

Lung Function Evolution and Respiratory Symptoms

N.A. Molfino

Otsuka Maryland Research Institute, Rockville, MD, United States of America.

The respiratory system is the result of adaptation to the Earth's atmosphere. The ability to tolerate hypoxia and, to a lesser degree, hypercapnia is characteristic of the human species. The Gaia theory states that the composition of the atmosphere that we breathe is determined primarily by biological processes occurring on the planet.¹ For example, the ozone layer, which provides protection against ultraviolet radiation, is decreasing while the amount of carbon dioxide (CO₂), which prevents solar heat from escaping, is rising.

Before the emergence of living organisms on earth, the atmosphere contained approximately 10% CO₂ and no oxygen molecules (O₂), which probably appeared on the planet around 3.5×10⁹ years ago with the appearance of organisms capable of photosynthesis.^{2,3} When the atmospheric concentration of O₂ reached 0.2%, aerobic organisms were present in the lakes and oceans. Organisms emerged on land when O₂ levels reached 2%. The O₂ concentration reached 3% some 1.9×10⁹ years ago.⁴ When the O₂ concentration reached 10%, photosynthesis was at a maximum, leading to an even greater concentration of O₂ and a decrease in CO₂. This decrease in CO₂ produced an increase in hydrogen peroxide (H₂O₂), superoxide ions, and oxygen radicals, all of which are potentially lethal to cells. As a result, a compensatory reduction in photosynthesis occurred, leading to the stable O₂ concentration (approximately 21%) that exists today. This stabilization occurred around 6×10⁸ years ago and led to the evolution of animals with skeletons, such as the dinosaurs.^{2,3}

Today, changes in the concentration of O₂ may come about as a result of human activity. Chlorofluorocarbons and other compounds destroy the ozone layer and permit the passage of more ultraviolet radiation. Carbon is reoxidized to CO₂ in the atmosphere. Tropical forests are being destroyed and the sun is emitting more

heat. These changes influence the climate on earth, although the O₂ concentration has not yet been affected.¹⁻³

Around 400 million years ago, aerobic organisms emerged in a watery environment in which the O₂ concentration was determined by the partial pressure of oxygen and its solubility in water. Therefore, at 37°C the concentration of O₂ in water is 40 times less than in the air (Table). CO₂, in contrast, is highly soluble and has a higher concentration in water than in air.

Fish have solved the problem of obtaining sufficient O₂ by developing a branchial apparatus. A large volume of water perfuses the gills, which efficiently extract nearly all of the O₂. The O₂ level in the blood exiting the gills is similar to that leaving the human lung. In the tropics, flowing water is scarce due to high temperatures and aquatic creatures therefore developed primitive limbs to allow them to look for water, although they also developed primitive lungs in the posterior pharynx. The combination of primitive lungs and gills was effective. Primitive lungs evolved in reptiles, whereas parabronchial breathing with aligned capillaries—an effective system of gas exchange—developed in birds. Amphibians, on the other hand, desquamated, exposing vascularized skin able to exchange gases directly with water. In fact, this could be considered the origin of extracorporeal elimination of CO₂, a technique in use today and by which gas exchange is separated into O₂ uptake through the lungs and CO₂ elimination through an artificial organ.⁵

The mammalian lung as we know it today developed in the midst of these divergent species. In air-breathing

TABLE
Concentration of Oxygen in Water and Air

	Units	O ₂	CO ₂
Atmospheric concentration	Volume/Volume	0.2093	0.0003
Solubility in water at 1 atm and 20°C	Volume of gas/volume of water	0.031	0.88
Solubility in water at 1 atm and 37°C	Volume of gas/volume of water	0.024	0.55

Correspondence: Dr. N.A. Molfino, MD, MSc, FCCP.
Otsuka Maryland Research Institute,
2440 Research Boulevard, 3rd floor,
Rockville, MD, 20850, United States of America.
E-mail: nestorm@otsuka.com

Manuscript received February 5, 2004. Accepted for publication February 17, 2004.

fish and amphibians, oxygenation occurs mainly through the lung, while CO₂ is eliminated through the gills or skin. Air-breathing vertebrates maintain a considerable respiratory acidosis that is compensated for by an appropriate concentration of bicarbonate.⁵

Neonatal human and other mammalian lungs are filled with fluid immediately before birth. The ionic composition of this fluid indicates that active ionic transport processes occur in the epithelial cells of the alveolar spaces. Concentrations of sodium, potassium, chlorine, and proteins in this fluid are also similar to those found in marine reptiles such as the turtle, suggesting that the same mechanism may be responsible for lung development in various species.⁶

Nevertheless, evolution towards dependence on molecular O₂ for the production of energy has left land mammals at a disadvantage and we remain under threat of acute asphyxia, which leads to the intracellular triad of hypoxia, hypercapnia, and acidosis. Transfer from an environment of air to watery or liquid surroundings is the most common cause of asphyxia.⁷ It is not completely clear why the human lung is less efficient than that of other beings considered “inferior” when, theoretically, all animals have faced the same obstacles and challenges during evolution.⁸ For example, when branchial respiration emerged in fish around 400 million years ago, only one primitive lung, ventilated through a buccal pump, was involved. Land tetrapods and amphibians adopted the same system. In amniotes, the buccal pump has been replaced by a costal aspiration pump. In mammals, the pump has evolved into the lung and bronchoalveolar tree. In reptiles, the lung has a single cavity or is divided into several in which both gas exchange and O₂ storage occur, thus permitting long periods of apnea. In birds, the breathing apparatus is a tubular structure with unidirectional flow ventilation, permitting a high level of O₂ consumption.⁹ This seems to be the case with insects as well.¹⁰ Pulmonary and systemic circulation are completely separated only in mammals and birds, and this division appears to be essential for protecting the fine alveolocapillary barrier from high pressures.¹¹

The structural and functional diversity of the lung in vertebrates seems to be a response to diverse environments, phylogenic differentiation, and the

challenge of acquiring the O₂ necessary for aerobic metabolism. However, given that the human lung does not tolerate sudden changes in O₂ or CO₂ and is unable to tolerate prolonged periods of apnea, it is worth asking how it will adapt to the greenhouse effect—which is sure to occur if present atmospheric conditions continue.² Likewise, humans exhibit common symptoms—such as coughing, bronchospasm, and dyspnea—when exposed to environmental substances (such as pollution and allergens) or noxious ones (such as tobacco or workplace toxins). These symptoms, diagnosed as asthma or chronic obstructive pulmonary disease, may in reality be ineffective, counterproductive, and—in many cases—progressive defense mechanisms requiring treatment.

The hypothesis that the lung is adapting to environmental changes rather than “suffering the consequences” of these changes is unproven, but should be considered when discussing the increase in the prevalence of respiratory diseases and methods for their prevention.¹²

REFERENCES

1. Lovelock J. Gaia: the living earth. *Nature* 2003;426:769-70.
2. Kasting JF, Siefert JL. Life and the evolution of Earth's atmosphere. *Science* 2002;296:1066-8.
3. Levine JS. The early atmosphere: a new picture. *Sci Act* 1986; 23:6-16.
4. Pilcher CB. Biosignatures of early earths. *Astrobiology* 2003; 3:471-86.
5. Nolte S. Evolutionary biological aspects of the physiology of extracorporeal CO₂ removal. *Anaesthesist* 1989;38:622-5.
6. Maloney JE, Darian-Smith C, Russell B, Varghese M, Cooper J, Limpus CJ. An evolutionary link for developing mammalian lungs. *J Dev Physiol* 1989;12:153-5.
7. Gooden BA. The evolution of asphyxial defense. *Integr Physiol Behav Sci* 1993;28:317-30.
8. Maina JN. Comparative respiratory morphology: themes and principles in the design and construction of the gas exchangers. *Anat Rec* 2000;261:25-44.
9. Roux E. Origin and evolution of the respiratory tract in vertebrates. *Rev Mal Respir* 2002;19:601-15.
10. Westneat MW, Betz O, Blob RW, Fezzaa K, Cooper WJ, Lee WK. Tracheal respiration in insects visualized with synchrotron x-ray imaging. *Science* 2003;299:558-60.
11. West JB. Thoughts on the pulmonary blood-gas barrier. *Am J Physiol Lung Cell Mol Physiol* 2003;285:L501-L13.
12. Lenton TM, Lovelock JE. Daisyworld is Darwinian: constraints on adaptation are important for planetary self-regulation. *J Theor Biol* 2000;206:109-14.