The Neonatal Neuromechanical Unit: Generalities of Operation

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Educational Aims

- General principles of operation of the neonatal respiratory system examined as a neuromechanical unit, that is, the translation of neural output into mechanical events, and the neurochemical feedback
- Implications of the highly compliant chest wall on the neonatal breathing pattern
- Dynamic elevation of the functional residual capacity: mechanisms and implications
- Importance of hypometabolism in neonatal hypoxia and its implications on the level of pulmonary ventilation

2.1 Generalities

Many examples could be offered to illustrate the concept that the respiratory physiology of the newborn is markedly distinct from that of the adult. Some of the differences are determined by body size, others by the stage of development and maturation, and others yet by the tumultuous events accompanying birth. With respect to body size, the newborn's small body mass reduces the heat capacitance of the body and the high body surface-to-volume ratio favors heat loss. Hence, a large weight (W)-specific metabolic rate is required to offset the propensity for hypothermia. This translates into high values of oxygen uptake ($\dot{V}_{O_2}/kg$), which imply a proportionally large pulmonary ventilation ($\dot{V}_E$), achieved mostly by breathing at high rates. Indeed, fast breathing is a common characteristic of all newborn mammals. With respect to maturation, the development of the lung and respiratory apparatus is never completed at birth, even in the most precocial species. The lungs continue to grow postnatally, in a centripetal direction, with formation of peripheral airways and alveoli, implying that in newborns the central airways comprise a larger proportion of the total air space and contribute to a relatively large anatomical dead space. The incomplete myelinization and low conduction velocity of neural fibers, including those of the laryngeal, vagi, and carotid sinus nerves, limit the afferent sensory information involved in the regulation of breathing. Finally, with respect to the adaptation to air breathing at birth, a multitude of events among the most dramatic of the whole life occur quite rapidly, such as the transition from filtration to absorption of the pulmonary fluid, the drastic changes in pulmonary circulation, and the rise in oxygenation with its implications on the function of the chemoreceptors.

This chapter touches on the general principles of operation of the neonatal respiratory system

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P.C. Rimensberger (ed.), *Pediatric and Neonatal Mechanical Ventilation*,
DOI 10.1007/978-3-642-01219-8_2,

Table. 2.1 Terminology, abbreviations adopted in text, common units

Cw	Chest wall compliance	ΔVolume/ΔPressure
CL	Lung compliance	ΔVolume/ΔPressure
f	Breathing frequency	Breaths/min
FRC	Functional residual capacity	ml
P	Pressure	cm H_2O or mmHg
Pab	Abdominal pressure	cm H_2O
PaO_2	Arterial pressure of oxygen	mmHg
$PACO_2$	Alveolar pressure of carbon dioxide	mmHg
Pdi	Transdiaphragmatic pressure	cm H_2O
PEEP	Positive end-expiratory pressure	cm H_2O
Ppl	Pleural pressure	cm H_2O
T	Tension	dyne/cm
T_E	Expiratory time	s
T_I	Inspiratory time	s
V	Volume	ml
$\dot{V}$	Flow	ml/s
$\dot{V}_A$	Alveolar ventilation	ml/min
$\dot{V}_E$	Pulmonary ventilation	ml/min
$\dot{V}_{O_2}$	Oxygen consumption	ml/min
$\dot{V}_{CO_2}$	Carbon dioxide production	ml/min
V_r	Resting volume of the respiratory system	ml
V_T	Tidal volume	ml
W	Weight	kg

examined as a neuromechanical unit that operates to generate the optimal $\dot{V}_E$ responses by integrating peripheral information with metabolic requirements. The general principles of operation of the neuromechanical unit (that is, translation of neural output into mechanical events, evaluation of the adequacy of $\dot{V}_E$ from neurochemical feedback) are the same throughout the whole postnatal life. However, some functional aspects are peculiar to the neonatal period. The goal of this chapter is to highlight the functional properties characteristics of the newborn. References are not extensive, with preference given to review articles where the interested reader can trace the background information and technical details. A short list of terminology and abbreviations adopted in the text is given in Table 2.1.

2.2 Neural Output

The mechanisms involved in the generation of the neural output responsible for the breathing rhythm are still largely unexplained. Several approaches have attempted to unveil the origin of respiratory rhythmogenesis with reduced preparations, such as brainstem with or without the spinal cord or brainstem slices, commonly from neonatal rats. In vitro, it appears that a respiratory rhythm can be generated in very discrete brainstem regions (Haddad 2003), and the maturation of the putative respiratory centers has been studied extensively (Hilaire and Duron 1999). Nevertheless, discrepancies between the in vitro neural pattern and the natural breathing pattern in vivo are common and difficult to explain (Achard et al. 2005). Partly, these differences could be due to technical issues, adequate oxygenation of the preparation, and modification or abolition of the normal afferent inputs. Partly, they could reflect a fundamental flaw in the assumption that, normally, rhythmogenesis is independent of peripheral metabolic, neural, or chemical inputs. The major obstacle for a unifying interpretation of the results regarding the development of the neonatal network is the lack of an accepted model of respiratory rhythmogenesis.

What are the mechanisms that make breathing a continuous process at birth after the intermittent pattern of the fetal period is an unsolved mystery in perinatal physiology. The number and intensity of stimuli at birth – tactile, pressure, thermal, visual, and acoustic – are large. In addition, internal afferent inputs, like those of the chemoreceptors and of the airway mechanoreceptors, change markedly because of the rapid changes in oxygenation and in transpulmonary pressure. Under controlled experimental conditions, each of the putative stimuli in isolation can be shown to be important in initiating breathing. In fact, it is reasonable to assume that any stimulus can take a dominant role in specific situations (Jansen and Chernick 1991). Arousal, oxygenation, and a general state of stress (Lagercrantz and Slotkin 1986) increase metabolic rate, which by itself (through the increase in CO_2 production) stimulates breathing. Experiments on animal fetuses have indicated that exteriorization and clamping of the chord are not sufficient to trigger

and maintain continuous breathing unless also CO_2 is allowed to rise (reviewed in Mortola 2001). In birds, the trigger, increase, and maintenance of $\dot{V}_E$ at hatching are believed to be caused by the rise of metabolically produced CO_2 (Mortola 2009). Hence, it is quite possible that the risen level in metabolic rate at birth represents the main mechanism sustaining continuous $\dot{V}_E$.

In newborns, the phrenic output is typically an abrupt and short burst of activity with few spikes, quite different from the activity-reach ramp-shaped firing of the adult phrenic nerve. The rapid and short-lasting neural burst leaves little room for fine modulation. Presumably, this is one reason for the fact that in newborns peripheral inputs often play only a course control on the breathing pattern, which is typically irregular and variable. In fact, in the neonatal period peripheral neural afferents, despite being less in number and with lower firing frequency than in adults, can generate quite drastic reflex effects on breathing (2.5.1).

2.3 Translation of Muscle Contraction into Pulmonary Ventilation

The $\dot{V}_E$ generated by the contraction of the respiratory muscle results from three key steps (Fig. 2.1). First, the intrinsic mechanical characteristics of the muscle fibers determine the force that the muscle is able to generate. Then, the force translates into pressure, the magnitude of which depends on the geometrical characteristics of the muscle and the structure over which the force is applied. Finally, the pressure generates airflow and causes changes in lung volume according to the flow-resistive and elastic properties of the respiratory system.

2.3.1 Step 1. Force Generation

For a long time it was suspected that the respiratory muscles of the newborn operate close to the fatigue threshold, as if they were barely capable to fulfill the ventilatory requirements. This view probably stemmed from the observation that breathing in neonates, especially premature infants, often is irregular and interspersed with periods of short apneas. The finding that the so-called "fatigue-resistant" muscle fibers were underrepresented fueled the idea that muscle failure was a contributor to periodic breathing and apneas (Keens et al. 1978; Le Souëf et al. 1988; Watchko et al. 1992; Vazquez et al. 1993). In reality, diaphragm fiber typing does not necessarily correlate with muscle fatigability (Sieck and Fournier 1991), and changes in diaphragmatic activity do not correlate with the infant's periodic breathing or apneas (Nugent and Finley 1985). Studies on newborns of various species have shown the neonatal diaphragm to be at

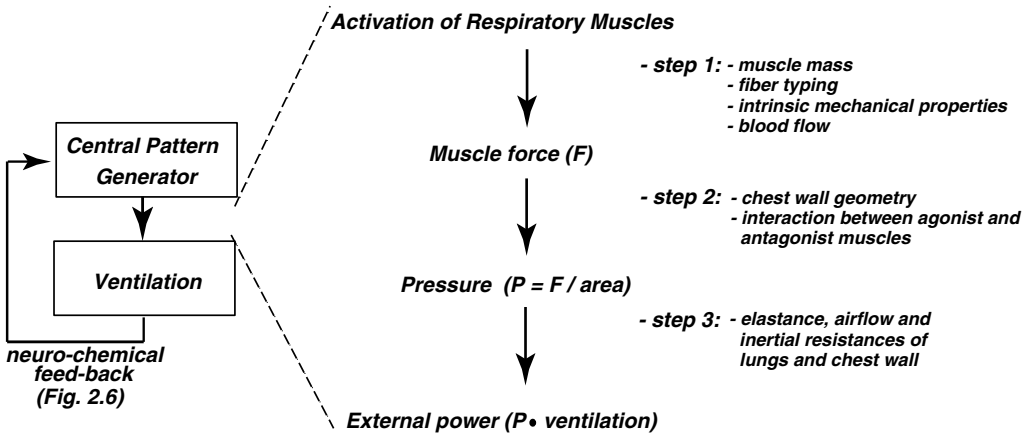

Fig. 2.1 Schematic representation of the neuromechanical unit for the operation of the respiratory system, with a generator, an output, and a feedback control. At right are indicated the main steps involved in the translation of muscle activation into pulmonary ventilation

least as fatigue-resistant as the adult's diaphragm, capable of performing well even in the face of major workloads (Lieberman et al. 1972; Maxwell et al. 1983; Powers et al. 1991). Blood perfusion of the neonatal diaphragm is at least as adequate as it is in adult (Soust et al. 1989; Berger et al. 1994), even at high contraction rates or against resistive loads.

2.3.2 Step 2. Pressure Generation

In mammals, the total mass of the respiratory muscles, in relation to body mass, is almost a fixed proportion irrespective of species and animal age. The force produced by a muscle is proportional to its cross-sectional area, and the resulting pressure is the ratio between the force produced and the surface which the force is applied on. Because of their small size, the neonatal respiratory muscles produce little force by comparison to adults (Sieck et al. 2002). However, the surface over which such force is applied is proportionally small; hence, mammals of all sizes and ages do not differ much in the pleural pressure that their respiratory muscles can generate (Mortola 2001).

The shape of the diaphragmatic dome is an additional factor in the translation of force into pressure. In fact, by application of the Young-Laplace relationship, for a given diaphragmatic tension T, the resulting transdiaphragmatic pressure Pdi[1] depends on the radius of curvature r of the dome ($Pdi = T/r$). In newborns, the fact that r is much smaller than in adults favors the generation of a greater Pdi for a similar T. In conclusion, despite the fact that muscle mass and muscle force are undoubtedly less in newborns than in adults, the tidal swings in pleural pressure (Ppl) are similar at all ages, about 5–7 cm H_2O.[2] If needed, the healthy newborn can generate much higher Ppl values, up to 100 cm H_2O, as is the case during the first inspiration (Mortola 2001). The infant's maximal inspiratory pressures during crying (Shardonofsky et al. 1989) are not much lower than the maximal static inspiratory pressures developed by adults.

Contraction of the diaphragm raises abdominal pressure (Pab). This increase causes the outward motion of the frontal abdominal wall during inspiration and the expansion of the lower portion of the rib cage. The latter occurs because of the mechanical interdependence between the abdomen and rib cage and because Pab gets transmitted to the thoracic wall through the apposition area. The apposition area is the lowermost region of the rib cage that the diaphragmatic dome faces without interposed lungs. In infants, differently from the adult, in inspiration the expansion of the lower rib cage is small because of two reasons. First, the high abdominal compliance limits the rise in Pab during diaphragmatic contraction. Second, the rather rounded shape of the ribs and their almost perpendicular attachment to the vertebral column limit the size of the area of apposition (Allen and Gripp 2002). With growth, the area of apposition increases because of the gradual downward orientation of the ribs, presumably caused by the gravitational pull. The result of this anatomical arrangement is that in newborns the increase in Pab during diaphragmatic contraction does not contribute to the expansion of the lower ribs as much as it does in adults. Switching from the supine to the prone position stiffens the abdomen; in fact, this postural change is functionally equivalent to binding the infant's abdomen and improves diaphragmatic efficiency (Fleming et al. 1979; Guslits et al. 1987; Laing et al. 1988; Wolfson et al. 1992) with positive effects on blood oxygenation (Numa et al. 1997). As an aside, it is interesting to note that the sudden infant death syndrome (SIDS) has a greater prevalence in the prone position (Silvestri and Weese-Mayer 2003). This implies that in the prone position the posture-related factors involved in the physiopathology of SIDS, whatever they may be, more than offset the advantage in the mechanical operation of the respiratory system.

[1] Pdi is the pressure difference between the abdomen and the pleural space, or Pab – Ppl.

[2] For analogous reasons, the tidal pleural pressure swings have similar values in species of very different body size.

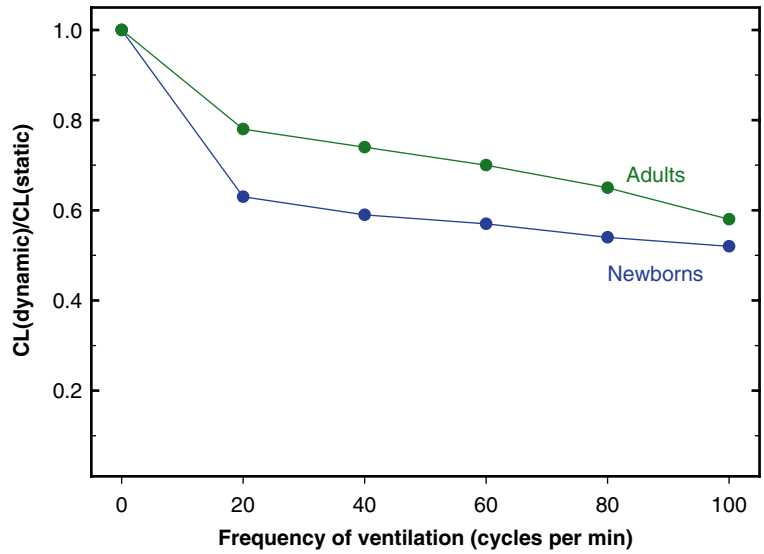

Fig. 2.2 An example of dynamic lung compliance progressively lower than the static value the higher the frequency of ventilation. The phenomenon, often labeled "frequency dependence of compliance," is contributed by the stress relaxation of the pulmonary structures and by peripheral resistance. These experimental data refer to newborn and adult cats (Redrawn from the data of Sullivan and Mortola (1986))

2.3.3 Step 3. Lung and Chest Wall Mechanics

As it is the case for many other internal organs, the W-specific mass of the lung (lung weight-body weight ratio) is large in newborns and decreases during postnatal growth. Despite the large mass, air spaces are still incompletely developed, the pulmonary elastin and collagen contents are low, and during the first postnatal hours or days, some fluid is trapped in the peripheral airways and lung interstitium. All these factors contribute to values of lung compliance (CL, Δvolume/Δpressure) lower in newborns than in adults, when the comparison is made on the basis of lung volume or lung weight. The peripheral inequalities in airway resistance and the viscous properties of the pulmonary tissue prolong the response time of the lungs both in inspiration and in expiration. For these reasons, the differences between dynamic and static CL (and, possibly, the phenomenon of frequency dependence of CL[3]) are more pronounced in newborns than in adults (Fig. 2.2).

The chest wall anatomically and functionally comprises two main compartments, the rib cage (or thorax) and the abdomen-diaphragm. Chest wall compliance (Cw) has been measured in newborns of many species and in infants; the results have been uniform in revealing high values (after normalization by body W) in comparison to the adult. The high Cw in newborns is a structural necessity for the passage through the birth canal. Cw decreases gradually during postnatal growth (Papastamelos et al. 1995), probably because of the stiffening of the cartilaginous structures and changes in abdominal and thoracic configuration.

Because the Cw-CL ratio is a dimensionless parameter, it can be compared directly among individuals of different age or body size, with no needs for normalization. In adult humans, because Cw and CL have similar values, their ratio is approximately equal to one. In infants, Cw is about five times higher than CL (Polgar and Weng 1979). In fact, the high Cw-CL ratio is a characteristic feature of the respiratory system of all neonatal mammals investigated (Mortola 2001). The fact that Cw is so high relative to CL implies that in infants CL is the major determinant of the compliance of the respiratory system (Crs) and that changes in Crs are an excellent indicator of changes in CL. From a practical viewpoint, this is quite convenient because measurements of CL in infancy can be difficult (due to the uncertainties in the measurements of Ppl), while measurements of Crs can be performed easily (England 1988; Wohl 1991; Mortola 2004).

[3] Whereby CL decreases, the faster the ventilation rate.

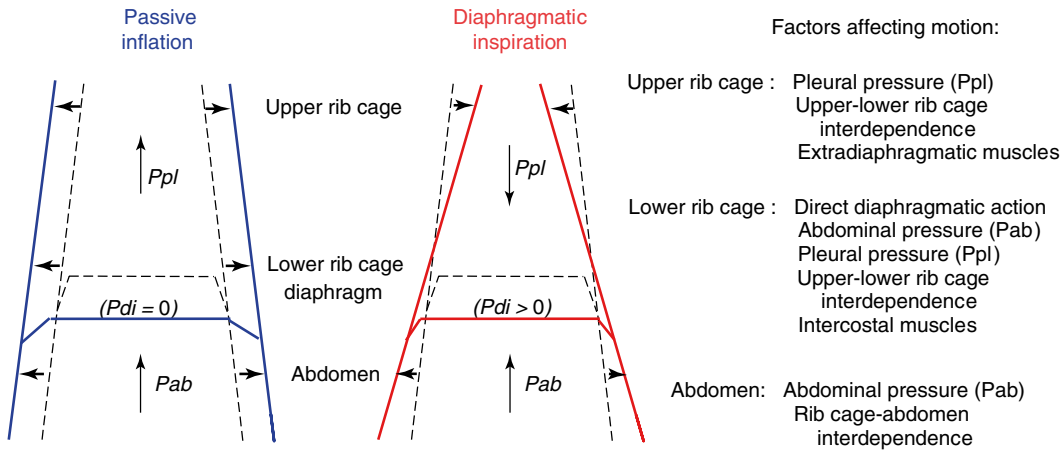

Fig. 2.3 Schematic representation of the two main compartments of the chest wall (*dashed line*), the rib cage and abdomen, separated by the diaphragm. During passive inflation (*panel at left*), the pressure across the diaphragm (transdiaphragmatic pressure, *Pdi*) is zero because the diaphragm is relaxed. In this condition, pleural pressure (*Ppl*) and abdominal pressure (*Pab*) increase by similar amounts, and both compartments expand. When the diaphragm contracts (Pdi>0, *panel at right*), Pab increases and Ppl decreases. The result is that the abdomen expands while the rib cage moves little in its lower portion and caves inward in its upper portion

2.4 Mechanical Constraints and Breathing Pattern

The high Cw-CL ratio of the newborn has two major implications. First, in inspiration, the tendency of the chest wall to distort is greater than in adults. Second, during expiration, the low ratio reduces the outward pull of the chest on the lungs and facilitates lung emptying and a low resting volume of the respiratory system (V_r). These mechanical characteristics have an impact on the neonatal pattern of breathing.

2.4.1 Chest Wall Distortion

In any solid structure, distortion can be defined as a configuration that differs from that requiring minimal energy. In the case of the chest wall, distortion occurs in active conditions (i.e., during respiratory muscle contraction) when the shape deviates from the configuration assumed in the passive situation.[4] This latter is the configuration attained at any lung volume when the respiratory muscles are relaxed, as is the case, for example, during mechanical ventilation. By definition, the occurrence of distortion implies that the respiratory muscles need to spend extra energy to generate a given tidal volume (V_T). In inspiration, distortion is the unavoidable consequence of the location of the diaphragm between the two main chest wall compartments, the abdomen and thorax. In fact, during contraction (i.e., with Pdi>0) the diaphragm operates simultaneously as a positive pressure pump for the abdomen, raising Pab, and as a negative pressure pump for the thorax, lowering Ppl. Therefore, differently from the passive inflation in which Pab and Ppl rise homogeneously and expand both abdomen and thorax, during active inspiration the abdomen expands while the rib cage caves inward (Fig. 2.3). The suction on the rib cage can be appreciated visually in tetraplegic patients, who have no control of the extradiaphragmatic muscles (Mortola and Sant'Ambrogio 1978; Thach et al. 1980). In normal conditions, the tendency to distortion is less in adults than in newborns because adults have a more rigid chest wall and greater compensatory action of the extradiaphragmatic muscles. In newborns, the highly compliant chest wall, the small area of apposition (2.3.2), and the limited mechanical linkage between lower and upper rib

[4] The terms *active* and *passive*, *static* and *dynamic*, refer to the modes of operation of the respiratory system. *Active* and *passive* indicate, respectively, the presence or absence of respiratory muscle contraction. *Static* and *dynamic* indicate, respectively, the absence or presence of airflow.

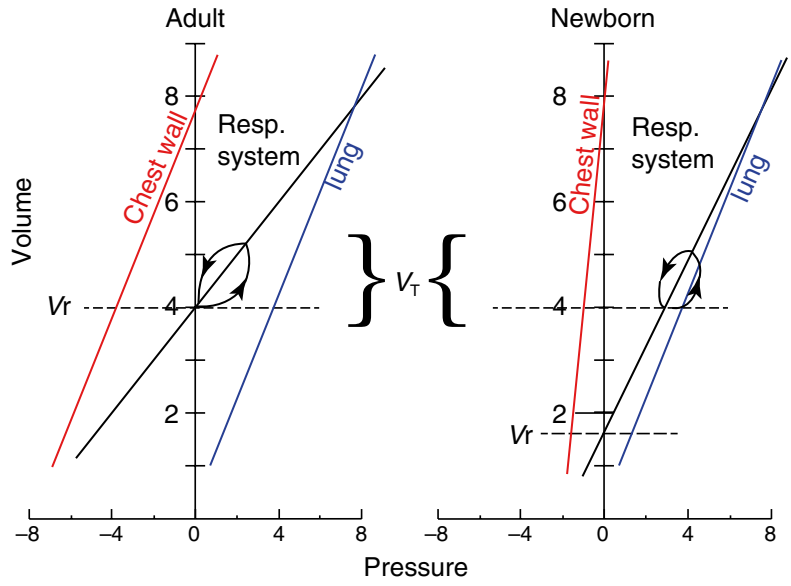

Fig. 2.4 Schematic pressure-volume (P-V) relations of the lungs, chest wall, and respiratory system (*heavy line*) in adult (*left*) and newborn (*right*). For simplicity, the P-V relations are indicated by *straight lines*, the slope of which represents the compliance. At left, the compliance of the chest wall (Cw) is similar to that of the lungs (CL). At right, the Cw-CL ratio is about five times higher. The result is that in the newborn the resting volume of the respiratory system (V_r, *dashed line*) is lower than in adults. Tidal volume (V_T, with inspiratory-expiratory loops indicated by *arrows*) is approximately at the same absolute lung volume in both newborns and adults, because newborns keep their end-expiratory level dynamically elevated

cage are the main factors responsible for chest distortion, of which the most obvious aspect is the paradoxical inward motion of the rib cage during inspiration and expansion in expiration. In addition, the poor activity and mechanical coordination of the intercostals muscles, especially during some phases of sleep (Muller et al. 1979), further contribute to the limited stability of the neonatal thorax.

It is difficult to estimate the energetic price of distortion. Taking the abdominal expansion as an index of diaphragmatic shortening during inspiration, in newborns during resting breathing, chest wall distortion reduces by half the inspiratory efficiency of the diaphragm (Mortola 1995). This means that, in first approximation, to achieve a given V_T, the diaphragm must contract twice as much than it would need had the system expanded along its passive configuration. An additional burden caused by chest distortion is the deformation of the lungs, which reduces CL (Sullivan and Mortola 1985) and probably worsens the ventilation-perfusion matching. As mentioned above (3.2.), the prone position, by stiffening the chest wall, reduces its distortion during inspiration and improves the mechanical efficiency of breathing.

2.4.2 Low Resting Volume: Problems and Solutions

A highly compliant chest wall exerts a lesser outward pull on the lungs than a stiffer chest does, with the result that the passive resting volume of the respiratory system (V_r, the volume at which lungs and chest recoil pressures offset each other) is low (Fig. 2.4). Indeed, V_r (after normalization by lung weight) is lower in newborns than in adults of several species and in infants by comparison to the adult man (Cook et al. 1958; Fisher and Mortola 1980). The fact that V_r is low carries consequences on the functional residual capacity (FRC), which has a prominent role in the efficient operation of the mammalian respiratory system. FRC buffers the oscillations and maintains the stability of the alveolar and arterial gases and is a reserve of oxygen during occasional periods of hypoventilation or apneas. Most important is the fact that inflation of the lungs

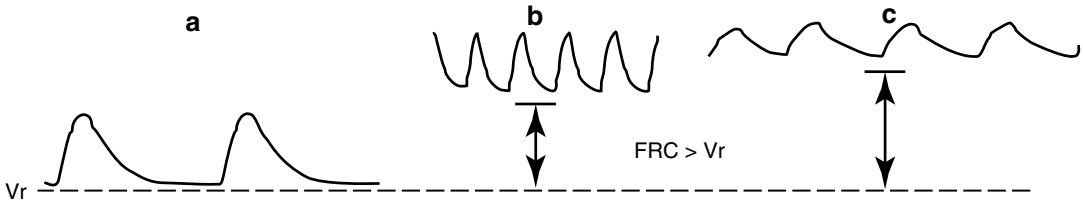

Fig. 2.5 Schematic representation of the dynamic elevation of the end-expiratory level (FRC). (**a**) represents the breathing pattern with expiration ending at resting volume (V_r); this is the common resting pattern of adult humans. (**b**, **c**) Represent patterns commonly seen in infants, in whom FRC is above V_r because of fast breathing (**b**) or because of laryngeal expiratory breaking (**c**)

from FRC requires substantially less pressure than inflation from a collapsed state. In adults during resting breathing, FRC is essentially equal to V_r. Infants, on the contrary, compensate the potentially disadvantageous mechanical situation of the low V_r by keeping FRC dynamically elevated; hence, differently from adults, in infants FRC exceeds V_r (Fig. 2.4).

The core mechanism that permits a dynamic elevation of FRC above V_r is a mismatch between the time needed for expiratory flow (mechanical expiratory time) and the neural expiratory time (T_E), with the former being longer than the latter. In this way, inspiration begins before the air is fully exhaled, causing lung hyperinflation. At least three mechanisms operate to achieve this goal, the post-inspiratory activity of the expiratory muscles, laryngeal braking in expiration, and high breathing frequency (Fig. 2.5). The former two prolong the mechanical T_E and the latter shortens the neural T_E. All of them are operative, either together or individually, in infants (Eichenwald and Stark 2003) and in newborns of many other species (Mortola 2001). In infants, the FRC – V_r difference is 10–15 ml, or about 3 ml/kg. In cases of apnea (long neural T_E) FRC invariably decreases toward V_r. During mechanical ventilation, the presence of an endotracheal tube eliminates the newborn's laryngeal control of expiratory flow; in this case, the application of an end-expiratory load (or positive end-expiratory pressure, PEEP) of a few cm H_2O is necessary to counteract the otherwise unavoidable drop in FRC. This becomes even more necessary in conditions of low CL because of lung disease, which further increases the Cw-CL ratio (Gregory et al. 1971; Berman et al. 1976). In fact, the FRC – V_r difference can be seen as a mechanism that generates an internal PEEP of a few cm H_2O. Although small, this positive airway pressure probably contributes to the absorption of the pulmonary fluid from the alveolar spaces into the lung interstitium during the first hours after birth (Strang 1991).

2.5 Feedback Regulation

Because gas exchange is the primary purpose of breathing, O_2 and CO_2 chemoreceptors could be considered sufficient to provide the pertinent information about the function of the neuromechanical unit (Fig. 2.1). However, although essential, the information on blood gases is not adequate for immediate responses to perturbations on breathing, because of the long delay built in the chemoreceptor feedback system. In fact, chemical feedback operates on a time scale of minutes and is most effective in managing the proper matching between alveolar ventilation ($\dot{V}_A$) and metabolic requirements. A separate and purely neural feedback provides instantaneous information on the status of lung expansion, with reflex responses operational within the breath itself (Fig. 2.6). Some of this feedback originates from airway mechanoreceptors (pulmonary stretch receptors), specifically concerned with the status of lung expansion.[5] Proprioceptors within the respiratory muscles provide additional

[5] The tension in the airway wall is the stimulus for these receptors.

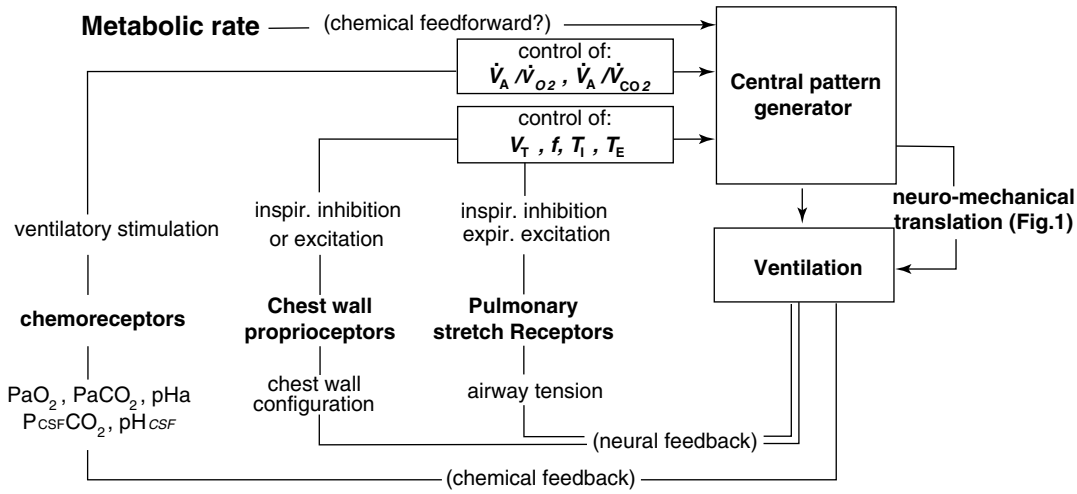

Fig. 2.6 Schema of the main feedback loops regulating breathing. The neural control is a rapid loop primarily concerned with the breathing pattern, tidal volume (V_T), inspiratory (T_I) and expiratory time (T_E), and breathing frequency (f). The chemical control is a slower loop aiming to stabilize oxygen, carbon dioxide, and acid–base in blood and cerebrospinal fluid (CSF), by matching alveolar ventilation ($\dot{V}_A$) to gaseous metabolism (oxygen consumption $\dot{V}_{O_2}$ and carbon dioxide production $\dot{V}_{CO_2}$). Metabolism can provide a feedforward stimulus on ventilation, although this is a controversial issue because no plausible mechanisms for metabolism detection are known

neural information used predominantly to optimize the integration of breathing with non-respiratory functions, posture, and locomotion.

2.5.1 Vagal Feedback

The vagal feedback from the slowly adapting airway receptors is of primary importance in the regulation of the breathing pattern and of lung volume. This rapid neural information is essential for the stability of breathing when the respiratory system is confronted by mechanical loads, such as a reduction in compliance or increase in resistance, or changes in chest configuration, as with changes in body posture or muscle exercise (Milic-Emili and Zin 1986; Daubenspeck 1995).

Many experiments in several species have indicated that in newborns the response to a respiratory load that limits lung expansion happens within one breath, with a compensatory ability at least as efficient as that of adults (Mortola 2001). Premature infants have good reflex compensatory mechanisms (Kosch et al. 1986; Fox et al. 1988). Following lung expansion or during PEEP, breathing becomes slow, a response common to all newborn species investigated, including infants; a similar response has been observed in fetuses (Ponte and Purves 1973). These compensatory responses to respiratory loads or lung inflation are mediated by the vagi nerves; indeed, many animal experiments have shown that bilateral section of the vagi not only causes deeper and slower breathing pattern but also diminishes or abolishes the compensatory responses to mechanical loads. In addition to its role in the regulation of the breathing pattern, the vagal afferent innervation seems to be of crucial importance in the transition from fetal to postnatal life (Lalani et al. 2001). According to some reports, cervical bilateral vagotomy in newborns can cause severe or fatal respiratory insufficiency (Coombs and Pike 1930; Schwieler 1968). One important caveat in the interpretation of these latter experiments, though, is that cervical section of the vagi not only abolishes the afferent information from the airways but also interrupts efferent neural traffic that could have an impact on breathing. For example, vagotomy eliminates the motor control of the larynx via the

recurrent laryngeal nerve, which is important in the control of FRC (2.4.2), and the efferent control of airway smooth muscle, with effects on the activity of the airway receptors (Fisher et al. 2003). In addition, the vagal pulmonary innervation influences the secretion of surfactant and lung compliance.

In newborns, the activity of the pulmonary airway receptors at end expiration and during lung expansion is less than in adults (Fisher et al. 1991). Many neural fibers are of small diameter and are not myelinated, with low conduction velocity (Schwieler 1968; Marlot and Duron 1979; Hasan et al. 1993). As mentioned above (2.2), during the neonatal period the combination of a limited peripheral afferent input with a strong reflex response is not infrequent, and the pulmonary vagal reflexes are one example of this combination. Hypoxia and hyperthermia, either singly or combined, strengthen the vagal reflex inhibition of breathing, a phenomenon that could have some importance in the genesis of breathing irregularities (Mortola 1999).

2.5.2 Extrapulmonary Ventilatory Reflexes

From studies in adult humans and animals, it is clear that stimuli from the most disparate sources – internal (e.g., carotid sinus, bladder and abdominal viscera, nasal, pharyngeal, and laryngeal regions) and external (e.g., visual, tactile, thermal, auditory) – can have reflex effects on breathing. Out of this multitude of extrapulmonary ventilatory reflexes, only a few have been studied with sufficient depth in the neonatal period.

The upper airways are involved in multiple functions; in newborns, reflexes from this area exert mostly inhibitory influences on breathing. Experiments on neonatal mammals have shown that liquids instilled in the pharyngolaryngeal area trigger apneas and bradycardia, the severity of which decreases with postnatal growth. Small $[Cl^-]$, high $[K^+]$, and extreme deviations of the pH of the liquid cause the strongest episodes of apnea (Boggs and Bartlett 1982). Observations in infants, although very limited (Plaxico and Loughlin 1981; Davies et al. 1989; Wennergren et al. 1989), suggest that the results in animals are applicable to the human case and may be part of the reflexes lowering $\dot{V}_E$ during oral feeding (Mathew 2003). Cooling of the laryngeal mucosa or sustained negative pressures in the upper airways are other powerful inhibitory stimuli on breathing (Fisher et al. 1991), responsible for reflex apneas that can persist beyond the removal of the stimulus. The evolutionary significance of the ventilatory inhibition triggered by upper airway reflexes is unclear. The inhibition of breathing may be considered the most obvious response against foreign bodies in the upper airways, irritants, or gastroesophageal reflux. The associated reflexes designed to clear the upper airway passages, like sneezing, coughing, and other responses common in adults, in newborns have modest efficacy (Mortola and Fisher 1988; Chernick 2002).

Gentle touching of the skin can facilitate breathing; presumably, this is one purpose for the maternal grooming and licking of the pups at birth practiced by many mammals. In humans, the skin-to-skin contact between infant and mother ("kangaroo care") seems to reduce apneas and increase the regularity of the breathing pattern (Anderson 1991). However, the reflex response to skin stimulation is not necessarily facilitating breathing, since inhibitory effects, including apnea, have been described (reviewed in Mortola 2001). The large range of responses probably reflects the interplay of numerous factors of difficult control in an experimental setting, the intensity and location of the stimulus, association with other inputs, metabolic condition, state of alertness or sleep stage, etcetera. It seems probable that under normal circumstances, inputs from the chest wall have low priority on the regulation of breathing by comparison to inputs from the lungs and the chemoreceptors.

2.5.3 Chemical Feedback

The O_2 and CO_2 chemoreception important for respiratory control is organized at two sites, the arterial blood (carotid body) and the ventral

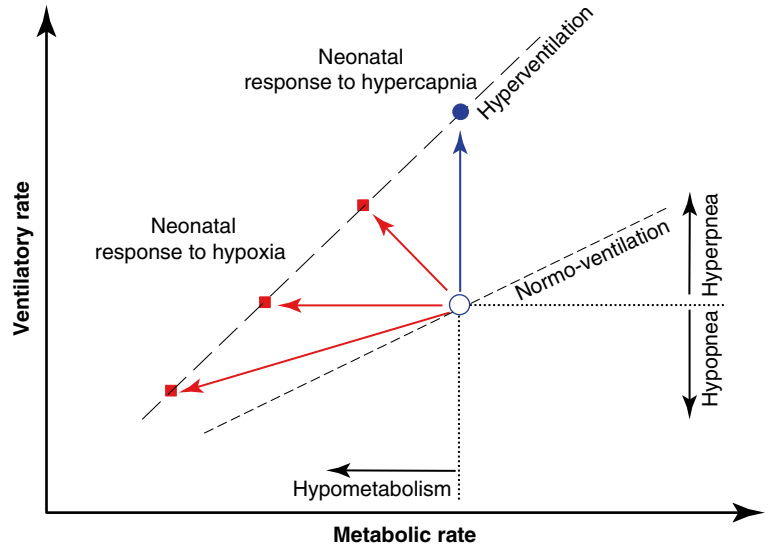

Fig. 2.7 Metabolism-ventilation diagram. The oblique *short-dashed line* joins various combinations of metabolism and ventilation during normo-ventilation, of which the open circle represents one case. Hyperventilation is the increase in the ventilation-metabolism ratio, as represented by the steeper *long-dashed line*. In newborns, hypercapnic hyperventilation (*filled circle*) is obtained by an increase in $\dot{V}_E$ (hyperpnea) with no hypometabolism. Differently, hypoxic hyperventilation is obtained by various combinations of hypometabolism and hyper- or hypopnea (*squares*)

surface of the medulla in close contact with the respiratory neurons. Only the former senses changes in oxygenation by monitoring the arterial partial pressure of O_2 (PaO_2). With some variations, this arrangement is common at all mammals and ages; however, the degree of operation of the receptors and their ventilatory reflexes differ between newborns and adults.

2.5.3.1 Hypoxia

The ventilatory response to hypoxia during the early postnatal period has been the object of extensive investigation after the earliest observations that in newborn infants the hypoxic increase in $\dot{V}_E$ is minimal by comparison to adult humans. In fact, during hypoxia $\dot{V}_E$ can even drop below the normoxic value (e.g., Brady and Ceruti 1966; Cohen et al. 1997; Horne et al. 2005). These results have been confirmed on a large number of neonatal species. The interpretation of the $\dot{V}_E$ response to hypoxia is complex (Mortola 1996; Powell et al. 1998). In newborns, a major factor is the metabolic response to hypoxia, usually quantified as a change in oxygen consumption ($\dot{V}_{O_2}$). Measurements in infants (Brady and Ceruti 1966; Rigatto and Brady 1972) and in neonatal animals have shown that arterial PCO_2 does not increase in hypoxia even when $\dot{V}_E$ is below the normoxic level. The only explanation is that the drop in $\dot{V}_E$ is accompanied by a parallel decrease in metabolism.[6] In fact, many studies have indicated that newborn mammals drop $\dot{V}_{O_2}$ during hypoxia, as reported first in human infants (Cross et al. 1958). Hyperventilation, defined as an increase in the ventilation-metabolism ratio and expressed by the drop in alveolar or arterial PCO_2, equally results from hyperpnea (increase in $\dot{V}_E$) or hypometabolism (drop in $\dot{V}_{O_2}$), in any combination (Fig. 2.7). In adult humans the hyperpnea represents the common way to hyperventilate; in newborns, hypometabolism is the main mechanism to achieve hypoxic hyperventilation, usually with minimal hyperpnea (Mortola 1999). The hypometabolism results from the downregulation of various energy-consuming functions, especially thermogenesis (with a drop in body temperature) and body growth. The benefit of hypoxic hypometabolism is a hypoxic resistance far superior to adults. The physician's failure to recognize hypometabolism as the key strategy adopted by the newborn to cope with hypoxia can lead to unnecessary or mistaken interventions on the infant's ventilation and body temperature.

[6] In fact, $PaCO_2$ is in equilibrium with the alveolar pressure of CO_2 ($PACO_2$), which, for a given barometric pressure Pb, is solely determined by the ratio between CO_2 production ($\dot{V}_{CO_2}$) and alveolar ventilation ($\dot{V}_A$), according to the alveolar gas equation $PACO_2 = \left(\dot{V}_{CO_2}/\dot{V}_A\right) \cdot Pb$.

Recordings from neural afferent fibers of the carotid sinus nerve or from its cell bodies in the sensory petrosal ganglion have indicated that the carotid body is tonically active in newborns and probably in the fetus (Mulligan 1991). However, neither the tonic activity at resting PaO_2 nor the carotid body neural afferent response to hypoxia or hypercapnia is as marked as at older ages (Carroll et al. 1993). During maintained hypoxia, the excitation of the carotid sinus nerve is sustained over time, even when the ventilatory output is declining; this indicates that the modest or absent hyperpnea of the hypoxic newborn cannot be attributed to adaptation of the chemoreceptors. Hyperoxia lowers or completely silences the tonic activity of the carotid body. The rapid oxygenation at birth in the transition from the fetal to postnatal life probably saturates the chemoreceptors and silences them temporarily, until they gradually reset to the postnatal value of PaO_2.

Chemodenervation, either surgically or functionally induced by hyperoxia, reduces $\dot{V}_E$ and causes irregularities in breathing. Whether or not the absence of this peripheral chemo-feedback in the newborn results in severe respiratory insufficiency and eventually death is unclear; in fact, experimental studies have produced conflicting results (reviewed in Mortola 2001).

2.5.3.2 Hypercapnia

All newborn species investigated respond to hypercapnia with hyperpneic hyperventilation (absolute increase in $\dot{V}_E$, Fig. 2.7), although the postnatal temporal evolution of the response may vary from species to species (Putnam et al. 2005). The neonatal hypercapnic response has two qualitative differences from the hypoxic response. First, the hyperventilation is entirely contributed by the hyperpnea even in those newborns that do not increase $\dot{V}_E$ in hypoxia, with minimal changes in $\dot{V}_{O_2}$. Second, the hyperpnea is characterized predominantly by an increase in V_T in both animals and human infants (Brady and Dunn 1970; Haddad et al. 1980; Martin et al. 1985; Mortola and Lanthier 1996), contrary to the shallow and rapid breathing of the response to hypoxia.

After peripheral chemodenervation, the $\dot{V}_E$ response to CO_2 is still present, meaning that the chemoreceptors located centrally close to the medulla are functional (Purves 1966). Other approaches, on the whole animal or in reduced preparations, have confirmed that the central chemosensory areas are active in the newborn and that are responsive to changes in CO_2 and pH (Wolsink et al. 1991; Issa and Remmers 1992; Wennergren and Wennergren 1980, 1983; Whittaker et al. 1990). With CO_2 exposure, neurons expressing Fos-protein, taken as a marker of the immediate early gene c-Fos, were found in the ventrolateral medulla of neonatal rats; the incidence of these neurons was not lower than in older rats (Belegu et al. 1999). All together, these and other observations indicate that the central chemosensory area is active since birth and probably in the late fetal phases (Nattie 1991) and that the $\dot{V}_E$ response to its stimulation is, at least qualitatively, similar to the adult.

Conclusions

As mentioned at the onset of this chapter, respiratory physiology in the neonate differs from that of the adult in many aspects intertwined in a complex web. Any arbitrary attempt to point at just a few of them is bound to be restrictive and superficial. Nevertheless, after having focused our attention to the generation of mechanical output and the feedback operation, in the opinion of this author, the most fundamental peculiarities of the neuromechanical unit in the neonatal period can be summarized as follows:

(a) The high Cw (and high Cw-CL ratio) is a functional characteristic responsible for the low V_r, with consequences on inspiration (chest distortion and extra inspiratory work) and expiration (dynamic elevation of FRC).
(b) The low number of myelinated fibers (small conduction velocity) in the vagus, laryngeal, and carotid sinus nerves limits the effectiveness of peripheral feedback control.
(c) The abrupt and brief burst of neural output activity contributes to the fact that changes

in feedback information produce rather course changes in amplitude and duration of inspiration. This could contribute to the variable breathing pattern and to the apparent paradox that in newborns, despite (b), peripheral inputs can provoke dramatic effects on $\dot{V}_E$.

(d) During hypoxia, the hypometabolism is a neonatal strategy of fundamental importance and great effectiveness. It has implications on the control of the set point of body temperature and permits adequate hyperventilation with minimal hyperpnea.

Essentials to Remember

- In infancy, chest wall compliance (Cw) relative to lung compliance (CL) is higher than in adults. A useful practical consequence is that measurements of the compliance of the respiratory system (which can be performed easily both during spontaneous breathing and mechanical ventilation) are excellent indicators of CL.
- During mechanical ventilation, the presence of an endotracheal tube eliminates the newborn's laryngeal control of expiratory flow; in this case, the application of an end-expiratory load (or positive end-expiratory pressure) of a few cm H_2O is necessary to counteract the otherwise unavoidable drop in end-expiratory volume. This becomes even more necessary with lung diseases that lower CL and further increase the Cw-CL ratio.
- In the neonatal period, peripheral neural afferents, despite being less in number and with lower firing frequency than in adults, can generate drastic reflex effects on breathing. During mechanical ventilation, reflex inhibition on inspiration originates from the distention of the lungs and central airways, especially at elevated PEEP. The reflex inhibition on breathing may be desirable to eliminate infant-ventilator interaction, but may be misleading in assessing the infant's capacity for spontaneous breathing.
- Liquids instilled in the pharyngolaryngeal area trigger apneas and bradycardia, especially at the youngest ages.
- In newborn infants, hypoxia decreases metabolic rate much more readily than it does in adults. This metabolic drop lowers the inspiratory output and the level of pulmonary ventilation and is often accompanied by a decrease in thermogenesis and body temperature. Failure to recognize hypometabolism as the key strategy adopted by the newborn to cope with hypoxia can lead to unnecessary or mistaken interventions on the infant's ventilation and body temperature.

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http://www.springer.com/978-3-642-01218-1

Pediatric and Neonatal Mechanical Ventilation
From Basics to Clinical Practice
Rimensberger, P. (Ed.)
2015, X, 1642 p. 405 illus., 109 illus. in color.,
Hardcover
ISBN: 978-3-642-01218-1