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Control of Ventilation and Regulation of Acid-Base Status from Fish to Man

Control de la ventilación y regulación del estado ácido-base del pez al hombre

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Plus ça change, plus c'est la même chose.
Alphonse Karr (1808-1890)

ABSTRACT

This article analyzes certain evolutionary aspects of gas exchange, lung development, the respiratory pump, the acid-base status and control of ventilation in relation to a significant event: the passing from aquatic to terrestrial life. By studying this, we can understand certain aspects that are present in the clinical practice: Why do people with extreme respiratory muscle weakness breathe as frogs? (frog breathing); why do newborns with breathing difficulties have nasal flaring and expiratory grunting?; how is it possible that abdominal muscles, which are typically expiratory, assist with inspiration in cases of diaphragmatic paralysis?; why does the breathing pattern of respiratory failure has less variability and becomes more rigid? and, finally, is it possible to imagine a neutral pH that doesn't have the 7.0 value?; what's the use of this knowledge, and how should gases in hypothermia be interpreted?
Water-to-land transition is one of the most important and inspiring major transitions of vertebrate evolution. Given the amazing diversity of living organisms, it is tempting to imagine an enormous amount of evolutionary adaptation processes to solve the different challenges of living on earth faced by each species. There are certain early development processes that share some crucial factors, and some of the close and distant gene regulatory networks are conserved. We are witnesses of clinical findings that serve as testimony of the species that lived in remote times and left us their evolutionary history.

Key words: acid-base equilibrium, hypothermia, imidazole, biological evolution, respiratory paralysis, respiratory center

RESUMEN

Este artículo analiza ciertos aspectos evolutivos en el intercambio gaseoso, el desarrollo pulmonar, la bomba respiratoria, el estado ácido-base y el control de la ventilación en relación con un evento trascendente: el pasaje de la vida acuática a la terrestre. Su estudio puede permitir comprender ciertos aspectos con los que lidiamos en la práctica clínica: ¿Por qué las personas con debilidad muscular respiratoria extrema respiran como ranas (respiración *frog*)?, ¿Por qué los recién nacidos con dificultad

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respiratoria tienen aleteo nasal y quejido espiratorio?, ¿cómo es posible que los músculos abdominales, típicamente espiratorios, asistan a la inspiración en casos de la parálisis diafragmática?, ¿por qué en la insuficiencia respiratoria el patrón respiratorio tiene menos variabilidad y se torna más rígido? y, por último, ¿es posible imaginar un pH neutro que no tenga el valor de 7,0, para qué sirve este conocimiento y como se deben interpretar los gases en hipotermia?
La transición del agua a la tierra es una de las más importantes e inspiradoras de las grandes transiciones en la evolución de los vertebrados. Ante la sorprendente diversidad de organismos vivos, es tentador imaginar una cantidad enorme de adaptaciones evolutivas para resolver los diferentes desafíos que cada especie tiene para la vida en la tierra. Hay desarrollos tempranos que comparten algunos factores cruciales y algunas de las redes genéticas regulatorias cercanas y lejanas están conservadas. Somos testigos de hallazgos clínicos que son el testimonio de especies que han vivido en épocas remotas y nos han legado su historia evolutiva.

Palabras clave: equilibrio ácido-base; hipotermia; imidazol; evolución biológica; parálisis respiratoria; centro respiratorio

The objective of this article is to analyze certain breathing-related evolutionary aspects, particularly gas exchange, lung development, the respiratory pump, the acid-base status and control of ventilation in relation to a significant event: the passing from aquatic to terrestrial life.

By studying this, we can understand certain aspects that are frequently present in the clinical practice: Why do people with extreme respiratory muscle weakness breathe as frogs? (frog breathing); why do newborns with breathing difficulties have nasal flaring and expiratory grunting?; how is it possible that abdominal muscles, which are typically expiratory, assist with inspiration in cases of diaphragmatic paralysis?; why does the breathing pattern of respiratory failure has less variability and becomes more rigid (apart from being fast and superficial)? and, finally, is it possible to imagine a neutral pH that doesn't have the 7.0 value?; what's the use of this knowledge, and how should gases in hypothermia be interpreted?

Water-to-land transition is one of the most important and inspiring major transitions of vertebrate evolution. The first fish appeared 438 million years ago, and the transition of the tetrapod from water to land occurred around 375 million years ago; tetrapods were the main characters of this unique event: they emerged from the water and breathed air. They were exothermic and incapable of sustaining high levels of physical activity, and evolved into two classes of vertebrates with high levels of maximal oxygen consumption: mammals and birds.[1] Terrestrial ability appears to coincide with the origin of limbs; there was a coexistence of aquatic features, such as the gills and tail fin with the limbs.[2]

CHANGES IN THE COMPOSITION OF GASES IN THE BIOSPHERE

Fluctuations in O_2 and CO_2 levels in the biosphere have determined the way and means through which O_2 was incorporated and CO_2 was eliminated. During the late Paleozoic era (around 300 million years), for a period of approximately 120 million years, the O_2 level increased to a maximum of 35% and then dropped abruptly to a minimum of 15% in the Triassic. These changes doubled in the water and resulted in great events, such as mass extinctions.

The highest CO_2 levels occurred in the Ordovician and Silurian periods, whereas in the Carboniferous, the CO_2 level had decreased to the current value (0.036%), although at the end of the Permian it had increased by a factor of three. The structure and function of initial gas exchangers were produced mostly by natural selection under environmental conditions that were totally different from the current ones.[3]

THE AQUATIC AND TERRESTRIAL ENVIRONMENTS

The gasometric composition of air is well-known by us. Oxygen in seawater derives mostly from the air, so it is composed of the same gases of the atmosphere. Since the oxygen is more soluble in water than nitrogen, there is a higher proportion of oxygen in water than in the air. But from the point of view of dissolved oxygen (molecular), the air has 210 cm^3 of O_2/L, and seawater contains only 9 cm^3/L. So, in general terms, dissolved oxygen is much less abundant in water than in air.

The presence of macro- and microalgae contributes directly with lighting to the oxygenation of seawater. Only 1% of the light that has an impact on the surface of the sea reaches 200 m of depth (photic zone).[4] Thus, O_2 availability decreases significantly as water depth increases.

GAS EXCHANGE

The most significant modification in gas exchange was produced as a consequence of the change in the structure of teguments. Gas exchange in water was produced by two routes: teguments and incipient respiratory structures. With the passing to terrestrial life and the appearance of scales (reptiles), teguments would provide protection against desiccation, but would become less permeable to gas exchange.

In birds and mammals, the feathers and fur prohibited skin gas exchange for good. That function would then be exclusively performed by the lung, with air inlet through the mouth. The alveolar air started to form, an intermediate station between atmospheric air and blood, with remarkably stable gasometric composition, temperature and humidity. So the lungs of mammals evolved in order to face a unique set of challenges:

– Ensure the sufficient supply of inspired oxygen to all the pulmonary units whose exchange surface would reach around 70-150 m^2 in humans, inside a confined thoracic space,
– That large gas exchange surface had to be associated with a minimum barrier thickness, and,
– A microvascular network had to be generated to accommodate the cardiac output of the right ventricle and resist cyclic mechanical tensions, which increase many times from rest to exercise.

The organs of the respiratory system of various aquatic animals, such as the fish, are the gills and the operculum. The opening and closing dynamics of the gills is controlled by the cranial nerves that derive from the gill arches (trigeminal, facial, and glossopharyngeal). The innervation of the gill area in frogs is developed from the facial, glossopharyngeal, and vagus cranial nerves.[5] Figure 1 shows the morphological aspect of the lungs in vertebrates according to JN Maina.[3]

Mammals and birds are the two large classes of vertebrates that have high levels of maximum oxygen consumption.[1] A significant feature of these two groups is that even though the physiology of the cardiovascular, renal, gastrointestinal, endocrine and nervous systems shows many similarities, the lungs are radically different.[6]

Our perspective of self-aware mammals could make us think that we have been more successful

Figure 1. Morphological aspect of the lungs in vertebrates according to JN Maina.3 From left to right: lungs of an urodele amphibian (salamander), an anure amphibian (toad, frog), a reptile (savannah monitor lizard), a mammal (rabbit) and a bird (chicken). In general, the evolutionary trend has gone from simple sacs with a small exchange surface to complex lobular structures and large exchange surfaces.

than birds. Taking into account other aspects, it seems to be quite the opposite. West and Watson proposed that the lung of birds is superior to that of mammals, and that evolution in mammals has gone the wrong way:[1]

- An important difference is the fact that the ventilation of the gas exchange area (West respiratory zone) has a continuous flow pattern in birds, but shifts in mammals.
- Birds move the gases through convection, whereas mammals also need diffusion in the terminal airways.[7]
- Birds have a more uniform parenchyma with small terminal spaces that are largely intertwined with the capillaries, minimum membrane thickness and ultimately, more efficient gas exchange.
- Birds have separated the ventilatory and gas exchange functions, they seem to be less vulnerable to bronchoaspiration and their oxygen consumption in relation to their body weight is higher than that of mammals.

For all those reasons, from a structure-function standpoint, the bird lung is superior.[1] Humans weren't the evolution goal (evolution doesn't have a goal), still less the mammal lung. Evolution occurs gradually, not necessarily towards more complex structures.[8]

In view of the great development of his brain, the man is an acutely self-aware creature, more immensely capable than any other animal of taking advantage of the individual and social experience. While a climber struggles to get to the top of the Everest, the geese are waiting for him, flying over his head.

THE RESPIRATORY PUMP

Evolution to terrestrial life limited the gas exchange to the lungs, which evolved into a large exchange surface exposed to a very much controlled alveolar air that had to be moved (ventilated) in order to take air from the atmosphere. The respiratory pump, with its different versions, was in charge of this.[9]

Figure 2 shows a graphic representation (dendrogram) of several groups of vertebrates in relation to the strategy used regarding the respiratory pump.[9] We can observe the change from a **buccal pump** driven by branchiomeric (of the pharyngeal tract) and hypobranchial muscles (larynx,

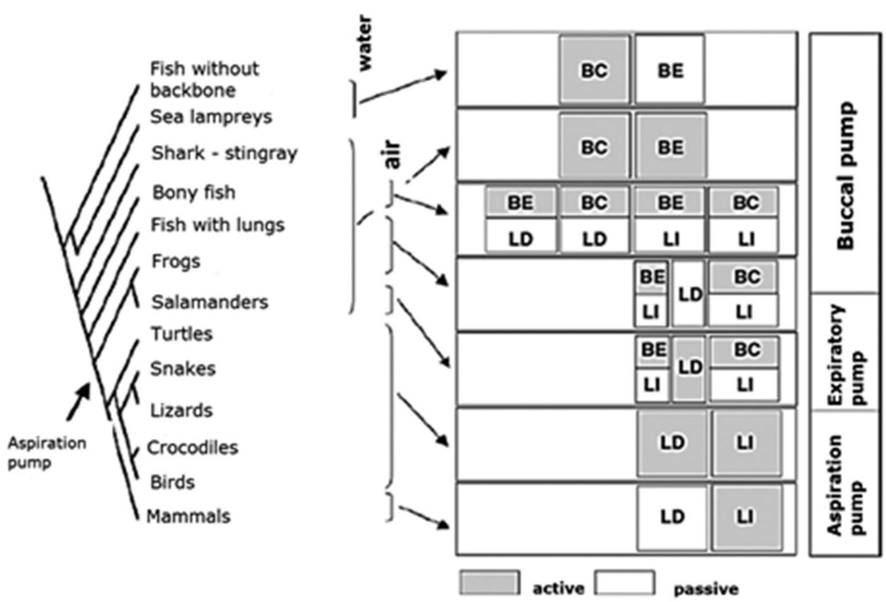

Figure 2. Dendrogram of several groups of vertebrates that shows the active/passive phases of the buccal/pulmonary ventilation cycles associated with aquatic and aerial respiration. BE = buccal expansion, BC = buccal compression, LD = lung deflation, LI = lung inflation. Modified by WK Milsom.9

tongue, jaw) innervated by cranial nerves to a thoracic-abdominal **aspiration pump** driven by axial muscles innervated by spinal nerves with premotor neurons situated in the ventral respiratory column.

The first steps in the evolution of air-breathing were a modification of the behavior at the surface and changes in the **valves of the mouth/blowhole/nostrils, the operculum and the glottis (or their equivalent)**, that is to say, changes in the activation of the muscles that expand or contract several openings. This allowed both aquatic and air-breathing. Changes in the muscles of the respiratory pump evolved later.[10] So, the evolution of respiratory mechanisms in vertebrates occurred from aquatic ventilation promoted mainly by a buccal strength pump to air ventilation driven mostly by a **suction or aspiration pump.** Only mammals have a muscle diaphragm, of axial origin, innervated by spinal motor neurons (phrenic nerve) and not by cranial nerves.

Between both ends of the buccal and aspiration pumps, there was the **active expiration** (Figure 2, expiratory pump).[9] This intermediate mechanism between the buccal pump of fish and amphibians and the aspiration pump of reptiles, birds and mammals was barely known. It has been proven that many amphibians use the axial muscles for active expiration along with the buccal pump for active inspiration. This suggests that aspiration breathing evolved in two steps:

- from buccal pumping alone to buccal pumping for inspiration and axial muscles for expiration, and then
- aspiration breathing alone using axial muscles for both expiration and inspiration.

In mammals we can see a change in the relative contributions of the chest wall distensibility and resistance of the airflow to the respiratory effort (the first predominates in birds and reptiles, the latter acquires greater importance in mammals). We can also observe evolution into a **muscle diaphragm** and a decreased need for active lung deflation as the system returns to the state of equilibrium after inhalation (elastic recoil). Thus, the functional residual capacity (FRC) is formed, that is the volume remaining in the lungs at the end of passive expiration that represents the balance between the forces expanding the lung and the ones that tend to collapse it (respiratory rest).

In fish, amphibians and most reptiles, there is certain division between the thoracic and abdominal cavities. This partition is incomplete and not very efficient as a respiratory pump. In developed reptiles and all mammals, there is a complete separation of the thoracic and abdominal cavities; this separation has a muscular layer in the case of mammals. So, there is the diaphragm as a muscle and also aspiration breathing (negative pressure).[10]

EVOLUTION OF ACID-BASE REGULATION

In humans, the $PaCO_2$ is strictly controlled. Throughout the day and night and even with the participation of other non-respiratory functions, $PaCO_2$ varies only in a few mmHG. Furthermore, unlike the PaO_2 that decreases with age, the $PaCO_2$ remains constant for life. So any sustained deviation from the $PaCO_2$ shall be seen as a significant alteration in homeostasis.[11]

What is the importance of such a strict control of the $PaCO_2$? And, how is it achieved? The study of the evolution of vertebrates from aquatic to terrestrial life and the capacity to regulate body temperature allows us to understand why the $PaCO_2$ has to be kept within such narrow limits.

In **aquatic life** under a poikilothermic dynamic, body temperature isn't constant, it varies according to room temperature. The PCO_2 suffers a great deal of variations and, although it is easily removed (teguments permeable to CO_2), the main problem is oxygenation (the PO_2 of water is lower than the atmospheric one), and due to various reasons we will see later on, it is impossible to keep a constant pH value.

In **terrestrial life**, on the other hand, the peripheral chemoreceptors (PQRs) stop working due to high room PO_2 (they are sensitive to PaO_2 below 60 mmHg), body temperature can be kept constant (homeothermia), but now the sole CO_2 elimination route is expired air (due to the development of teguments that prevent desiccation).

With a well-developed thermoregulation capacity and the precise regulation of $PaCO_2$, the resulting, remarkably stable pH allows mammals to maintain the ionization of the enzymes and the products of internal metabolism, so that they are kept inside the cell (the enzymes would escape from the cell if they lost ionization). This strategy is called pH-stat: it is extremely important for homeotherms to keep a constant pH (very narrow limits). Metabolic intermediates and enzymes are completely ionized in the region that is close to neutral pH (neutral pH from 7.0 to 25 °C) and have a low tendency to escape from the cell by going through the membranes.

In other words, if the room pH gets far off the ionization window of metabolic intermediates, these would lose their charge and escape the cell. Hence the importance of keeping the pH constant (pH-*stat*). This was elegantly expressed as "the importance of being ionized".[12]

In order to understand why this strategy isn't effective in poikilotherms, it is important to mention a fact that isn't usually taken into account: a body temperature of 37 °C doesn't suggest a relationship between temperature and pH (except in certain cases such as accidental or therapeutic hypothermia): *Temperature changes the pH neutrality value due to changes in the equilibrium constant of water or kW (ion product of water). Thus, pure water has a neutral pH (value of 7.0) only at 25 °C, whereas at 10 °C and 35 °C, the neutral pH value is 7.27 and 6.98, respectively**.

In water, at low temperatures, the internal pH of poikilotherms (fish, amphibians, reptiles) tends to increase and consequently becomes far off the ionization window of proteins and enzymes which as buffers can lose ionization but, fortunately histidine with its α-imidazole group keeps a constant ionization; so, that ionization keeps enzymes inside the cell and active regardless of temperature variations. This is the so-called α-stat strategy.[12-15]

Histidine is a particular amino acid. It has three groups that are capable of being charged: amine (pK 9.17), carboxyl (pK 1.82) and imidazole (pK 6.0); and its net charge (or degree of dissociation) remains constant throughout the whole temperature range and is the basis of Reeves' α-stat theory.[15]

In fact, aquatic poikilotherms appeared long before terrestrial homeotherms and we had to find a homeostatic strategy when teguments lost permeability to CO_2. The PCO_2 constancy is a success in terrestrial life and maybe it wouldn't have occurred without the dramatic complexity developed by the controlling structures of breathing.

But pH constancy in humans is also the result of the interaction between multiple buffer systems in which protein systems are found and the exact regulation of the bicarbonate/carbonic acid system through ventilatory and renal control. It is evident that all of this has been possible thanks to the evolution of the *respiratory centers*.

EVOLUTION OF VENTILATION CONTROL

In the aquatic environment, the PQRs of poikilotherms are in charge of regulating ventilation and the level of immersion, minute after minute. Their respiratory centers consist of groups of relatively simple cells capable of generating a very simple breathing pattern; for example, amphibians use only two groups of motoneurons that mediate ventilation. Far from acquiring the phrenic nerve, the first nerves involved in the act of breathing were the facial and glossopharyngeal.

With the passing to terrestrial life, the structures that generate the respiratory rate were now oscillatory neural networks of six groups of interconnected motoneurons, and chemoreceptors sensitive to CO_2 were developed. The new neural circuits were stable but responsive to changes in the levels of O_2, CO_2, pH, exercise, sleep, etc. Also, there needed to be coordination with phonation, swallowing, airway reflexes, coughing, sniffing and locomotion. There's also long-term adaptation due to alterations in the thoracic cavity, the lung, and the respiratory muscles caused by aging, weight gain or loss, pregnancy and diseases. Finally, the new suprapontine structures control the respiratory muscles voluntarily and in relation to a "evolutionary curiosity": *emotions*.

The model of respiratory centers in mammals with the pneumotaxic and apneustic centers, the dorsal respiratory group and the ventral respiratory group, is already part of the history of medicine. This model arose from cross-section cuts of the trunk of sedated cats, decerebrated at the

* If the pH increases as temperature falls, this does not mean that water becomes more alkaline at lower temperatures. A solution is alkaline if there is an excess of hydroxyl ions over hydrogen ions (that is to say, pOH > pH). As long as the concentration of hydrogen ions and hydroxide ions stays the same, water will still be neutral (pH = pOH), even if its pH changes. The problem is that we are all familiar with 7.0 being the pH of pure water (non-ionized), so anything else feels really strange. In order to calculate the neutral value of pH it is necessary to know the Kw, which increases with temperature, and if it changes, then the neutral value of pH changes as well. At 25 °C the Kw ($mol^2\ dm^{-6}$) value is 1.00 x 10^{-14}, the pH is 7.00 and the pOH is 7.00. So, 7.00 + 7.00 = 14. At 10 °C we will have a Kw value of 0.681 x 10^{-14}, pH of 7.08 and pOH of 7.08. So, 7.08 + 7.08 = 14.16. So, the pH of 7.00 and 7.08 at 25 °C and 10 °C, respectively, is neutral because it has $H^+ = OH^-$.[34]

intercolicular height, impaired, with or without vagus, and from the observation of changes in breathing patterns and then from a total of six transverse sections at different trunk levels.[16, 17]

At present, it's impossible to address the topic of the respiratory centers without speaking about the preBötzinger complex as a critical area for the generation of the respiratory rate, and the retrotrapezoid nucleus and parafacial respiratory group for the generation of active expiration and the relationship with non-respiratory functions.[17-20] Figure 3 shows the schematic organization of the respiratory system.

So, the evolution of respiratory control from fish to mammals is characterized by higher complexity and is related to the homeostasis of O_2, CO_2, pH and temperature.

- PQRs sensitive to hypoxia ($PaO_2 \leq 60$ mmHg and highly active under water) stopped functioning in terrestrial areas.
- When the constancy of the $PaCO_2$ and the pH were prioritized (pH-stat strategy*)*, new areas were developed that were very sensitive to CO_2.
- The simple pacemaker cells gave place to the preBötzinger complex, as well as the parafacial respiratory group and retrotrapezoid nucleus.[23, 24]
- Connections were developed with non-respiratory functions to coordinate respiration with phonation, swallowing and vomiting.[25]
- We have a sort of homunculus (primary motor area of the cortex, posterior frontal lobe, precentral gyrus) that is capable of voluntarily commanding respiration over autonomic control.[26]
- Telencephalization reached full development in humans. The cortex and subcortical/limbic system structures (amygdala, cingulate gyrus, hippocampus, etc.) mediate the emotions and influence respiration.
- The ponto-medullary respiratory network, which produces the ***rhythmic central command*** for respiration makes up *stable, coordinated and adaptable* structures.

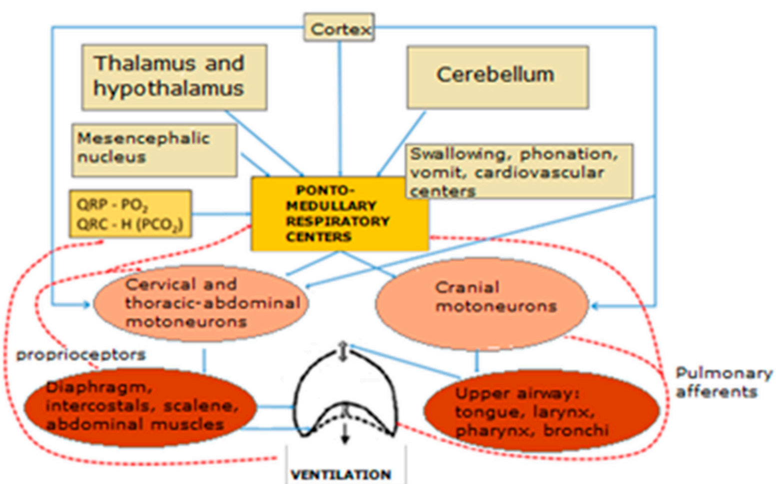

Figure 3. The ponto-medullary respiratory network, which produces the **rhythmic central command** for respiration, controls the cranial, cervical and thoracic and lumbar respiratory motoneurons that command the upper respiratory airways, the diaphragm and the "accessory" respiratory muscles of the thoracic cavity, respectively. The contractions of respiratory muscles activate proprioceptive afferents that regulate the activity of homonymous and heteronymous motoneurons through the short and central long loops. The activity in the respiratory centers is modulated through various afferences, such as those from the carotid body and chemoreceptors, the pulmonary stretch receptors and other pulmonary and non-pulmonary receptors and non-respiratory centers (swallowing, vomiting). Furthermore, some upper structures such as the cortex act both in respiratory motoneurons and in the respiratory centers.[21, 22]

CONTROL OF VENTILATION AND ACID-BASE STATUS CLINICAL-EVOLUTIONARY LESSONS

Only in developed reptiles and all mammals, there is a complete separation of the thoracic and abdominal cavities; this separation has a muscular layer in the case of mammals: the diaphragm. Thus, **aspiration breathing** is developed in terrestrial and aquatic mammals, but our gene pool seems to remember other evolutionary steps.

- Some people with neuromuscular diseases and important respiratory muscle weakness use the **frog breathing**, which allows the inlet of air at positive pressure. *Frog breathing at positive pressure (**buccal pump**), was one of the first ventilatory modes of vertebrates.*
- **Nasal flaring and expiratory grunting** are signs of respiratory difficulties in newborns,[27] babies and toddlers.[28] These indicate an increase in breathing effort. This mechanism is unusual in adults.[28] *Various coordinated cranial nerves move those structures and remember breathing with **valves of the mouth/blowhole/nostrils and the operculum and glottis (or their equivalent)** like the first vertebrates.*
- In the case of bilateral diaphragmatic paralysis, **the abdominal muscles have an inspiratory action**. Their action reduces the FRC, so in the next inspiration the air enters in a passive way due to the state of equilibrium of the chest. *The abdominal muscles **(expiratory pump)** have an inspiratory function in certain vertebrates.*
- The **variability of the breathing pattern** is lower in cases of acute respiratory failure. The use of non-invasive ventilation reestablishes variability and gets close to normal, with higher support levels.[29] *The rigid breathing pattern with poor variability reminds us of poikilotherms. Evolution gained complexity and variability but, with charge increase, the breathing pattern becomes more rigid.*

The use of general body hypothermia for heart surgery has become a routine procedure. Consequently, the concept of neutral pH had to be reconsidered, and the experience of millions of years of our ancestors, the poikilotherms, had to be taken into account.

- **Definition of neutrality** (that belongs to Arrhenius, 1889): *it is not a "pH of 7.0" but the presence of equal amounts of ions H^+ and OH^-.* Since temperature has the same effect on the concentration of each one of them, neutrality is maintained regardless of temperature.[30]
- Regardless of the patient's temperature, arterial gases are always analyzed at 37°C (it is the temperature with which PO_2, PCO_2 and pH electrodes are measured). The gases of a hypothermic patient are also analyzed at 37°C, and if the PO_2, PCO_2 and pH values are within the normal range, the acid-base status of the patient will be suitable for his/her temperature.[31, 32]
- The *in vitro* anaerobically cooled blood of a mammal follows the acid-base status pattern of a poikilotherm. *Physiologically speaking, to correct the pH according to body temperature in hypothermia doesn't make any sense, because the neutrality of pH also changes with temperature.*

Given the amazing diversity of living organisms, it is tempting to imagine an enormous amount of evolutionary adaptation processes to solve the different challenges of living on earth faced by each species. There are certain early development processes that share some crucial factors, and some of the close and distant gene regulatory networks are conserved.

In France, before the Franco-Prussian War, there was a political satire about government changes that said: "We take the same and start again". Alphonse Karr (1808-1890)[33] added his famous phrase «*plus ça change, plus c'est la même chose*»: *the more things change, the more they stay the same*. According to the comparative biology, there seems to be immutable principles even with evident superficial or morphological differences. *It is heartbreaking to think that we are the sole witnesses of clinical findings that serve as testimony of the species that lived in remote times and left us their evolutionary history, our evolutionary history.*

Conflict of interest

he author has no conflict of interest to declare.

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