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How to breathe? Respiratory mechanics and breathing pattern

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ABSTRACT

On theoretical grounds any given level of pulmonary or alveolar ventilation can be obtained at various absolute lung volumes and through many combinations of tidal volume, breathing frequency and inspiratory and expiratory timing. However, inspection of specific cases of newborn and adult mammals at rest indicates that the breathing pattern reflects a principle of economy oriented toward minimal respiratory work. The mechanisms that permit optimization of respiratory cost are poorly understood; yet, it is their efficiency and coordination that permits pulmonary ventilation at rest to require only a minimal fraction of resting metabolism. The sensitivity of the breathing pattern to the mechanical properties implies that tidal volume, breathing rate, mean inspiratory flow or other ventilatory parameters cannot be necessarily considered indicators proportional to the central neural respiratory 'drive'. The broad conclusion is that the breathing pattern adopted by newborn and adult mammals is the one that produces the adequate alveolar ventilation with minimal cost, that is, in full recognition of the mechanical characteristics of the system.

1. Introduction

This article considers aspects of respiratory mechanics in newborns and adults, the constraints that they may impose on the breathing pattern and which pattern eventually best accommodates the mechanical characteristics, presumably, in the pursue of economy. The conditional tone is justified by the fact that no causative mechanistic links between a given set of mechanical characteristics, breathing pattern and optimization of respiratory cost have been firmly established.

2. The many (theoretical) opportunities

The needs to exchange gases in harmony with the organism's metabolic needs are the primary factor setting the level of pulmonary ventilation ($\dot{V}E$, ml/min), the product of breathing frequency (*f*) and the quantity of air inspired with each breath (tidal volume, VT; Table 1). Hence, any given $\dot{V}E$ theoretically can originate from a multitude of combinations between VT and *f*, that is, from a pattern of breathing extremely shallow and fast to one very deep and slow, with all the combinations in between. Furthermore, any given VT could be produced at different absolute lung volumes, above or below the passive resting volume of the respiratory system (Vr). In reality, and in contrast to this theoretical freedom, the breathing pattern has only limited options. In fact, $\dot{V}E$ needs to compromise its main function of gas exchange with other obligations like heat control and water balance, coordination with postural changes and locomotion, vocalization, all of which can severely limit the theoretical options available to the breathing pattern (Mortola and Maskrey, 2011; Bartlett and Leiter, 2012). In addition, and most important, the 'choice' of the breathing pattern must consider the mechanical properties of the respiratory system, to keep the ventilatory cost to a minimum. In healthy adults at rest the oxygen consumption ($\dot{V}_{O_2}$) due to breathing has been computed at ˜2% of the total[1] (Otis, 1954). Similar values (1–3%) were estimated in various newborn mammals from data of passive mechanics (Mortola, 2001), while direct measurements on premature infants indicated values slightly higher (˜6%; Thibeault et al., 1966). Hence, at rest, breathing requires a minimal fraction of the energy budget. For breathing to be as economical as it is, the breathing pattern must adjust to the mechanical properties of the respiratory system.

In some vertebrates (fish, birds) $\dot{V}E$ is obtained by unidirectional flow of the gas-carrying medium. Differently, in mammals the flow is oscillatory, which implies that only a portion of $\dot{V}E$, the alveolar ventilation ($\dot{V}A$), participates to gas exchange while, at rest, about one third of VT fills the conductive airways or 'dead space' (VD). Therefore, one obvious constraint to the apparent freedom of the breathing pattern is that VT must exceed VD. The needs of VT > VD precludes the

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[1] The VO_2 of the muscles responsible for breathing is not measured directly; rather, it is estimated. A common approach is, first, to construct the relationship between VE and VO_2 at various levels of VE. Then, the VO_2 measured by extending such plot backward to VE = 0 represents the non-respiratory VO_2, and its difference from the total is the VO_2 due to breathing.

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Table 1
Abbreviations adopted in text and common units.

CL	compliance of the lung (ml/cm H_2O)
Crs	compliance of the respiratory system (ml/cm H_2O)
Cw	compliance of the chest wall (ml/cm H_2O)
f	breathing frequency (breaths/min)
FRC	functional residual capacity (ml)
P	pressure (cm H_2O)
PEEP	positive end-expiratory pressure (cm H_2O)
Rrs	airflow resistance of the respiratory system (cm H_2O/ml/sec)
τrs	time constant of the respiratory system (sec)
TI	inspiratory time (sec)
TE	expiratory time (sec)
V	volume (ml)
Vr	resting volume of the respiratory system
$\dot{V}$	airflow (ml/sec)
$\dot{V}A$	alveolar ventilation (ml/min)
VD	volume of the dead space (ml)
$\dot{V}E$	pulmonary ventilation (ml/min)
$\dot{V}_{O_2}$	oxygen consumption (ml/min)
VT	tidal volume (ml)
W	body weight (kg)

possibility of very shallow breathing[2]. The presence of VD also implies that the larger the VT the closer $\dot{V}A$ approaches $\dot{V}E$ and improves the gas exchange effectiveness of $\dot{V}E$. Yet, like the very shallow breathing, the deep and slow pattern is not what is commonly observed, presumably because it would cause huge oscillations in alveolar and blood gases, with consequences on acid-base homeostasis and cardio-respiratory coupling. Furthermore, deep breathing would be energetically costly because of the stiffness (i.e., low compliance) of the respiratory system at high lung volumes; hence, VT can be neither too shallow nor too deep. The high *f* associated to the former would increase the airflow resistive component of the total work of breathing, while a large VT would increase the elastic portion of the respiratory work. Based on theoretical and experimental results, it was shown long ago (Otis et al., 1950) that for any given $\dot{V}A$ there is a range of *f* where the total respiratory work is minimal (Fig. 1A). Indeed, the *f* of humans breathing at rest falls within that range, a principle of minimal effort that applies also during exercise-hyperpnea. Later, the coincidence between actual *f* and optimal *f* has been confirmed in other species (e.g., Agostoni et al., 1959; Crosfill and Widdicombe, 1961). Newborn animals probably respect this general rule (Mortola, 1983) except, perhaps, in the first minutes after birth (Mortola et al., 1982), when the fetal pulmonary fluid remaining in the airways keeps *f* elevated (Fisher et al., 1982). Since then, numerous observations have shown resting *f* to approximate the value predicted on the basis of minimal work. Nevertheless, it is difficult to picture how the body is informed about the respiratory work and the components that represent it. Perhaps, muscle proprioceptors could relay information about muscle length and force. Indeed, Mead (1960), based on data from humans and guinea pigs, proposed that the average force of the respiratory muscles was the variable controlled to adjust *f* at minimal work.

Experimental increases in respiratory resistance (Rrs), by adding known resistances to the breathing apparatus, or reductions in respiratory compliance (Crs), by having subjects breathe in and out of closed spaces, changed the breathing pattern in the direction expected for work optimization (Fig. 1B and C) (McIlroy et al., 1956; Milic-Emili and Zin, 1986). Similarly, in patients with either high (emphysema) or low (fibrosis) lung compliance, or with other pathological conditions, the breathing pattern was found to be appropriate for work minimization (e.g., Christie, 1953).

From the view point of economization of work, it would be appropriate to breathe across Vr, rather than entirely above it, because the elastic work would be substantially lower (Fig. 2). This pattern, present and thoroughly investigated in the adult horse at rest (Koterba et al., 1988, and references therein), probably occurs in a few other equines (Amoroso et al., 1963), in Giraffidae (Mortola and Lanthier, 2005) and in dogs in the seated position (De Troyer et al., 1989). Nevertheless, it is a pattern rarely observed among newborn or adult mammals. In fact, despite the reduced elastic work, several considerations indicate that breathing across Vr may not be beneficial. Breathing across Vr implies a double alternation of active and passive phases; the recruitment of the expiratory muscles to lower lung volume, their relaxation for the first half of VT followed by activation of the inspiratory muscles for the second half of VT and their relaxation for the first half of expiration. Such coordination requires more chest wall muscles to be preoccupied with breathing than when VT is entirely above Vr, because in this latter case expiration is almost entirely passive. Having both inspiratory and expiratory muscles synchronized during resting breathing may add another layer of complexity to the generation of the central pattern. Finally, lowering lung volume below Vr could raise the chances of closure of the most gravity-dependent lung regions, which would compromise the ventilation-perfusion matching.

Then, why do the horse and a few other adult mammals breathe across Vr? One possible explanation was put forward by Koterba et al. (1988), from the consideration that the compliance of the chest wall (Cw) in the horse is particularly low. Although, as indicated above, a stiff respiratory system benefits from rapid breathing, the horse at rest needs a low *f* to leave ample ventilatory reserve for strenuous athletic performances. According to this interpretation, breathing across Vr at rest would represent the most appropriate breathing pattern to minimize the elastic work of breathing while keeping *f* quite low.

I am not aware of any neonatal mammal of any species, foal included (Koterba and Kosch, 1987), that at rest breathes across Vr. In the early postnatal period, newborns need to increase the air volume of the lungs. In fact, the neonatal breathing pattern is geared to maintain the end-expiratory lung volume higher than Vr, as it will be discussed below (5.). For newborns, therefore, breathing across Vr would be deleterious, despite the energetic advantage in lowering the elastic portion of the work of breathing.

3. Inter-species differences in respiratory mechanics

Many studies have compared the mechanical properties of the lungs and respiratory system among mammals. Most commonly comparisons are made by allometric analysis, whereby the variable of interest Y of each species is plotted against its corresponding body weight (W). The characteristics of the relationship (e.g., Y independent of W, or linearly or exponentially increasing or decreasing with W) can be used to make inference regarding general biological principles of design and functionality.[3] In adults, the allometric analyses of species covering a large range in body size (Crosfill and Widdicombe, 1961; Stahl, 1967; Schroter, 1980; Bennett and Tenney, 1982) has consistently indicated compliances to increase in direct proportion to the species W and resistances to decrease with species size. Both results should be expected, because lung volumes and pressure-volume (P–V) curves are proportional to W, and because airways get wider the larger the lungs of the bigger species. While Crs $\propto W^{1.0}$, Rrs scales to $W^{-0.75}$, meaning that the decline in Rrs with species size is less than proportional to W. Why this is so is not totally clear. Perhaps it has to do with the protection of VD.

[2] During high-frequency mechanical ventilation, by maximizing air convection and molecular diffusion, some gas exchange can be sustained even with a VT lower than the dead space (Slutsky, 1991).

[3] From the original exponential function of the raw data $Y = a \cdot W^X$, allometric relationship is the log-transformed version $\log Y = \log a + X \cdot \log W$, where the slope X is the exponent of the original equation. While a slope $= 1$ means that Y changes in direct proportion to W, slopes > 1 or < 1 indicate that Y changes disproportionately, respectively, more or less with the increase in the species' W.

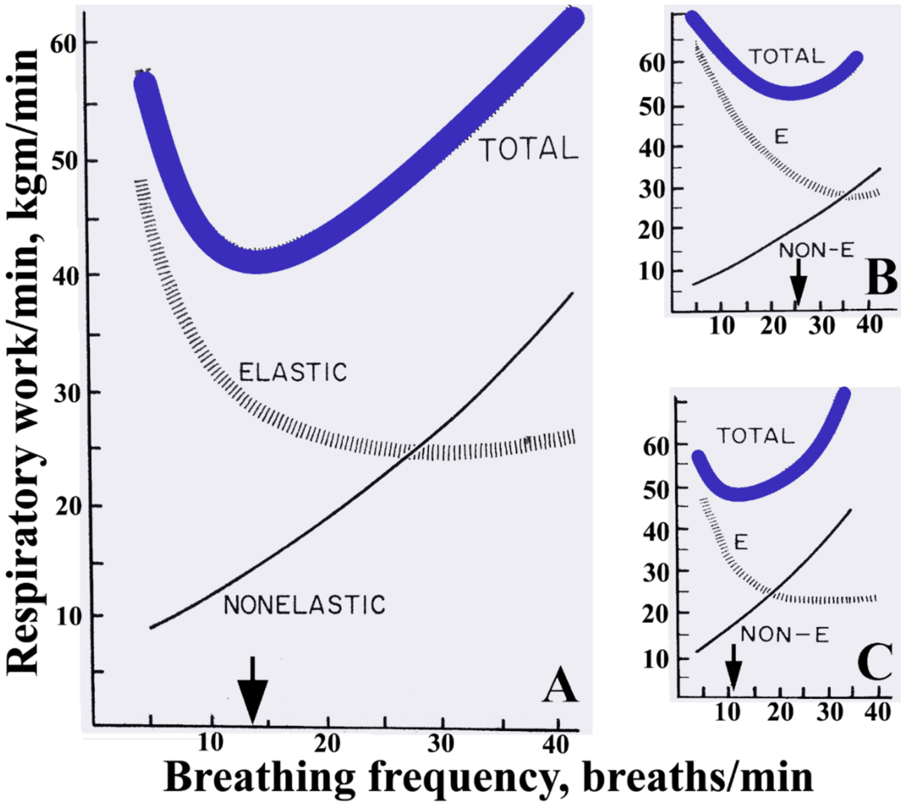

Fig. 1. A: relationship between breathing frequency (*f*) and the respiratory work/min for a constant alveolar ventilation. As the breathing pattern becomes progressively shallower and faster the elastic work of breathing (proportional to the ratio between tidal volume and the compliance of the respiratory system, Crs) decreases while the non-elastic component (proportional to the product between air flow and respiratory system resistance, Rrs) increases. The minimum total work (heavy blue) is at ˜14 breaths/min (arrow), which corresponds to the most common spontaneous *f* at rest. In conditions of low Crs (B) or high Rrs (C) the *f* of optimal work, respectively, increases and decreases (From Otis et al., 1950; Nunn, 1993).

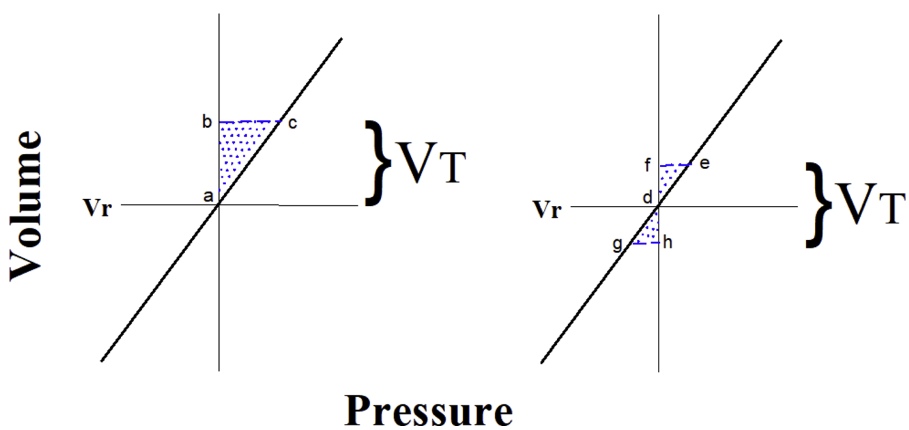

Fig. 2. Schematic representation of the pressure-volume (P–V) function of the respiratory system assumed, for simplicity, to be linear. At left, tidal volume (VT) occurs entirely above the resting volume of the respiratory system (Vr). At right, the same VT occurs partially above, partially below Vr. The elastic work of breathing above Vr corresponds to the area a-b-c, while the elastic work of breathing across Vr is one half of it (d-e-f + d-g-h = ½ a-b-c).

In fact, if Rrs was decreasing in direct proportion to W, the VD of the biggest mammals would be very large. Be that as it may, the allometric scaling of Crs and Rrs implies that their product, the time constant of the respiratory system (τ, sec), increases with W, as $\tau rs \propto W^{1.0} \cdot W^{-0.75} = W^{0.25}$. Therefore, for the same diaphragmatic activation, the time to lung inflation is longer in larger species, as experimentally demonstrated (Leiter et al., 1986). Equally, once inspiration is terminated, the time needed for passive expiration is longer in larger animals. These mechanical differences in response time are adequately matched by the timing of the resting breathing pattern, because both inspiratory (TI) and expiratory time (TE) are progressively longer the bigger the species (Bennett and Tenney, 1982). In fact, since Bert's (1870) early measurements of breathing in various species, it was clear that the *f* of larger species is less than in smaller species. Then, numerous data have consistently confirmed that $f \propto W^{-0.25}$, that is, *f* shares the same exponent as τrs, but of opposite sign. Therefore, in the larger species the longer τrs is in harmony with a lower *f*. This combination permits *f* at rest to match the value necessary for minimal work, as confirmed experimentally (Crosfill and Widdicombe, 1961). At the same time, VT is directly proportional to W (VT $\propto W^{1.0}$, or ˜10 ml/kg), an efficient aspect for the operation of the respiratory pump (Bennett and Tenney, 1982; Leiter et al., 1986), and $\dot{V}E$ and $\dot{V}A$ are directly proportional to metabolic rate, resulting in similar values of alveolar and blood gases among mammals of very different sizes (Tenney and Boggs, 1986; Mortola and Seguin, 2009).

The matching between mechanical properties and resting breathing pattern emerged from analysis of the allometric functions of adult mammals probably applies also to neonates, although data are fewer and differences in perinatal development complicate the inter-species comparisons. Among newborns, $\dot{V}E$ and $\dot{V}_{O_2}$ have allometric exponents closer to unity than they are in adults, respectively, $M \propto W^{-0.92}$ and $\dot{V}E \propto W^{0.91}$, and *f* is less size-dependent than among adults ($f \propto W^{-0.08}$). A compilation of data from different sources with different methodologies resulted in Crs $\propto W^{1.01}$ and Rrs $\propto W^{-0.80}$ (Mortola, 2001). Therefore, among newborn species $\tau rs \propto W^{1.01} \cdot W^{-0.80} = W^{0.21}$, which would be quite different from the scaling exponent of *f*. However, measurements by identical methods on seven neonatal species (from rats to human infants) indicated that Crs and Rrs were almost inversely proportional to each other; hence, from this set of data, it would seem that τrs changed little among species ($\tau rs \propto W^{0.05}$; Mortola, 1983), in agreement with the interspecies pattern of *f*.

One aspect to consider is that in newborns, more than in adults, values of *passive* mechanics may not coincide with those of *active* mechanics; this latter refers to the mechanical behavior of the respiratory system during spontaneous breathing and is the more relevant aspect in the analysis of optimal respiratory work; yet, it is by far the more difficult to measure and numerical values are based on various approximations (Mortola, 2001). Many factors introduce differences between *active* and *passive* mechanics[4], and we still do not know if their importance varies systematically with the species' W.

In conclusion, in adult mammals at rest the inter-species differences in breathing pattern match very well the differences in respiratory mechanical properties, so that uniformity in blood gas homeostasis is achieved with minimal respiratory work. The same cannot be concluded yet for newborns, although among neonatal species size-related differences in $\dot{V}_{O_2}$, $\dot{V}E$, $\dot{V}A$ and *f* are less marked than among adults.

4. When Cw is low

A reduction in Cw can be seen in obesity, in pregnancy and in some ruminants. Because a stiff chest wall lowers Crs and raises the elastic work of breathing, the cost-optimization theory expects tachypnea to be the prevalent breathing pattern in these circumstances (Fig. 1C).

4.1. Obesity

In obesity (patients with W > 150% ideal) $\dot{V}E$ increases to match the higher metabolic rate, except when obesity becomes so severe to cause hypoventilation. The latter is because obesity reduces the compliance of the chest wall and, possibly, that of the lungs (Rochester and Enson, 1974; Zwillich et al., 1975; Eberlein et al., 2014). The drop in Crs shortens τrs, despite some increase in airway resistance due to the reduction in lung volumes. In these patients the eupneic breathing pattern has a normal or quasi-normal VT, shorter TE and higher *f* than non-obese subjects (Burki and Baker, 1984), in agreement with the optimization of respiratory cost.

Experimental chest wall strapping has many similarities to obesity from the view point of the changes in lung volumes and compliances that the procedure entails (Eberlein et al., 2014). Healthy adult subjects with chest wall strapping breathed with reduced VT and higher *f*, both at rest and during exercise (O'Donnell et al., 2000), a pattern compatible with the theory of optimization of respiratory cost.

4.2. Pregnancy

The abdominal load of the uterine content in pregnant women close to term lowers Cw and Crs by some 20%; both return to normal upon parturition (Farman and Thorpe, 1969; Marx et al., 1970). Similar changes were observed in pregnant rats (Faridy, 1981). In addition, airway resistance decreases because of bronchial smooth muscle relaxation. In parallel with these mechanical changes, $\dot{V}A$ increases, largely because of the increase in VT, with small or no rise in *f* (Pernoll et al., 1975; Metcalfe and Bissonnette, 1987). Hence, during pregnancy the rapid and shallow pattern expected to optimize the cost of breathing is not what most commonly observed. Rather, the hyperventilation caused by the rise in metabolic rate and the surge of female hormones (Regensteiner et al., 1989) influence breathing into a pattern sub-optimal from the view point of respiratory work. Furthermore, the arterial partial pressure of CO_2 decreases, indicating that the pattern is sub-optimal also from the view point of gas-exchange. Presumably, in the last phase of pregnancy the hyperventilation helps the mother to lose heat and to provide a heat sink for fetal heat dissipation (Mortola and Maskrey, 2011). Hence, the breathing pattern adjusts to accommodate the priority of thermal control, even if this requires some loss of blood-gas homeostasis and increases the respiratory work.

4.3. Large rumen

Cows, goats and sheep have long been known to breathe faster than other mammals of similar W. The CO_2 stimulus produced by bacterial fermentation in the rumen was thought responsible for their tachypnea. Against this interpretation were the observations that experimental changes in rumen CO_2 did not significantly affect breathing (Kuhlmann et al., 1985) and that blood CO_2 did not increase during the hours of rumination (Piccione et al., 2004). Furthermore, not all members of the four ruminant families (Bovidae, Camelidae, Cervidae and Giraffidae) breathe faster than expected for their body size; rather, only those belonging to the Bovidae family do so (Fig. 3, filled circles), which also happen to be the only species with a rumen that occupies a large portion of the abdomen (22–24% of body weight, about twice as much as ruminants of the other families; Mortola and Lanthier, 2005). A large rumen and its intra-luminar pressure constitute an elastic load to the function of the respiratory system, and lower Crs (Musewe et al., 1979; Hofmann, 1988; Gallivan et al., 1989). Hence, in Bovidae the rapid shallow pattern probably reflects the most economical adaptation to the mechanical constraints produced by their large rumen.

5. When Cw is high

All neonatal mammals are born with a soft and deformable chest wall, a necessity for the delivery through the pelvic canal. However, as soon as birth is over, a respiratory system with high Cw reveals its potential mechanical problems; hence, it is of interest to examine how the breathing pattern accommodates these difficulties.

Neonates of all species examined have Cw (normalized by W) higher than that of the corresponding adults and, most importantly, have a high Cw-CL ratio, some 2-to-5 times the adult's value (Mortola, 2001). This dimensionless ratio is convenient because it can be readily compared among age-groups and species without needs for normalization. It is directly responsible for the level of the passive resting volume of the respiratory system, Vr, and its high value in newborns has implications to both inspiration and expiration.

5.1. Inspiration

Infants have higher metabolic rates and $\dot{V}E$ (per body W) than adults and do so by breathing with higher *f* and similar VT/kg (Mortola, 2001). At first sight, this pattern may seem at odds with the high Cw and the principle of economy; in fact, the high Cw (and, therefore, high Crs) is expected to lower the elastic work, which should favor a deep and slow breathing pattern (Fig. 1C). It needs to be considered, though, that in inspiration the newborn's highly compliant chest wall undergoes major distortion, especially in the supine position. In fact, as the diaphragm contracts and lowers its dome into the abdomen, the rib cage is subjected to the drop in pleural pressure (Fig. 4). Furthermore, because

[4] In newborns, the major factors responsible for the differences in Crs between spontaneous breathing (active) and passive conditions are the distortion of the chest wall, which lowers Crs, the stress-relaxation of the lung tissue, which lowers Crs in dynamic conditions, and the upper airway-control of expiratory flow, which increases Rrs (Mortola, 2001). How these factors scale allometrically among newborns is not known.

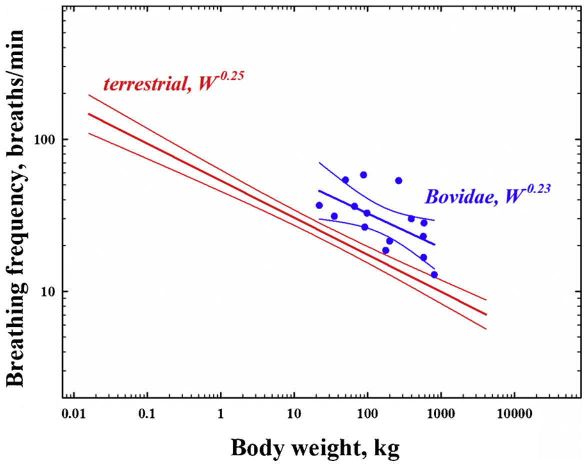

Fig. 3. Allometric curves (log-log representation) of resting breathing frequency (*f*) in terrestrial mammals excluding Bovidae (thick red line) and in Bovidae (blue line). The relationship of terrestrial mammals originates from the data of 31 species spanning in W from 30 g to 3 tons. Each symbol is the average value of a species. Heavy lines are the best fit linear regressions through the data points; thin lines are the corresponding 95% confidence intervals. Monotremes and Marsupials were excluded because of their low metabolic rate. Values are the exponents b of the original exponential functions $f = a \cdot W^b$, where W indicates body weight (from the data in Mortola and Lanthier, 2005).

of the small area of apposition[5], the rise in abdominal pressure during inspiration exerts minimal inflatory action on the rib cage. In combination with the poor proprioceptive control of the intercostals muscles characteristic of the early postnatal age, the lowering of the pleural pressure causes the rib cage to move paradoxically inward. The inspiratory paradoxical inward movement severely curtails VT and the ventilatory efficiency of the diaphragm (Mortola et al., 1985). In conclusion, during spontaneous inspiration the newborn's chest wall behaves as if it was much stiffer than apparent from passive measures. Presumably these mechanical events contribute to the general tendency of newborn mammals to increase *f*, rather than VT, to achieve the levels of $\dot{V}$E adequate for their metabolic needs.

5.2. Expiration

A chest wall highly compliant (relative to the lungs) counteracts the collapsing tendency of the lungs less effectively than a stiff chest wall does, with the result of a small Vr (Fig. 5). In adults during resting breathing Functional Residual Capacity (FRC) is essentially equal to Vr. If the same occurred in newborns FRC would be much too low, jeopardizing the efficiency of the respiratory system. In fact, an adequate FRC is necessary to buffer the oscillations of the alveolar gas composition for the stability of the arterial gases and is a reserve of oxygen during occasional periods of hypoventilation or apneas. In addition, inflation of the lungs from an FRC of adequate size requires substantially less pressure than inflation from a semi-collapsed state.[6]

Therefore, since birth, neonatal mammals need to progressively expand their FRC by keeping it dynamically elevated above Vr (Fig. 5). In a few-days old human infants, the FRC-Vr difference is 5-to-15 ml, or about 2–3 ml/kg (Mortola et al., 1982). The main mechanism to elevate FRC is a prolongation of the expiratory τrs. This is obtained by persistent activity of the inspiratory muscles well into the expiratory phase and, mainly, by narrowing the glottis to increase expiratory airflow resistance (Mortola et al., 1984b; Kosch and Stark, 1984). The result of these mechanisms is a prolongation of the mechanical TE, so that the next inspiration initiates before the previous expiration is completed.[7] In addition, the high *f* reduces the neural TE, which contributes to keep FRC above Vr (Mortola, 2001; Eichenwald and Stark, 2003). Periods of central apneas, even if of brief duration, unavoidably lower FRC toward Vr (Lopes et al., 1981; Kosch and Stark, 1984).

One physiological implication of the dynamic elevation of FRC is that the newborn's respiratory system behaves as if it was under positive end-expiratory pressure ("internal" PEEP), by a magnitude equal to the recoil pressure of the respiratory system at FRC. Although just a few cm H_2O, during the first hours after birth this positive airway pressure probably contributes to the absorption of the pulmonary fluid from the alveolar spaces into the lung interstitium (Strang, 1991). When infants are intubated for clinical procedures the endotracheal tube bypasses the vocal folds and eliminates the newborn's laryngeal control of expiratory flow, lowers Rrs and shortens τrs, with the consequence that FRC drops toward Vr. In these cases, to maintain the lungs sufficiently aerated, the attending clinician must add an external PEEP of a few cm H_2O, which is meant to replace the infant's internal PEEP during spontaneous breathing. This is yet more indispensable in those infants who, because of severe prematurity or lung diseases, have low CL and very high Cw-CL ratio. During the first postnatal months and years, as the chest wall stiffens and distortion diminishes (Papastamelos et al., 1995), Vr rises, expirations with interrupted airflows become less frequent and *f* slows down toward the adult's values (Colin et al., 1989).

6. Conclusions

How is it possible that breathing at rest has evolved to be a very economical mechanism despite the differences in anatomical and mechanical characteristics with body size, postnatal development and internal loads? Probably the single most important factor that explains this feat is that the breathing pattern accommodates the mechanical characteristics of each specific condition in the pursue of minimal work. Optimality of the breathing pattern must reflect coordination between lung mechanoreceptors, sensing absolute and tidal changes in lung volumes, and chest wall proprioceptors, sensing muscle length and force. In animals with experimental vagotomy, in absence of the pulmonary stretch afferents, the breathing pattern often no longer matches the Crs and Rrs values, with the consequence of raising the work of breathing (e.g., Lim et al., 1958; Mortola et al., 1984a; Clement et al., 1986; Rossi and Mortola, 1987). Nevertheless, how the peripheral inputs are integrated centrally to minimize the respiratory work remains unknown.

The mean inspiratory flow (VT /TI) was proposed (Milic-Emili and Grunstein, 1976), and is commonly used, to reflect the "central respiratory drive" and its changes. However, one should not overlook the fact that the breathing pattern, being sensitive to changes in the mechanical properties, may be a poor indicator of changes in the central neural output. For example, the same neural drive (by supramaximal stimulation of the phrenic nerves) produced a large variety of VT/TI among species that differed in mechanical properties; rather, VT/TI was found to be proportional to the species' τrs (Leiter et al., 1986). The broad conclusion, therefore, is that the breathing pattern adopted by newborn and adult mammals, out of the many theoretical options, is the one that produces the adequate $\dot{V}$A with minimal cost, that is, in full recognition of the mechanical characteristics of the respiratory system.

[5] Apposition area is the region of the abdomen facing the lower portion of the rib cage without interposed lung.

[6] In normal lungs, higher values of transpulmonary pressures occur during inflation than during deflation; this difference can become extremely large when inflation begins from very small lung volumes (Hoppin et al., 1986).

[7] Seals and probably other diving mammals have a high Cw/CL (Leith, 1976), which favors lung compression during the dive. When resting ashore their breathing pattern is reminiscent of the - newborn mammal, with expiratory closure of the glottis in expiration as a mechanism to raise FRC above Vr (Mortola and Limoges, 2006).

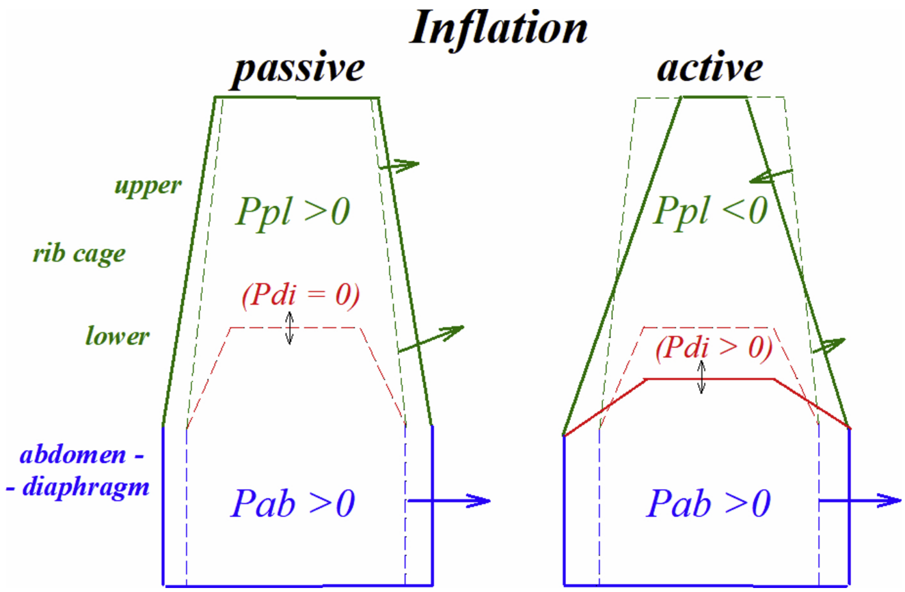

Fig. 4. Schematic representation of the chest wall with its two functional compartments, rib cage (upper and lower portions) and abdomen-diaphragm. The dashed lines envelope the silhouette at rest. During passive inflation (left) the diaphragm is relaxed; hence, the trans-diaphragmatic pressure (Pdi) is zero, and pleural pressure (Ppl) and abdominal pressure (Pab) increase by similar amounts, expanding the respective compartments. During spontaneous inspiration ('active', at right), the contraction of the diaphragm raises Pdi and Pabd. This latter expands the abdomen and the lower rib cage through the area of apposition. However, the drop in Ppl tends to pull the rib cage inward, especially in its upper portion. In infants this paradoxical motion of the upper rib cage is rarely compensated by the intercostal muscles. The functional consequence is that during active breathing the chest wall behaves as if it was stiffer (lower compliance) than during passive inflation.

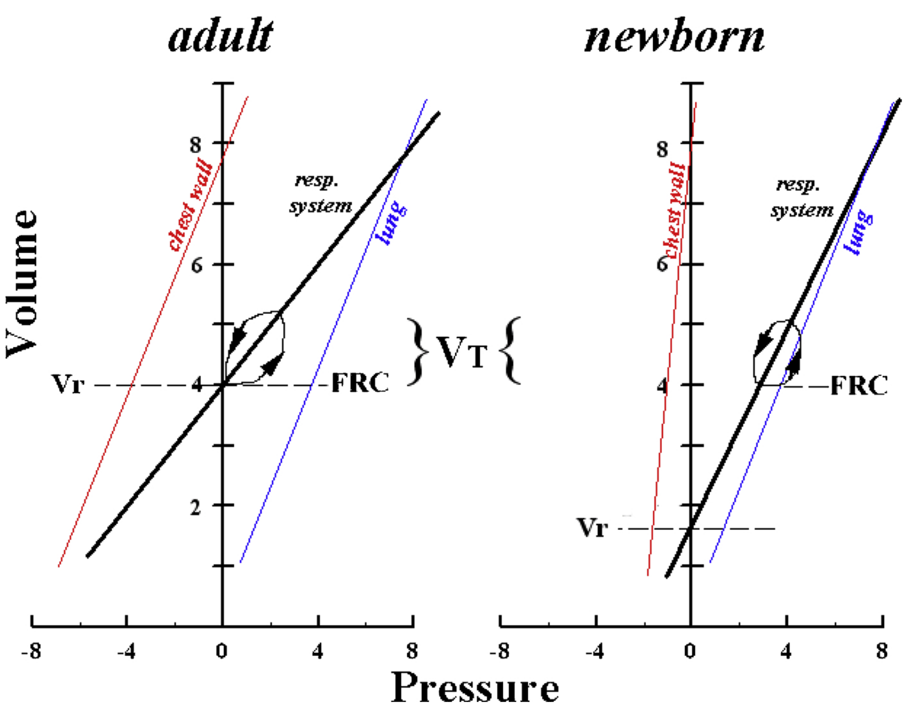

Fig. 5. Schematic Pressure-Volume relations (P–V, with V in arbitrary units) of lungs, chest wall and respiratory system (heavy line) in adult men (left) and newborn infants (right). For simplicity, the P–V relations are represented as straight lines, the slope of which represents the compliance. **At left**, the compliance of the chest wall (Cw) is similar to that of the lungs (CL). **At right**, Cw and the Cw-CL ratio are about five times higher than in adult men. The result is that in the newborn the resting volume of the respiratory system (Vr, dashed line) is lower than in adults. Tidal volume (VT, with inspiratory-expiratory loops indicated by arrows) -can be at a similar -relative lung volume in both newborns and adults, because newborns keep their end-expiratory level (or functional residual capacity, FRC) dynamically elevated (reproduced from Mortola, 2015, with permission from Springer Nature, https://link.springer.com/book/10.1007/978-3-642-01219-8, licence # 4,426,720,155,107).

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