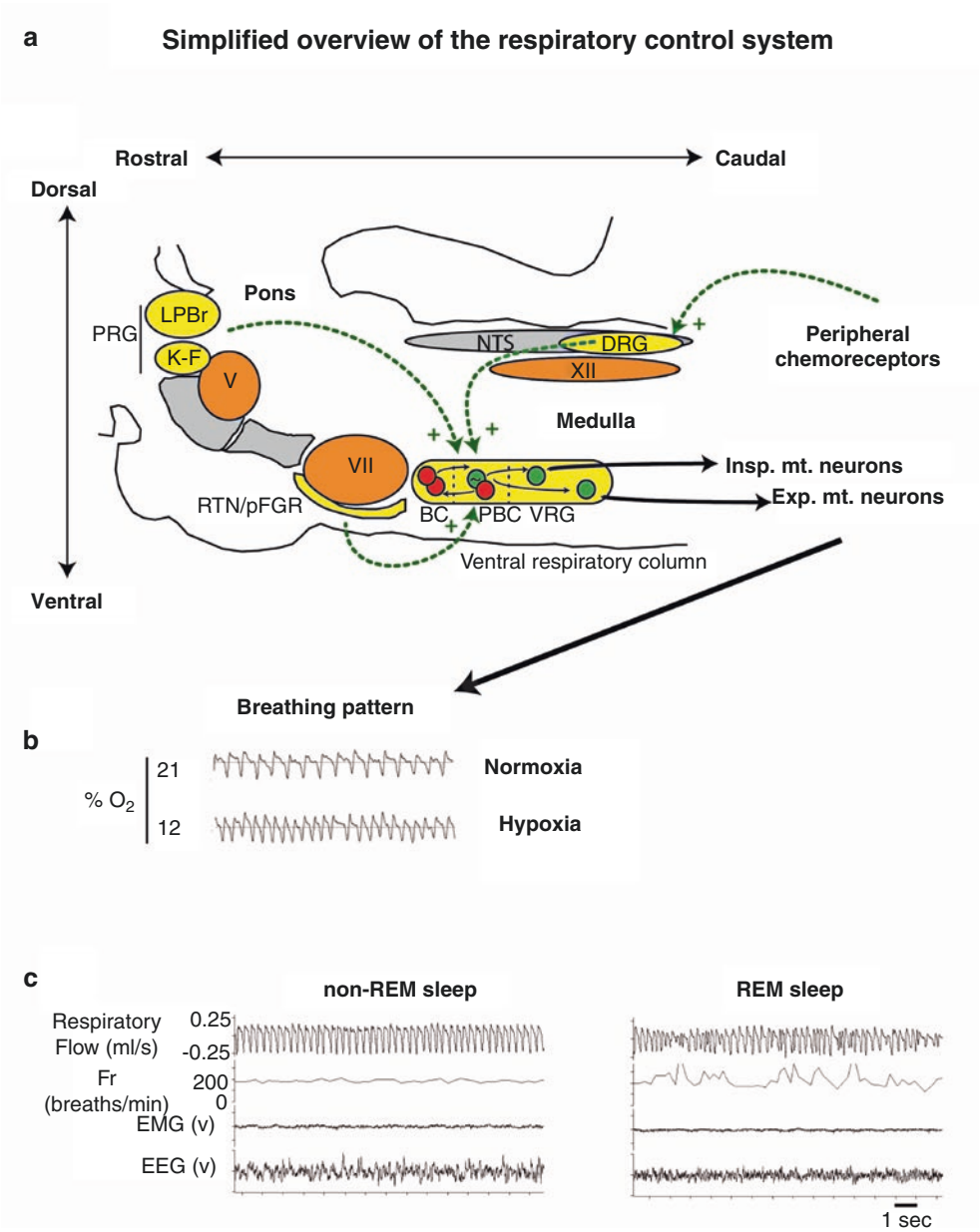

Fig. 2.1 (**a**) Sagittal view of the lateral medulla with the main groups of respiratory neurons (*yellow*) extending along the rostro-caudal axis up to the dorsal part of the pons. The Vth, VIIth, and XIIth motor nuclei are presented (*orange*) as anatomical landmarks. Groups of interconnected excitatory (*green*) and inhibitory neurons (*red*) are distributed along the ventral respiratory column. The microcircuit responsible for the generation of the breathing rhythm is localized in the PreBötzinger complex (PBC). The Bötzinger complex mostly contains expiratory neurons inhibiting inspiratory neurons of the PBC. Bulbospinal premotoneurons relaying inspiratory or expiratory drives to the spinal motoneurons are localized in the ventral respiratory group (VRG). Chemoreflex drives are provided by the peripheral chemoreceptors and their central projections to the dorsal respiratory group (DRG) of the caudal nucleus tractus solitarius (NTS), and by the central chemoreceptors of the retrotrapezoid nucleus/parafacial respiratory group (RTN/pFRG). The pontine respiratory group (PRG) includes the lateral parabrachial and Kölliker-Fuse nuclei (LPBr–K-F); it regulates the phase transition between inspiration and expiration, and is a relay of suprapontine afferents contributing to the respiratory drive. K-F also contains premotor neurons that control laryngeal muscles and upper airway resistances. The strength of the chemoreflex drives is dictated by levels of arterial blood gases. (**b**) Typical respiratory traces in normoxia and in response to hypoxia (recorded in a 10-day-old mouse, toward the end of the postnatal maturation of the respiratory control system). (**c**) Typical respiratory recording during non-rapid eye movement (non-REM) and REM sleep recorded in an adult mouse. Traces show the respiratory flow, respiratory frequency (breath-by-breath), electromyogram (EMG), and electroencephalogram (EEG). (Redrawn and adapted from Smith et al. [119] with permission from Elsevier. Respiratory traces adapted from Refs. [120, 121])

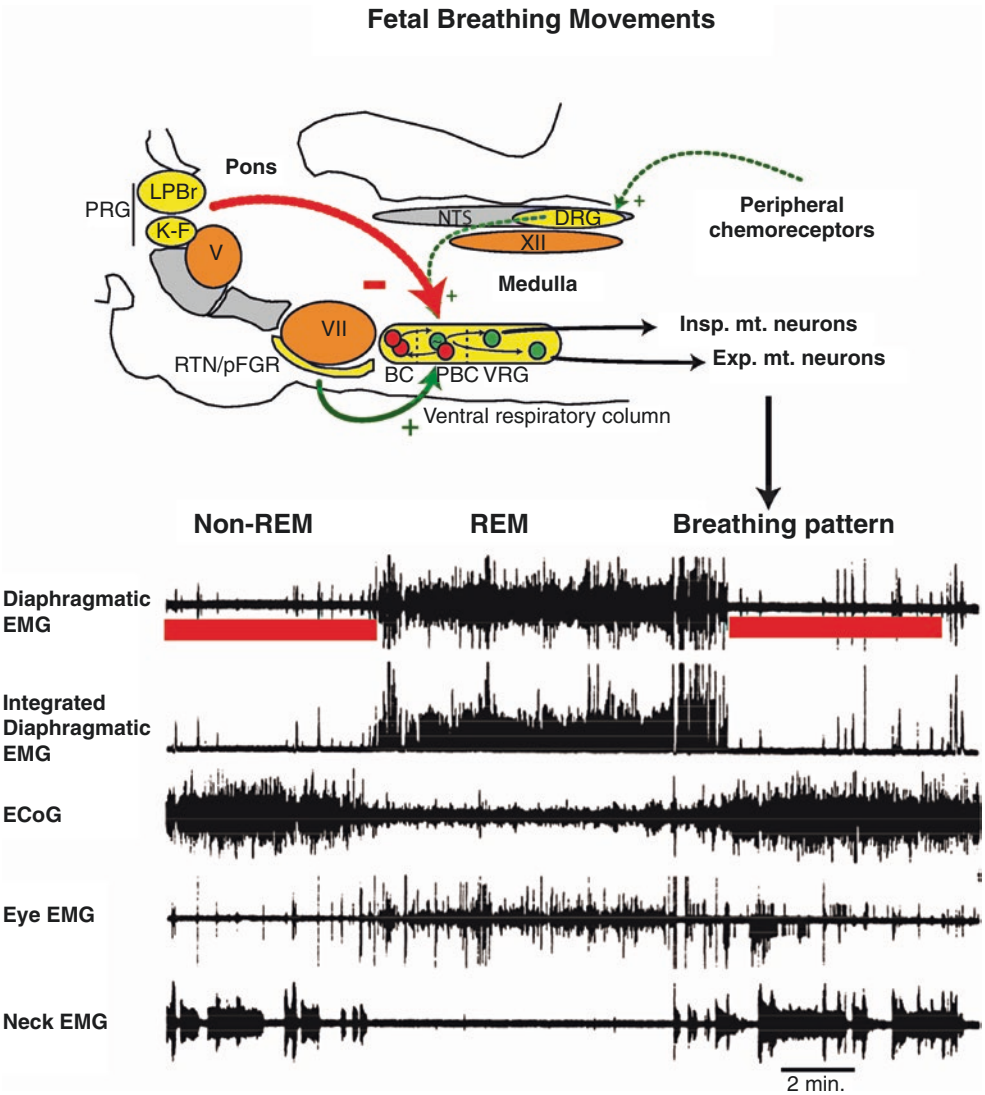

Fig. 2.2 Occurrence of fetal breathing movements during REM sleep in a near-term fetal lamb. (Recordings from Jansen and Chernick [11]. Reprinted with permission from The American Physiological Society). The pontine respiratory group exerts a potent inhibition on the activity of the respiratory neuronal groups of the ventrolateral medulla (*red arrow*). However, during REM sleep fetal breathing movements are visible. The pontine inhibition masks the effect of peripheral chemoreceptors during hypoxic exposures, but central chemoreceptor exerts a tonic activation (see text). See legend of Fig. 2.1 for further details

the intricate relationships. One of the most important drives to the respiratory control system arises from the wake-promoting neuronal networks localized in the medulla and hypothalamic nuclei. When the wake drive disappears during non-rapid eye movement (non-REM) sleep, ventilation is slightly reduced, and arterial levels of CO_2 increase by 2–8 mmHg. This reduced respiratory activity leaves the respiratory control system under metabolic regulation and even a transient and modest reduction in $PaCO_2$ that will have no consequence during wakefulness, will induce an apnea during sleep.

Furthermore, the resistance of the upper airway increases two- to fivefold during sleep. Recordings performed in rodents have shown that the activity of the XIIth cranial nerve, that innervates the genioglossus muscle, is decreased during non-REM sleep compared to wakefulness, and is completely suppressed during REM sleep, secondary to the withdrawal of excitatory inputs to the airway motor neurons [5]. During REM sleep, breathing is generally more variable, and the breathing pattern is influenced by non-metabolic stimuli [4]. Breathing frequency typically increases during periods of rapid eye movements compared to non-REM sleep, while tidal volume and minute ventilation are further depressed [6]. While some studies have shown that in apneic patients, the frequency of apneas is slightly higher during REM sleep than during non-REM sleep [7], others have not reported such differences [8].

Control of Breathing in the Fetus

In the fetus, respiratory exchanges occur through the placenta and the maternal respiratory system. However, fetal breathing movements (FBM), while limited, are nonetheless

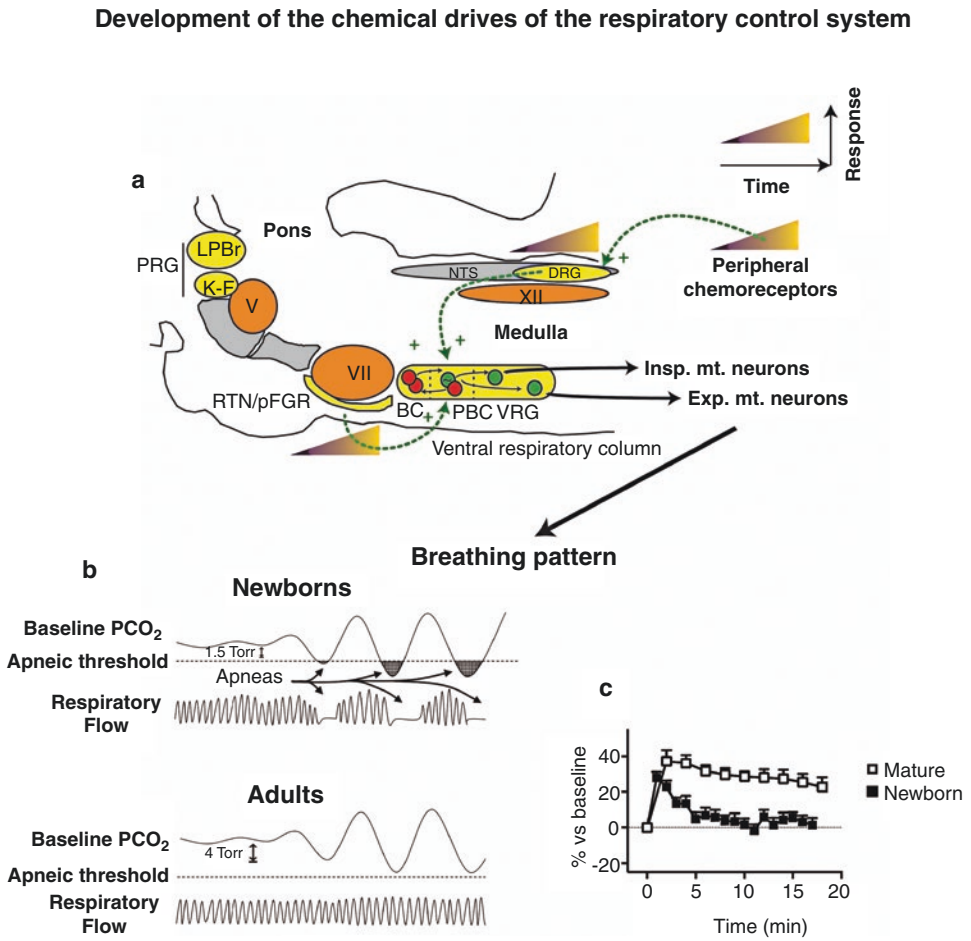

Fig. 2.3 (**a**) Schematic representation of the early postnatal maturation of the central and peripheral components of the chemoreflex drives to breath, showing general trends of increased efficiency with maturation. (**b**) Maturation of the central respiratory drives widens the "CO_2 reserve," driving eupneic breathing further away from the apneic threshold. (From Alvaro R [122]. Reprinted with permission from Springer Nature). (**c**) Postnatal maturation of the hypoxic ventilatory response in mice. Minute ventilation recorded by whole body plethysmography at postnatal days 3–4 (newborn) and 12 (mature). Graph shows percentage changes of minute ventilation (Tidal volume × Respiratory frequency) vs baseline value during a 20-minute exposure to 10% O_2. Note the sustained response in mature animals, and the biphasic pattern of the newborn, with a peak followed by a decline to baseline values. Data from Joseph & Bairam laboratories

observable in almost all mammalian species and have been particularly well studied in humans [9–11], lambs [12–14], and rats [15–17]. FBM play an important role in lung growth and respiratory muscle development [18], in particular for the diaphragm muscle, which develops concurrently with the establishment of the inspiratory drive in utero [16]. In humans, FBM can be detected by ultrasound as early as the 11th week of gestation [19]. At this early stage the FBM are continuous with a regular pattern, but they become clearly irregular and episodic in nature during the last trimester of gestation [9, 20, 21]; an episode of breathing can last 10–30 minutes with a mean frequency around 60/minute and is associated with increased body movements, decreased heart rate, and increased heart rate variability [10, 20, 22]. Between episodes, there is no breathing activity, and this "apneic" period might last up to 120 minutes [10, 20]. This developmental period of FBM is associated with the beginning of a clear differentiation of the low- and high-voltage electrocortical activity that are the signatures of sleep/wake states [23].

Interestingly, similar steps for the appearance of FBM and their association with cortical brain organization for sleep are observed in fetal sheep, which has been for many decades a powerful animal model to characterize the physiology of breathing before birth [11, 12, 14]. During the last 3 months of gestation, healthy non-anesthetized fetal lambs spend roughly 40% of their time in a state characterized by low-voltage electrocortical activity, with rapid eye movements (REM sleep state), 50% of the time is characterized by high-voltage electrocortical activity associated with non-rapid eye movements (non-REM sleep state) [12, 24], and the remaining time is classified as an undetermined state. In fact, the typical "wake" behavior (opened eyes with gross body and head movements) is only observed after birth [25]. FBM typically occur during REM sleep in fetal lambs [26], and in human [20], and are notably absent during non-REM sleep

[24, 25]. The isolated breaths during non-REM sleep are associated with body movements and can represent tonic diaphragmatic discharges rather than typical FBM [25].

The precise mechanisms explaining the absence of FBM during non-REM sleep remain unclear, but it is worth mentioning that sections through the upper pons or mid-collicular regions induce FBM independently of the state of electrocortical activity (REM or non-REM) [16, 27–29] (Fig. 2.2). Therefore, during non-REM sleep state, there is a powerful inhibitory pathway arising from the lateral pons and midbrain contributing to reduce the activity of the medullary respiratory rhythm generator.

Collectively, the pattern of fetal FBM during the course of gestation has been suggested to be an indicator of fetal health and nervous system development [30–32], providing information about the developmental course of the respiratory control system in utero [9]. Notably, an absence of FBM on ultrasound examination can be used to detect a short-term risk of preterm birth [33].

Regulation of FBM by Chemoreflex Drives

Hypoxic Drive and Peripheral Chemoreceptors

Fetuses live in a severe hypoxic environment with PaO_2 being low (about 25–30 mmHg) compared to after birth (55–70 mmHg) or standard levels beyond the postnatal period (95–100 mmHg). Despite this very low PaO_2, the activity of the peripheral chemoreceptors has been recorded in lambs and displays a functional response to hypoxia [34]. However, hypoxia [12, 13, 35], or experimental anemia [36], drastically inhibits the frequency and amplitude of the FBM, and also reduces the proportion of time in REM sleep state. A prolonged exposure to hypoxia for 24 hours inhibits FBM only during the first few hours of exposure [37]. After electrolytic lesion of the lateral pons, in a region corresponding to the lateral parabrachial and Kölliker-Fuse nuclei [29], hypoxic exposures increase FBM, showing the central origin of this inhibition (Figs. 2.1 and 2.3). Interestingly, inhibition of FBM in REM sleep state is stronger in fetus near term of gestation suggesting an age-dependent maturity of this central inhibitory pathway [12]. Finally, it is worth mentioning that hyperoxia has no effect on FBM or sleep state, indicating that fetal PaO_2 does not limit the normal expression of FBM [35].

Hypercapnic Drive and Central Chemoreceptors

In response to hypercapnia or hypocapnia during REM sleep, there are respectively an increased and a decreased incidence and amplitude of FBM [28, 38]. The response to hypercapnia is stronger in near term than in younger fetuses [13, 35, 39]. Interestingly, the effect of age and CO_2-concentration was evaluated in 30 human fetuses divided into 3 groups of 24–26, 28–30, and 32–34 weeks of gestation, while mothers breathed CO_2 at 2% or 4%. These fetuses show an age- and CO_2-concentration-dependent increase in FBM response, with higher responses at 32–34 weeks than 24–26 weeks of age [9].

Hence, in the fetus, the sensory mechanisms that underlie the responses to hypoxia and hypercapnia develop during gestation, and FBM are predominantly controlled by central mechanisms rather than by peripheral chemoreceptors (see Fig. 2.2). Although high CO_2 levels (hypercapnia) appear to be an important stimulus to regulate FBM, hypercapnia does not induce continuous breathing during non-REM sleep, further supporting the suggestion that central inhibitory mechanisms on the respiratory control system are strong during the fetal life. Maternal and intrauterine conditions can modify FBM pattern and several studies suggest that these factors can induce changes in the normal developmental course of the respiratory control system after birth, such as alteration of the ventilatory response to hypoxia [40], increased frequency of apnea [41], and disruption of the brainstem respiratory rhythm generation [42]. Different mechanisms have been proposed to explain such alterations in respiratory control in neonates born from stressed mothers, such as disturbances in neurotransmitter function (GABAergic and serotoninergic systems [41, 43] and enhancement in the neuro-inflammatory processes in the brainstem and spinal cord [42].

Control of Breathing in the Newborn

After the transition from liquid to gas breathing at birth, and once the continuous breathing pattern has been established (a topic not covered here), wakefulness and arterial blood gases remain the most powerful respiratory drives. As mentioned earlier, however, the "CO_2 reserve"—which represents the tolerance of breathing to a drop of $PaCO_2$ before an apnea occurs—is much smaller in newborn (about 1.0–1.3 mmHg in term and preterm neonates) than in adults (around 3.5 mmHg) [1] (Fig. 2.3b). With this small reserve, periodic breathing and apneas are commonly observed. In term infants at a mean age of 27 days, even a very small, spontaneous, increase in ventilation (frequency increasing from 32.8 to 33.9 breaths/min) can "precipitate" a decrease in $PaCO_2$ below the apneic threshold (from 39.7 to 38.7 mmHg) and initiate a sequence of periodic breathing or apnea [1]. In preterm neonates, the apneas during periodic breathing are typically associated with decreased arterial oxygen saturation [44, 45]; thus, this is a highly significant clinical concern exposing the newborn to intermittent hypoxia.

Postnatal development of the respiratory control system involves the peripheral and central chemoreceptors, the central integration pathways in the brainstem, and the effector muscles (respiratory diaphragmatic and intercostal muscles)

[46]. This maturation widens the CO_2 reserve, and consequently the newborns become less prone to exhibit recurrent apneas (Fig. 2.3). In humans, the maturity of the respiratory control system occurs progressively during the first year of life, in parallel with the maturation of sleep architecture [23, 47, 48]. The low- and high-voltage electrocortical activity in the fetus correspond in the newborn to active (AS) and quiet sleep (QS), respectively, and are considered as precursors of infant and adult REM and non-REM sleep. During the first postnatal year, there is a progressive increase in the proportion of time spent in AS and wakefulness, with a decrease in the proportion of time spend in QS [23, 49, 50].

Additional insight into mechanisms underlying ventilatory pattern instability during infancy can be derived from the concept of loop gain (LG), a dimensionless number that describes the stability of the respiratory control system [51]. When LG is low, respiratory control is stable and rapidly returns to a stable condition after a perturbation such as a sigh or movement. High LG indicates a tendency for breathing to become unstable and oscillate when the respiratory control system is perturbed. Calculation of LG from the ventilatory response to spontaneous sigh, in sleeping (QS) infants over the first 6 months of life, revealed low LG in 1–2 days after birth (stable), steadily increasing LG until ~4 weeks of age (increasing instability), followed by gradual fall in LG to a more stable level by 6 months of age (late postnatal stabilization) [51, 52]. Analysis of the components that comprise LG strongly indicated that early postnatal ventilatory pattern instability and subsequent stabilization reflect, in large part, maturation of peripheral chemoreceptor responses [51].

The contribution of the peripheral chemoreceptors to resting normoxic ventilation can be determined by suddenly exposing infants to hyperoxia while measuring the immediate response of minute ventilation within 15–30 seconds (the "hyperoxic test"). The sudden rise in PaO_2 silences the peripheral chemoreceptors, leading to sudden withdrawal of their input; the resulting drop in minute ventilation reflects the proportion of resting drive from the peripheral chemoreceptors. Using this approach, the contribution of the peripheral chemoreceptors to normoxic resting ventilatory drive in full-term infants during QS was found to be ~6% at 24 hours, ~25% at 10 days, ~40% at 10 weeks, and ~50% at 6 months [53, 54]. This remarkable developmental increase in peripheral chemoreceptor drive during the first 6 months of life is believed to be responsible, in large part, for the changes in LG noted above and the high degree of ventilatory pattern instability observed during infancy [51].

When LG is high, any disturbance affecting breathing (such as a sigh or body movement), will likely trigger periodic oscillations of ventilatory drive. Whether the respiratory control system oscillates with or without periodic apnea (periodic breathing) depends on the arterial PCO_2 and whether it dips below the apneic threshold as ventilatory drive oscillates [55]. A recent study using respiratory inductance plethysmography to record breathing in sleeping (QS) preterm infants at 36 weeks post-menstrual age confirmed that LG, determined from the ventilatory response to spontaneous sighs, strongly correlated with the percentage of periodic breathing [56]. This finding further unifies postnatal developmental changes in LG with numerous studies showing a low incidence of periodic breathing in the first days of life, an increase in periodicity until about 4 weeks of age, and a decline thereafter [57, 58]. A full discussion of LG and ventilatory pattern maturation are beyond the scope of this chapter. The reader is referred to a recent in-depth review of the numerous complex factors influencing ventilatory stability during infant development [51].

Regulation of Breathing in Neonates in Relation to Sleep, Chemoreflex Drives

Normoxic Breathing Pattern in Neonates in Relation to Sleep States

In newborns, it is generally accepted that minute ventilation is higher during AS, due to a higher respiratory frequency [59], and this contributes to a greater variability of arterial oxygen saturation [50] and of $PaCO_2$. Although apnea and periodic breathing are present in both AS and QS, their prevalence is higher in AS than in QS [60–62]. The frequency and duration of these apneic events are typically inversely proportional to the gestational age [49, 52, 63–65] and progressively decrease during the first year of life in either preterm or term infant [59, 62]. In preterm neonates, immaturity of the respiratory control system and exaggerated laryngeal chemoreflexes [66] greatly contribute to increase the frequency of apneas. Progressive development of these elements toward a mature phenotype contributes to a gradual reduction in apnea frequency [67] that becomes comparable to full-term infants near 1 month of corrected gestational age (44–46 weeks) [62, 68]. Interestingly, respiratory recordings performed in rats at 1, 4, 7, 12, 21, and 90 postnatal days illustrate this developmental sequence and the progressive establishment of a regular breathing pattern at rest, associated with a decreased apnea frequency [66, 67] (Fig. 2.4).

Hypoxic Ventilatory Responses (HVR) in Neonates in Relation to Sleep State

This response has been characterized in different mammalian species including in preterm and term human neonates [69–74]. The main feature of the hypoxic ventilatory responses (HVR) at this stage is its biphasic pattern, with an initial increase in ventilation, followed by a "roll-off" or inhibitory phase. During this inhibition, minute ventilation may decrease below the baseline normoxic level; the magnitude of this inhibition gradually decreases with age; see example from developing rats (Fig. 2.5). It is now under-

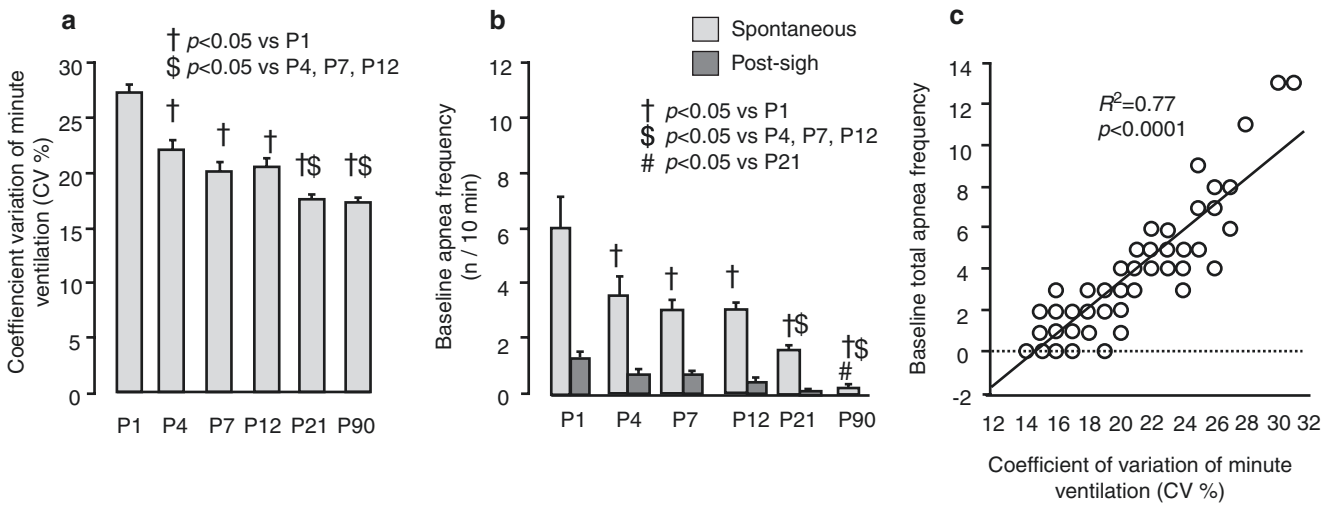

Fig. 2.4 Maturation of respiratory control in male rats between postnatal days 1 and 90 (P1–P90) illustrated by stabilization of the breathing pattern. (**a**) The coefficient of variation of minute ventilation (%) illustrates the variability of individual breaths around the mean for each rat. (**b**) Frequency of spontaneous or post-sigh apneas recorded at rest. (**c**) Positive correlation between the coefficient of variation and apnea frequency. (From Niane and Bairam [123], DOI: https://doi.org/10.4236/ojmip.2011.11001; and from Niane and Bairam [66]. Reprinted with permission from Springer Nature)

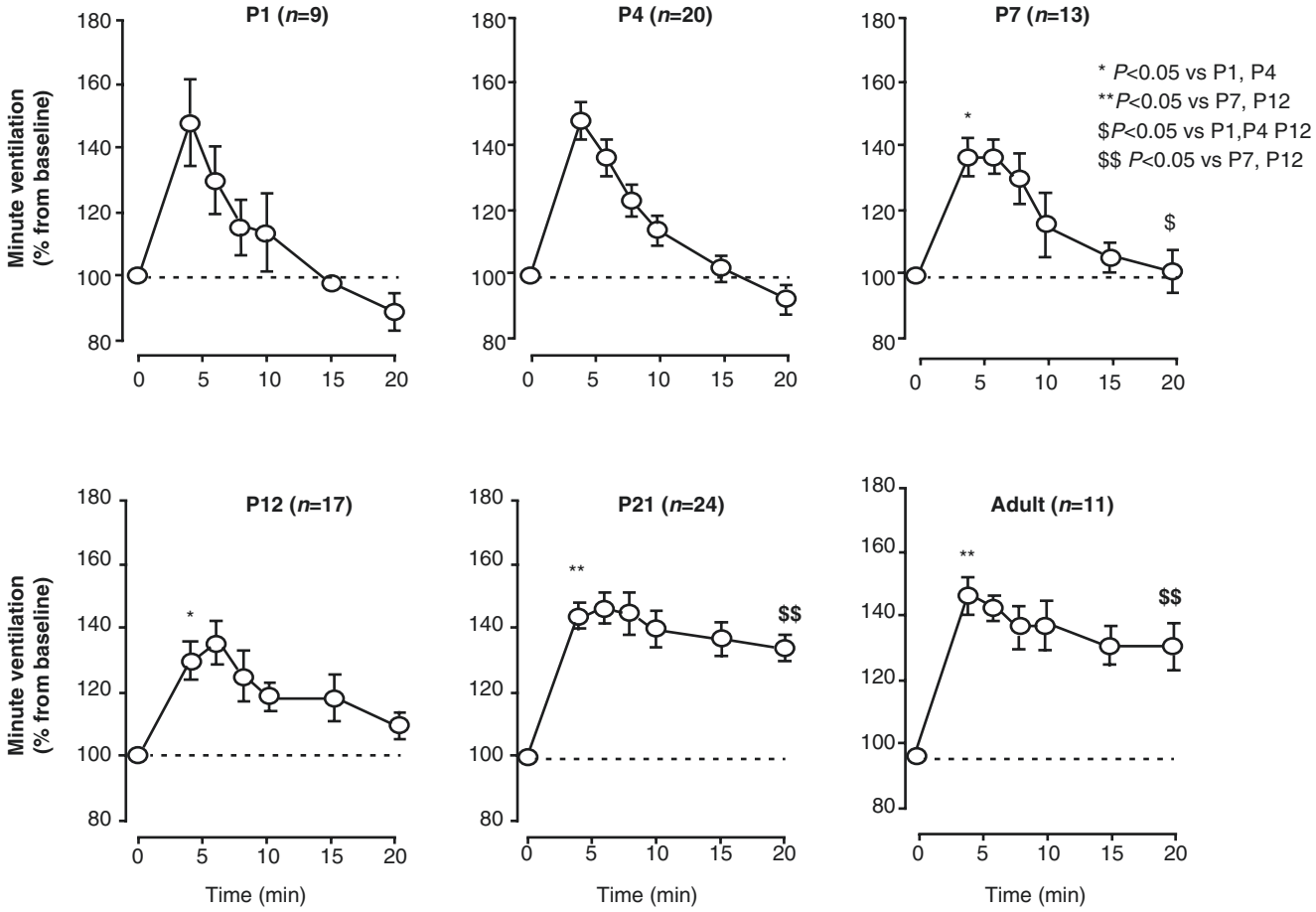

Fig. 2.5 Maturation of hypoxic ventilatory response in male rats between postnatal days 1 and 90 (P1–P90). Minute ventilation in response to moderate hypoxia (FiO_2 = 12%, 20 minutes) as percentage change from the baseline. Data are means ± SEM. Number of animal (*n*) indicated for each age group. (From Niane and Bairam [123]. DOI: https://doi.org/10.4236/ojmip.2011.11001)

stood that the initial phase of increase in ventilation results from stimulation of peripheral chemoreceptors (primarily located in the carotid bodies), while the late depressive phase is mediated by central inhibitory pathways under the control of mechanisms overriding the excitatory inputs from peripheral chemoreceptors (changes in metabolism, in cerebral circulation, and in inhibitory/excitatory neurotransmitters; Figs. 2.3c and 2.5) [72–75].

In relation to sleep state, studies in preterm and term infants showed that this biphasic response is present in both AS and QS [60] and persists until at least 6 months of age in infants born at term [76]. In humans, the sleep state did not affect the magnitude of the HVR [76, 77], but in lambs, ventilation during the late phase of a hypoxic test was higher in QS than AS [78], illustrating possible inter-species effects.

One study found that in infants born at term and that were followed at the age of 2–5 weeks, 2–3 months, and 5–6 months, hypoxic exposures during AS are systematically associated with arousal [76], while this occurs only in half of the infants during QS [76]. Arousal was related to a faster and deeper decrease in arterial oxygen saturation, suggesting that this awakening during hypoxia is a protective mechanism against further desaturation. Furthermore, during QS, and for the exposures that did not induce an arousal, the HVR was clearly following a maturational course that was not fully completed by 6 months of age since the older infants did not demonstrated a sustained HVR throughout the hypoxic exposure (15% O_2—5 minutes). This leads to the suggestion that significant development of the HVR occurs in QS [76], and that this developmental course is somehow masked during QS sleep. These developmental changes in the pattern of the hypoxic response with age are related to maturation of O_2-sensing mechanisms and establishment of functional synapses in peripheral chemoreceptors [73–75, 79–81], to a reduced central inhibitory mechanism, and to development of excitatory pathways during hypoxia [72, 74, 75, 82].

Hypercapnic Ventilatory Response (HcVR) in Neonates in Relation to Sleep State

Under normoxic conditions, ventilation is largely dictated by arterial PCO_2, which is sensed mainly centrally within the brainstem. Nonetheless, the contribution of the peripheral chemoreceptors to hypercapnic ventilatory response (HcVR) is estimated to be around 20–40% depending on the species studied [17, 82]. Although CO_2 responsiveness in term infants is nearly mature at birth [53, 83], it increases progressively after birth in preterm neonates [69, 83]. In newborn animal models, the response to hypercapnia undergoes maturational changes during the first 2 weeks of life, and this maturation involves both the central (brainstem) and peripheral (carotid body) sites [17, 75, 82, 84, 85]. Furthermore, an additive and/or synergistic interaction between hypoxia and hypercapnia is also age-dependent in human [53] and animal [17, 85] during the postnatal development. However, a particularity in response to hypercapnia in preterm is that CO_2 administered during periodic breathing increases minute ventilation and the respiratory frequency. Contrastingly, if administered during a regular breathing pattern, CO_2 increases tidal volume [61]. In addition, these responses were not affected by sleep state. The changes in CO_2 response with age involve cellular, molecular, and genetic modifications, as well as modifications in neurotransmitter patterns in a site-dependent manner [17, 69, 75, 80, 81].

Alteration of Ventilatory Chemoreflexes in Neonates by Chronic Intermittent Hypoxia

The succession of hypoxemic events associated with apneas and periodic breathing exposes the newborn infants to chronic intermittent hypoxia. It is increasingly recognized that apneic preterm infants have quantitative and qualitative impairments of the peripheral and central ventilatory control system that, in turn, favor further development of respiratory instabilities. Compared to non-apneic, apneic neonates have lower basal arterial oxygen saturation [86], lower ventilation, and higher breathing irregularities [45, 87–89]; a weak response to hypercapnia under normoxic [88, 90–92] or hypoxic conditions [1, 17]; and, alterations of the initial phase of the ventilatory response to hypoxia or hyperoxia [87, 88, 90, 93]. The mechanisms underlying these effects are related to an immature response to O_2–CO_2 interaction and to an elevated peripheral chemosensitivity to hypoxia [87, 88, 93]. The elevated peripheral chemosensitivity might further destabilize breathing by driving arterial PCO_2 below the apneic threshold in response to transient (and small) hypoxemic/hypercapnic events [70, 87, 88, 93, 94]. Altogether this participates in maintaining and increasing respiratory irregularities [45].

Similar to what is observed in preterm neonates, exposure to intermittent hypoxia in newborn rats enhances the carotid body chemosensory activity in response to hypoxia [95, 96] with greater magnitude than that observed in adult rats [97]. Exposure to intermittent hypoxia also decreases normoxic ventilation, increases the frequency of apnea [98, 99], and enhances the initial increase in ventilation in response to hypoxia [95, 99], while it reduces the late phase [99] and disrupts the ventilatory and chemoreceptor responses to O_2–CO_2 interactions [100]. Peripheral and central inflammatory reactions and production of reactive oxygen species in the central and peripheral nervous system have been proposed to mediate some effects of intermittent hypoxia on the breathing control system [101–104].

Sex and Control of Breathing at Neonatal Ages

The effect of sex in respiratory control before puberty and in neonates has not been adequately investigated, yet some data highlight, either directly or indirectly, its importance. The best example is that males are at higher risk for respiratory distress syndrome and sudden infant death syndrome [105], in which protective respiratory chemoreflexes are thought to be impaired. Suffocation accidents are also more often fatal in males than in females [106], and, finally, male neonates also develop more bronchopulmonary dysplasia and are less resistant to hypoxemic/ischemic cerebral injuries than females [107]. In a recent study, it has been found that treatment with caffeine for apnea in preterm infants is maintained for longer period in males than in females, indirectly suggesting a faster maturation of respiratory control in females than in males [108]. In this line of reasoning, experimental studies in newborn rats showed that males have more variabilities in respiratory frequency, tidal volume, and higher apnea frequency [41, 109]. Our understanding of such heterogeneity between males and females remains limited but some recent reviews discussed eventual underlying mechanisms [42, 109].

Respiratory Control in Older Children and Effects of Sleep State

Although respiratory control has been well studied in preterm and term infants, there are only a few studies in older children and very few that span the entire age range of childhood. There are even fewer studies that have examined the effects of sleep per se on respiratory control in older children and adolescents. In the following paragraphs, we describe normal ventilation and ventilatory responses to O_2 and CO_2 in older children. We do not address normal upper airway motor control or hypoxia and hypercapnia as stimuli for arousal from sleep, as these topics are addressed in Chaps. 4 and 36, respectively.

Respiratory Rate, Tidal Volume, and Minute Ventilation: Effects of Age and Sleep

Respiratory rate (RR) is highest during the newborn period and, in general, decreases with age during the first year of life [110] as breathing becomes more regular by about 8 months of age and the difference in RR between REM and non-REM sleep narrows [111]. A recent multicenter study of 209 healthy children ranging in age from 1 to 18 years confirmed that RR in quiet sleep is highest in infants and steadily

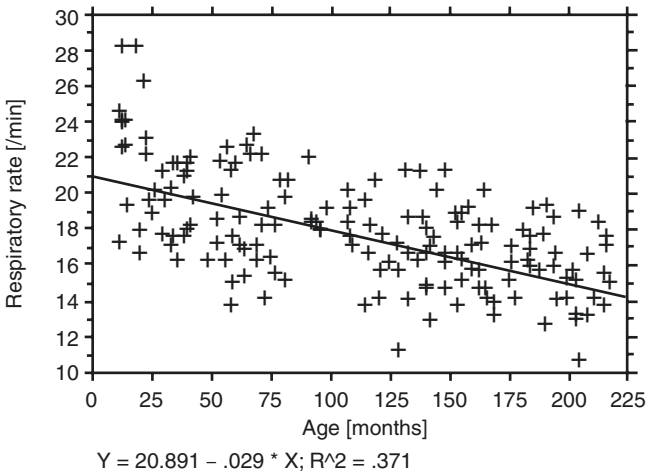

Fig. 2.6 Postnatal changes in respiratory rate during non-REM sleep. (From Scholle et al. [112]. Reprinted with permission from Elsevier)

decreases across the entire age spectrum [112] (Fig. 2.6). Specifically, RR in year 1 averaged ~22 breaths/min and by age mid-late adolescence average RR was ~15 breaths/min with a steady decrease over the age spectrum [112]. Interestingly, the variation in normal RR during quiet sleep was large, such that there was significant overlap in normal RR for 1- vs 18-year-old healthy subjects (Fig. 2.6). In normal, healthy adolescents, RR was highest during wakefulness, significantly decreased during stage 2 and 4 non-REM sleep, and intermediate in REM sleep [113]. Similarly, minute ventilation was highest during wakefulness, decreased about 8% during stage 2 and 4 non-REM sleep, and was intermediate in REM sleep. These changes in minute ventilation were entirely due to sleep-related changes in RR, as tidal volume (V_T) did not vary at all with sleep state [113]. As expected, the variability (coefficient of variation) for minute ventilation, V_T, and RR were all significantly higher during wakefulness and REM sleep compared to non-REM sleep in normal adolescents [113].

In the same study of normal adolescents, as RR slowed during non-REM sleep, inspiratory time (T_I) increased 25%, expiratory time (T_E) did not change, and T_I/T_{tot} did not change [113]. The increase in T_I in non-REM sleep, with no associated changes in V_T, resulted in a non-REM sleep-related 20% decrease in V_T/T_I (ml/s, mean inspiratory flow). In contrast to normal infants, which exhibit paradoxical inward rib cage motion (PIRCM) during REM sleep, PIRCM was not observed in any of the normal, healthy adolescents during REM sleep [113]. In a similar study of otherwise healthy adolescents diagnosed with moderate–severe asthma, paradoxical inward rib cage motion was observed during REM sleep in every subject, indicating that asthma alone can cause REM-sleep-related PIRCM in otherwise normal adolescents [114].

Ventilatory Response to Hypoxia and Hypercapnia: Effects of Age and Sleep

Beyond the first year of life, there are very few studies of ventilatory control in childhood and only one study spans the age range across the pediatric and adult age range. Hypoxic and hypercapnic ventilatory responses were studied in 59 healthy subjects ranging in age from 4 to 49 years [115]. Hypercapnic ventilatory responses (HcVR) were measured with a hyperoxic rebreathing method as described by Read [116] and hypoxic ventilatory responses (HVR) were measured using an isocapnic rebreathing method of Rebuck and Campbell [117]. Due to the very wide age and size range of the subjects, results were normalized by body weight [115]. The slope of the HcVR (normalized to weight) was highest in the youngest children, decreased with age until ~ age 10–15 years, and did not change thereafter. Similarly, the slope of the HVR (normalized to body weight) was greatest in the youngest children, decreased until ~ age 10 years, and remained unchanged thereafter in adults up to 49 years of age [115]. Although there is no consensus on the best approach to normalizing ventilatory response data, it is important to note that weight-normalized HVR and HcVR did not change between ~ ages 10 and 49 years, even though weight in a normal child nearly doubles between age 10 and 18. Another study of children 7–18 years of age found that the normalized (to body weight, surface area, or lean body mass) ventilatory response to CO_2 was highest in the youngest children, declined rapidly from age 7–8 to age 11–12, and then stabilized to age 18 [118]. However, the same study did not find differences in the hypoxic ventilatory responses of children from 7 to 18 years of age.

References

1. Khan A, Qurashi M, Kwiatkowski K, Cates D, Rigatto H. Measurement of the CO2 apneic threshold in newborn infants: possible relevance for periodic breathing and apnea. J Appl Physiol (1985). 2005;98(4):1171–6. https://doi.org/10.1152/japplphysiol.00574.2003.
2. Xie A. Effect of sleep on breathing – why recurrent apneas are only seen during sleep. J Thorac Dis. 2012;4(2):194–7. https://doi.org/10.3978/j.issn.2072-1439.2011.04.04.
3. Dempsey JA, Veasey SC, Morgan BJ, O'Donnell CP. Pathophysiology of sleep apnea. Physiol Rev. 2010;90(1):47–112. https://doi.org/10.1152/physrev.00043.2008.
4. Philipson EA, Bowes G. Control of breathing during sleep. Compr Physiol Supplement 11: Handbook of physiology, the respiratory system, control of breathing; 2011. p. 649–89. First published in print 1986. https://doi.org/10.1002/cpchy.cp030219.
5. Fenik VB, Davies RO, Kubin L. REM sleep-like atonia of hypoglossal (XII) motoneurons is caused by loss of noradrenergic and serotonergic inputs. Am J Respir Crit Care Med. 2005;172(10):1322–30. https://doi.org/10.1164/rccm.200412-1750OC.
6. Gould GA, Gugger M, Molloy J, Tsara V, Shapiro CM, Douglas NJ. Breathing pattern and eye movement density during REM sleep in humans. Am Rev Respir Dis. 1988;138(4):874–7. https://doi.org/10.1164/ajrccm/138.4.874.
7. Peregrim I, Gresova S, Pallayova M, Fulton BL, Stimmelova J, Bacova I, Mikulakova A, Tomori Z, Donic V. Does obstructive sleep apnea worsen during REM sleep? Physiol Res. 2013;62(5):569–75.
8. Loadsman JA, Wilcox I. Is obstructive sleep apnoea a rapid eye movement-predominant phenomenon? Br J Anaesth. 2000;85(3):354–8.
9. Connors G, Hunse C, Carmichael L, Natale R, Richardson B. Control of fetal breathing in the human fetus between 24 and 34 weeks' gestation. Am J Obstet Gynecol. 1989;160(4):932–8.
10. Patrick J, Challis J. Measurement of human fetal breathing movements in healthy pregnancies using a real-time scanner. Semin Perinatol. 1980;4(4):275–86.
11. Jansen AH, Chernick V. Fetal breathing and development of control of breathing. J Appl Physiol (1985). 1991;70(4):1431–46. https://doi.org/10.1152/jappl.1991.70.4.1431.
12. Clewlow F, Dawes GS, Johnston BM, Walker DW. Changes in breathing, electrocortical and muscle activity in unanaesthetized fetal lambs with age. J Physiol. 1983;341:463–76.
13. Ioffe S, Jansen AH, Chernick V. Maturation of spontaneous fetal diaphragmatic activity and fetal response to hypercapnia and hypoxemia. J Appl Physiol (1985). 1987;63(2):609–22. https://doi.org/10.1152/jappl.1987.63.2.609.
14. Bowes G, Adamson TM, Ritchie BC, Dowling M, Wilkinson MH, Maloney JE. Development of patterns of respiratory activity in unanesthetized fetal sheep in utero. J Appl Physiol Respir Environ Exerc Physiol. 1981;50(4):693–700. https://doi.org/10.1152/jappl.1981.50.4.693.
15. Kobayashi K, Lemke RP, Greer JJ. Ultrasound measurements of fetal breathing movements in the rat. J Appl Physiol (1985). 2001;91(1):316–20. https://doi.org/10.1152/jappl.2001.91.1.316.
16. Greer JJ, Martin-Caraballo M. Developmental plasticity of phrenic motoneuron and diaphragm properties with the inception of inspiratory drive transmission in utero. Exp Neurol. 2017;287(Pt 2):137–43. https://doi.org/10.1016/j.expneurol.2016.05.017.
17. Darnall RA. The role of CO(2) and central chemoreception in the control of breathing in the fetus and the neonate. Respir Physiol Neurobiol. 2010;173(3):201–12. https://doi.org/10.1016/j.resp.2010.04.009.
18. Harding R, Hooper SB. Regulation of lung expansion and lung growth before birth. J Appl Physiol (1985). 1996;81(1):209–24. https://doi.org/10.1152/jappl.1996.81.1.209.
19. Boddy K, Dawes GS. Fetal breathing. Br Med Bull. 1975;31(1):3–7.
20. Patrick J, Campbell K, Carmichael L, Natale R, Richardson B. A definition of human fetal apnea and the distribution of fetal apneic intervals during the last ten weeks of pregnancy. Am J Obstet Gynecol. 1980;136(4):471–7.
21. Cosmi EV, Anceschi MM, Cosmi E, Piazze JJ, La Torre R. Ultrasonographic patterns of fetal breathing movements in normal pregnancy. Int J Gynaecol Obstet. 2003;80(3):285–90.
22. Gustafson KM, Allen JJ, Yeh HW, May LE. Characterization of the fetal diaphragmatic magnetomyogram and the effect of breathing movements on cardiac metrics of rate and variability. Early Hum Dev. 2011;87(7):467–75. https://doi.org/10.1016/j.earlhumdev.2011.03.012.
23. Mirmiran M, Maas YG, Ariagno RL. Development of fetal and neonatal sleep and circadian rhythms. Sleep Med Rev. 2003;7(4):321–34.
24. Ioffe S, Jansen AH, Russell BJ, Chernick V. Sleep, wakefulness and the monosynaptic reflex in fetal and newborn lambs. Pflugers Arch. 1980;388(2):149–57.
25. Rigatto H, Moore M, Cates D. Fetal breathing and behavior measured through a double-wall Plexiglas window in sheep. J

Appl Physiol (1985). 1986;61(1):160–4. https://doi.org/10.1152/jappl.1986.61.1.160.
26. Dawes GS, Fox HE, Leduc BM, Liggins GC, Richards RT. Respiratory movements and rapid eye movement sleep in the foetal lamb. J Physiol. 1972;220(1):119–43.
27. Dawes GS, Gardner WN, Johnston BM, Walker DW. Breathing in fetal lambs: the effect of brain stem section. J Physiol. 1983;335:535–53.
28. Johnston BM, Gluckman PD. Lateral pontine lesions affect central chemosensitivity in unanesthetized fetal lambs. J Appl Physiol (1985). 1989;67(3):1113–8. https://doi.org/10.1152/jappl.1989.67.3.1113.
29. Johnston BM, Gluckman PD. Peripheral chemoreceptors respond to hypoxia in pontine-lesioned fetal lambs in utero. J Appl Physiol (1985). 1993;75(3):1027–34. https://doi.org/10.1152/jappl.1993.75.3.1027.
30. Bocking AD. Assessment of fetal heart rate and fetal movements in detecting oxygen deprivation in-utero. Eur J Obstet Gynecol Reprod Biol. 2003;110 Suppl 1:S108–12.
31. Allen CL, Kisilevsky BS. Fetal behavior in diabetic and nondiabetic pregnant women: an exploratory study. Dev Psychobiol. 1999;35(1):69–80.
32. Kisilevsky BS, Hains SM, Low JA. Maturation of body and breathing movements in 24-33 week-old fetuses threatening to deliver prematurely. Early Hum Dev. 1999;55(1):25–38.
33. Honest H, Bachmann LM, Sengupta R, Gupta JK, Kleijnen J, Khan KS. Accuracy of absence of fetal breathing movements in predicting preterm birth: a systematic review. Ultrasound Obstet Gynecol. 2004;24(1):94–100. https://doi.org/10.1002/uog.1062.
34. Blanco CE, Dawes GS, Hanson MA, McCooke HB. The response to hypoxia of arterial chemoreceptors in fetal sheep and new-born lambs. J Physiol. 1984;351:25–37.
35. Boddy K, Dawes GS, Fisher R, Pinter S, Robinson JS. Foetal respiratory movements, electrocortical and cardiovascular responses to hypoxaemia and hypercapnia in sheep. J Physiol. 1974;243(3):599–618.
36. Koos BJ, Sameshima H, Power GG. Fetal breathing, sleep state, and cardiovascular responses to graded anemia in sheep. J Appl Physiol (1985). 1987;63(4):1463–8. https://doi.org/10.1152/jappl.1987.63.4.1463.
37. Moore PJ, Parkes MJ, Nijhuis JG, Hanson MA. The incidence of breathing movements of fetal sheep in normoxia and hypoxia after peripheral chemodenervation and brain-stem transection. J Dev Physiol. 1989;11(3):147–51.
38. Kuipers IM, Maertzdorf WJ, De Jong DS, Hanson MA, Blanco CE. The effect of hypercapnia and hypercapnia associated with central cooling on breathing in unanesthetized fetal lambs. Pediatr Res. 1997;41(1):90–5. https://doi.org/10.1203/00006450-199704001-00548.
39. Jansen AH, Ioffe S, Russell BJ, Chernick V. Influence of sleep state on the response to hypercapnia in fetal lambs. Respir Physiol. 1982;48(1):125–42.
40. Ali K, Rosser T, Bhat R, Wolff K, Hannam S, Rafferty GF, Greenough A. Antenatal smoking and substance-misuse, infant and newborn response to hypoxia. Pediatr Pulmonol. 2017;52(5):650–5. https://doi.org/10.1002/ppul.23620.
41. Fournier S, Steele S, Julien C, Fournier S, Gulemetova R, Caravagna C, Soliz J, Bairam A, Kinkead R. Gestational stress promotes pathological apneas and sex-specific disruption of respiratory control development in newborn rat. J Neurosci. 2013;33(2):563–73. https://doi.org/10.1523/JNEUROSCI.1214-12.2013.
42. Johnson SM, Randhawa KS, Epstein JJ, Gustafson E, Hocker AD, Huxtable AG, Baker TL, Watters JJ. Gestational intermittent hypoxia increases susceptibility to neuroinflammation and alters respiratory motor control in neonatal rats. Respir Physiol Neurobiol. 2018;256:128–42. https://doi.org/10.1016/j.resp.2017.11.007.
43. Delhaes F, Fournier S, Tolsa JF, Peyter AC, Bairam A, Kinkead R. Consequences of gestational stress on GABAergic modulation of respiratory activity in developing newborn pups. Respir Physiol Neurobiol. 2014;200:72–9. https://doi.org/10.1016/j.resp.2014.05.015.
44. Eichenwald EC, Committee on F, Newborn AAoP. Apnea of prematurity. Pediatrics. 2016;137(1) https://doi.org/10.1542/peds.2015-3757.
45. Di Fiore JM, Poets CF, Gauda E, Martin RJ, MacFarlane P. Cardiorespiratory events in preterm infants: interventions and consequences. J Perinatol. 2016;36(4):251–8. https://doi.org/10.1038/jp.2015.165.
46. Mortola JP. Dynamics of breathing in newborn mammals. Physiol Rev. 1987;67(1):187–243. https://doi.org/10.1152/physrev.1987.67.1.187.
47. Curzi-Dascalova L. Physiological correlates of sleep development in premature and full-term neonates. Neurophysiol Clin. 1992;22(2):151–66.
48. Lehtonen L, Martin RJ. Ontogeny of sleep and awake states in relation to breathing in preterm infants. Semin Neonatol. 2004;9(3):229–38. https://doi.org/10.1016/j.siny.2003.09.002.
49. Bennet L, Walker DW, Horne RSC. Waking up too early – the consequences of preterm birth on sleep development. J Physiol. 2018;596(23):5687–708. https://doi.org/10.1113/JP274950.
50. Gaultier C. Cardiorespiratory adaptation during sleep in infants and children. Pediatr Pulmonol. 1995;19(2):105–17.
51. Edwards BA, Sands SA, Berger PJ. Postnatal maturation of breathing stability and loop gain: the role of carotid chemoreceptor development. Respir Physiol Neurobiol. 2013;185(1):144–55. https://doi.org/10.1016/j.resp.2012.06.003.
52. Fleming PJ, Goncalves AL, Levine MR, Woollard S. The development of stability of respiration in human infants: changes in ventilatory responses to spontaneous sighs. J Physiol. 1984;347:1–16.
53. Sovik S, Lossius K. Development of ventilatory response to transient hypercapnia and hypercapnic hypoxia in term infants. Pediatr Res. 2004;55(2):302–9. https://doi.org/10.1203/01.PDR.0000106316.40213.DB.
54. Sovik S, Lossius K, Eriksen M, Grogaard J, Walloe L. Development of oxygen sensitivity in infants of smoking and non-smoking mothers. Early Hum Dev. 1999;56(2–3):217–32.
55. Waggener TB, Frantz ID 3rd, Stark AR, Kronauer RE. Oscillatory breathing patterns leading to apneic spells in infants. J Appl Physiol Respir Environ Exerc Physiol. 1982;52(5):1288–95. https://doi.org/10.1152/jappl.1982.52.5.1288.
56. Edwards BA, Nava-Guerra L, Kemp JS, Carroll JL, Khoo MC, Sands SA, Terrill PI, Landry SA, Amin RS. Assessing ventilatory instability using the response to spontaneous sighs during sleep in preterm infants. Sleep. 2018;41(11) https://doi.org/10.1093/sleep/zsy161.
57. Barrington KJ, Finer NN, Wilkinson MH. Progressive shortening of the periodic breathing cycle duration in normal infants. Pediatr Res. 1987;21(3):247–51. https://doi.org/10.1203/00006450-198703000-00008.
58. Carse EA, Wilkinson AR, Whyte PL, Henderson-Smart DJ, Johnson P. Oxygen and carbon dioxide tensions, breathing and heart rate in normal infants during the first six months of life. J Dev Physiol. 1981;3(2):85–100.
59. Hoppenbrouwers T, Harper RM, Hodgman JE, Sterman MB, McGinty DJ. Polygraphic studies on normal infants during the first six months of life. II. Respiratory rate and variability as a function of state. Pediatr Res. 1978;12(2):120–5. https://doi.org/10.1203/00006450-197802000-00011.

60. Rigatto H, Kalapesi Z, Leahy FN, Durand M, MacCallum M, Cates D. Ventilatory response to 100% and 15% O2 during wakefulness and sleep in preterm infants. Early Hum Dev. 1982;7(1):1–10.
61. Kalapesi Z, Durand M, Leahy FN, Cates DB, MacCallum M, Rigatto H. Effect of periodic or regular respiratory pattern on the ventilatory response to low inhaled CO2 in preterm infants during sleep. Am Rev Respir Dis. 1981;123(1):8–11. https://doi.org/10.1164/arrd.1981.123.1.8.
62. Horne RSC, Sun S, Yiallourou SR, Fyfe KL, Odoi A, Wong FY. Comparison of the longitudinal effects of persistent periodic breathing and apnoea on cerebral oxygenation in term- and preterm-born infants. J Physiol. 2018;596(23):6021–31. https://doi.org/10.1113/JP275686.
63. Glotzbach SF, Baldwin RB, Lederer NE, Tansey PA, Ariagno RL. Periodic breathing in preterm infants: incidence and characteristics. Pediatrics. 1989;84(5):785–92.
64. Eichenwald EC, Aina A, Stark AR. Apnea frequently persists beyond term gestation in infants delivered at 24 to 28 weeks. Pediatrics. 1997;100(3 Pt 1):354–9.
65. Henderson-Smart DJ. The effect of gestational age on the incidence and duration of recurrent apnoea in newborn babies. Aust Paediatr J. 1981;17(4):273–6. https://doi.org/10.1111/j.1440-1754.1981.tb01957.x.
66. Davies AM, Koenig JS. Thach BT (1988) upper airway chemoreflex responses to saline and water in preterm infants. J Appl Physiol. 1985;64(4):1412–20. https://doi.org/10.1152/jappl.1988.64.4.1412.
67. Reis FJ, Cates DB, Landriault LV, Rigatto H. Diaphragmatic activity and ventilation in preterm infants. I. The effects of sleep state. Biol Neonate. 1994;65(1):16–24. https://doi.org/10.1159/000244022.
68. Ramanathan R, Corwin MJ, Hunt CE, Lister G, Tinsley LR, Baird T, Silvestri JM, Crowell DH, Hufford D, Martin RJ, Neuman MR, Weese-Mayer DE, Cupples LA, Peucker M, Willinger M, Keens TG, Collaborative Home Infant Monitoring Evaluation Study G. Cardiorespiratory events recorded on home monitors: comparison of healthy infants with those at increased risk for SIDS. JAMA. 2001;285(17):2199–207. https://doi.org/10.1001/jama.285.17.2199.
69. Abu-Shaweesh JM. Maturation of respiratory reflex responses in the fetus and neonate. Semin Neonatol. 2004;9(3):169–80. https://doi.org/10.1016/j.siny.2003.09.003.
70. Horne RS, Parslow PM, Harding R. Postnatal development of ventilatory and arousal responses to hypoxia in human infants. Respir Physiol Neurobiol. 2005;149(1–3):257–71. https://doi.org/10.1016/j.resp.2005.03.006.
71. Martin RJ, DiFiore JM, Jana L, Davis RL, Miller MJ, Coles SK, Dick TE. Persistence of the biphasic ventilatory response to hypoxia in preterm infants. J Pediatr. 1998;132(6):960–4.
72. Bissonnette JM. Mechanisms regulating hypoxic respiratory depression during fetal and postnatal life. Am J Physiol Regul Integr Comp Physiol. 2000;278(6):R1391–400. https://doi.org/10.1152/ajpregu.2000.278.6.R1391.
73. Carroll JL. Developmental plasticity in respiratory control. J Appl Physiol (1985). 2003;94(1):375–89. https://doi.org/10.1152/japplphysiol.00809.2002.
74. Teppema LJ, Dahan A. The ventilatory response to hypoxia in mammals: mechanisms, measurement, and analysis. Physiol Rev. 2010;90(2):675–754. https://doi.org/10.1152/physrev.00012.2009.
75. Darnall RA, Ariagno RL, Kinney HC. The late preterm infant and the control of breathing, sleep, and brainstem development: a review. Clin Perinatol. 2006;33(4):883–914; abstract x. https://doi.org/10.1016/j.clp.2006.10.004.
76. Richardson HL, Parslow PM, Walker AM, Harding R, Horne RS. Maturation of the initial ventilatory response to hypoxia in sleeping infants. J Sleep Res. 2007;16(1):117–27. https://doi.org/10.1111/j.1365-2869.2007.00575.x.
77. Parslow PM, Harding R, Cranage SM, Adamson TM, Horne RS. Ventilatory responses preceding hypoxia-induced arousal in infants: effects of sleep-state. Respir Physiol Neurobiol. 2003;136(2–3):235–47.
78. Johnston RV, Grant DA, Wilkinson MH, Walker AM. Repetitive hypoxia rapidly depresses cardio-respiratory responses during active sleep but not quiet sleep in the newborn lamb. J Physiol. 1999;519(Pt 2):571–9.
79. Gauda EB, Carroll JL, Donnelly DF. Developmental maturation of chemosensitivity to hypoxia of peripheral arterial chemoreceptors--invited article. Adv Exp Med Biol. 2009;648:243–55. https://doi.org/10.1007/978-90-481-2259-2_28.
80. Bairam A, Carroll JL. Neurotransmitters in carotid body development. Respir Physiol Neurobiol. 2005;149(1–3):217–32. https://doi.org/10.1016/j.resp.2005.04.017.
81. Bairam A, Niane LM, Joseph V. Role of ATP and adenosine on carotid body function during development. Respir Physiol Neurobiol. 2013;185(1):57–66. https://doi.org/10.1016/j.resp.2012.06.016.
82. Benarroch EE. Brainstem respiratory chemosensitivity: new insights and clinical implications. Neurology. 2007;68(24):2140–3. https://doi.org/10.1212/01.wnl.0000266560.60371.98.
83. Rigatto H, Brady JP, de la Torre VR. Chemoreceptor reflexes in preterm infants: II. The effect of gestational and postnatal age on the ventilatory response to inhaled carbon dioxide. Pediatrics. 1975;55(5):614–20.
84. Marchal F, Bairam A, Haouzi P, Crance JP, Di Giulio C, Vert P, Lahiri S. Carotid chemoreceptor response to natural stimuli in the newborn kitten. Respir Physiol. 1992;87(2):183–93.
85. Carroll JL, Bamford OS, Fitzgerald RS. Postnatal maturation of carotid chemoreceptor responses to O2 and CO2 in the cat. J Appl Physiol (1985). 1993;75(6):2383–91. https://doi.org/10.1152/jappl.1993.75.6.2383.
86. Di Fiore JM, Arko MK, Miller MJ, Krauss A, Betkerur A, Zadell A, Kenney SR, Martin RJ. Cardiorespiratory events in preterm infants referred for apnea monitoring studies. Pediatrics. 2001;108(6):1304–8.
87. Al-Matary A, Kutbi I, Qurashi M, Khalil M, Alvaro R, Kwiatkowski K, Cates D, Rigatto H. Increased peripheral chemoreceptor activity may be critical in destabilizing breathing in neonates. Semin Perinatol. 2004;28(4):264–72.
88. Katz-Salamon M. Delayed chemoreceptor responses in infants with apnoea. Arch Dis Child. 2004;89(3):261–6.
89. Sands SA, Edwards BA, Kelly VJ, Skuza EM, Davidson MR, Wilkinson MH, Berger PJ. Mechanism underlying accelerated arterial oxygen desaturation during recurrent apnea. Am J Respir Crit Care Med. 2010;182(7):961–9. https://doi.org/10.1164/rccm.201003-0477OC.
90. Gerhardt T, Bancalari E. Apnea of prematurity: II. Respiratory reflexes. Pediatrics. 1984;74(1):63–6.
91. Durand M, Cabal LA, Gonzalez F, Georgie S, Barberis C, Hoppenbrouwers T, Hodgman JE. Ventilatory control and carbon dioxide response in preterm infants with idiopathic apnea. Am J Dis Child. 1985;139(7):717–20.
92. Rigatto H, De La Torre VR, Gates DB. Effects of O2 on the ventilatory response to CO2 in preterm infants. J Appl Physiol. 1975;39(6):896–9. https://doi.org/10.1152/jappl.1975.39.6.896.
93. Cardot V, Chardon K, Tourneux P, Micallef S, Stephan E, Leke A, Bach V, Libert JP, Telliez F. Ventilatory response to a hyperoxic test is related to the frequency of short apneic episodes in late preterm neonates. Pediatr Res. 2007;62(5):591–6. https://doi.org/10.1203/PDR.0b013e318155868e.
94. Nock ML, Difiore JM, Arko MK, Martin RJ. Relationship of the ventilatory response to hypoxia with neonatal apnea in preterm

infants. J Pediatr. 2004;144(3):291–5. https://doi.org/10.1016/j.jpeds.2003.11.035.
95. Peng YJ, Rennison J, Prabhakar NR. Intermittent hypoxia augments carotid body and ventilatory response to hypoxia in neonatal rat pups. J Appl Physiol (1985). 2004;97(5):2020–5. https://doi.org/10.1152/japplphysiol.00876.2003.
96. Bavis RW, MacFarlane PM. Developmental plasticity in the neural control of breathing. Exp Neurol. 2017;287(Pt 2):176–91. https://doi.org/10.1016/j.expneurol.2016.05.032.
97. Pawar A, Peng YJ, Jacono FJ, Prabhakar NR. Comparative analysis of neonatal and adult rat carotid body responses to chronic intermittent hypoxia. J Appl Physiol (1985). 2008;104(5):1287–94. https://doi.org/10.1152/japplphysiol.00644.2007.
98. Julien C, Bairam A, Joseph V. Chronic intermittent hypoxia reduces ventilatory long-term facilitation and enhances apnea frequency in newborn rats. Am J Physiol Regul Integr Comp Physiol. 2008;294(4):R1356–66. https://doi.org/10.1152/ajpregu.00884.2007.
99. Julien CA, Joseph V, Bairam A. Alteration of carotid body chemoreflexes after neonatal intermittent hypoxia and caffeine treatment in rat pups. Respir Physiol Neurobiol. 2011;177(3):301–12. https://doi.org/10.1016/j.resp.2011.05.006.
100. Bavis RW, Millstrom AH, Kim SM, MacDonald CA, O'Toole CA, Asklof K, McDonough AB. Combined effects of intermittent hyperoxia and intermittent hypercapnic hypoxia on respiratory control in neonatal rats. Respir Physiol Neurobiol. 2019;260:70–81. https://doi.org/10.1016/j.resp.2018.11.002.
101. Perrone S, Negro S, Tataranno ML, Buonocore G. Oxidative stress and antioxidant strategies in newborns. J Matern Fetal Neonatal Med. 2010;23 Suppl 3:63–5. https://doi.org/10.3109/14767058.2010.509940.
102. Perrone S, Tataranno LM, Stazzoni G, Ramenghi L, Buonocore G. Brain susceptibility to oxidative stress in the perinatal period. J Matern Fetal Neonatal Med. 2015;28 Suppl 1:2291–5. https://doi.org/10.3109/14767058.2013.796170.
103. Gauda EB, Master Z. Contribution of relative leptin and adiponectin deficiencies in premature infants to chronic intermittent hypoxia: exploring a new hypothesis. Respir Physiol Neurobiol. 2017; https://doi.org/10.1016/j.resp.2017.12.003.
104. Chavez Valdez R, Ahlawat R, Wills-Karp M, Nathan A, Ezell T, Gauda EB. Correlation between serum caffeine levels and changes in cytokine profile in a cohort of preterm infants. J Pediatr. 2011;158(1):57–64, 64 e51. https://doi.org/10.1016/j.jpeds.2010.06.051.
105. Kinney HC, Thach BT. The sudden infant death syndrome. N Engl J Med. 2009;361(8):795–805. https://doi.org/10.1056/NEJMra0803836.
106. Mage DT, Donner EM. The fifty percent male excess of infant respiratory mortality. Acta Paediatr. 2004;93(9):1210–5.
107. Wang LW, Lin YC, Wang ST, Huang CC, on behalf of the Taiwan Premature Infant Developmental Collaborative Study G. Identifying risk factors shared by bronchopulmonary dysplasia, severe retinopathy, and cystic periventricular leukomalacia in very preterm infants for targeted intervention. Neonatology. 2018;114(1):17–24. https://doi.org/10.1159/000487505.
108. Bairam A, Laflamme N, Drolet C, Piedboeuf B, Shah PS, Kinkead R, Canadian Neonatal Network I. Sex-based differences in apnoea of prematurity: a retrospective cohort study. Exp Physiol. 2018;103(10):1403–11. https://doi.org/10.1113/EP086996.
109. Kouchi H, Uppari N, Joseph V, Bairam A. Sex-specific respiratory effects of acute and chronic caffeine administration in newborn rats. Respir Physiol Neurobiol. 2017;240:8–16. https://doi.org/10.1016/j.resp.2017.01.014.
110. Haddad GG, Epstein RA, Epstein MA, Leistner HL, Marino PA, Mellins RB. Maturation of ventilation and ventilatory pattern in normal sleeping infants. J Appl Physiol Respir Environ Exerc Physiol. 1979;46(5):998–1002. https://doi.org/10.1152/jappl.1979.46.5.998.
111. Parmelee AH, Stern E, Harris MA. Maturation of respiration in prematures and young infants. Neuropadiatrie. 1972;3(3):294–304. https://doi.org/10.1055/s-0028-1091768.
112. Scholle S, Wiater A, Scholle HC. Normative values of polysomnographic parameters in childhood and adolescence: cardiorespiratory parameters. Sleep Med. 2011;12(10):988–96. https://doi.org/10.1016/j.sleep.2011.05.006.
113. Tabachnik E, Muller NL, Bryan AC, Levison H. Changes in ventilation and chest wall mechanics during sleep in normal adolescents. J Appl Physiol Respir Environ Exerc Physiol. 1981;51(3):557–64. https://doi.org/10.1152/jappl.1981.51.3.557.
114. Tabachnik E, Muller NL, Levison H, Bryan AC. Chest wall mechanics and pattern of breathing during sleep in asthmatic adolescents. Am Rev Respir Dis. 1981;124(3):269–73. https://doi.org/10.1164/arrd.1981.124.3.269.
115. Marcus CL, Glomb WB, Basinski DJ, Davidson SL, Keens TG. Developmental pattern of hypercapnic and hypoxic ventilatory responses from childhood to adulthood. J Appl Physiol (1985). 1994;76(1):314–20. https://doi.org/10.1152/jappl.1994.76.1.314.
116. Read DJ. A clinical method for assessing the ventilatory response to carbon dioxide. Australas Ann Med. 1967;16(1):20–32.
117. Rebuck AS, Campbell EJ. A clinical method for assessing the ventilatory response to hypoxia. Am Rev Respir Dis. 1974;109(3):345–50. https://doi.org/10.1164/arrd.1974.109.3.345.
118. Honda Y, Ohyabu Y, Sato M, Masuyama H, Nishibayashi Y, Maruyama R, Tanaka Y, Nakajo I, Shirase H, Hayashida K. Hypercapnic and hypoxic ventilatory responses during growth. Jpn J Physiol. 1986;36(1):177–87. https://doi.org/10.2170/jjphysiol.36.177.
119. Smith JC, Abdala AP, Borgmann A, Rybak IA, Paton JF. Brainstem respiratory networks: building blocks and microcircuits. Trends Neurosci. 2013;36(3):152–62. https://doi.org/10.1016/j.tins.2012.11.004.
120. Potvin C, Rossignol O, Uppari N, Dallongeville A, Bairam A, Joseph V. Reduced hypoxic ventilatory response in newborn mice knocked-out for the progesterone receptor. Exp Physiol. 2014;99(11):1523–37. https://doi.org/10.1113/expphysiol.2014.080986.
121. Marcouiller F, Boukari R, Laouafa S, Lavoie R, Joseph V. The nuclear progesterone receptor reduces post-sigh apneas during sleep and increases the ventilatory response to hypercapnia in adult female mice. PLoS One. 2014;9(6):e100421. https://doi.org/10.1371/journal.pone.0100421.
122. Alvaro R. Control of breathing and apnea of prematurity. NeoReviews. 2018;19(4):e224–34. https://doi.org/10.1542/neo.19-4-e224.
123. Niane L, Bairam A. Selecting representative ages for developmental changes of respiratory irregularities and hypoxic ventilatory response in rats. Open J Mol Integr Physiol. (Website: https://www.scirp.org/journal/OJMIP/ or https://doi.org/10.4236/ojmip.2011.11001.