

BLOOD OXYGENATION SANS LUNG

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I. EVALUATION OF LUNG AS A BLOOD OXYGENATOR

ANIMALS obtain the bulk of their metabolic energy from oxidation. The supply of oxygen for oxidation and the elimination of carbon dioxide which results therefrom are the central functions of respiration. In the development of respiratory organs, Nature has been exceptionally inventive and where the metabolic needs of animals raised the demand for oxygen beyond the capacity of the general body surface, a great diversity of specialised surfaces for respiratory gas exchange resulted. Thus the evaginated gills for gas exchange with aquatic media and invaginated lungs for exchange with the atmosphere evolved.

Oxygen supply sans lung is the basis of respiration among many living species. Many bacteria, for example, metabolise rapidly and consume oxygen at rates far higher than those needed by large animals. In sponges, cilia or flagella generate water currents which supply not only food but also small quantities of oxygen. Lamelli branches have ctenidia or gills for the oxygenation of blood and cilia which promote water circulation. The low level of oxygen consumption and sluggish state of existence in sponges and molluscs contrast with the tracheal respiration of vigorous insects which can consume 167 times the rate of oxygen consumption at rest¹. The respiratory device in insects is an elaborate system of tracheal tubes starting from the surface and terminating in central tracheoles which permeate the tissues. The diffusion of O₂ and CO₂ in this system takes place by small pressure differences along the tracheole. The cardinal distinction here is the virtual exclusion of the vascular system from the transport of respiratory gases and the development of a method in which gas exchange and transport are combined within a single anatomic entity, the tracheal system.

When one turns to vertebrates, the skin has a small role in oxygen and carbon dioxide transport, but the respiratory exchange is concentrated in gills or lungs. In the respiration of amphibia, the skin may, however, continue to play a supportive role to the lung in the oxygenation of blood. The persistence of cilia in the respiratory passages of man is a reminder of the earlier phase of respiratory evolution when the lung had little or no role in respiration.

Even though evidence for an imperfect use of lung exists in fishes, it begins to contribute significantly to respiratory exchange only at the stage of reptiles whose size and metabolic demands were larger. The transition from the cold blooded state of reptiles to the warm blood habit of birds and mammals was marked by substantial increases in respiratory and circulatory ability and the evolution of the mammalian lung. In evolutionary terms, lung is indispensable for the sustenance of normal mammalian activities which can nevertheless be supported at a basal level by other means of gas exchange.

2. THE ROLE OF HUMAN LUNG IN BLOOD OXYGENATION

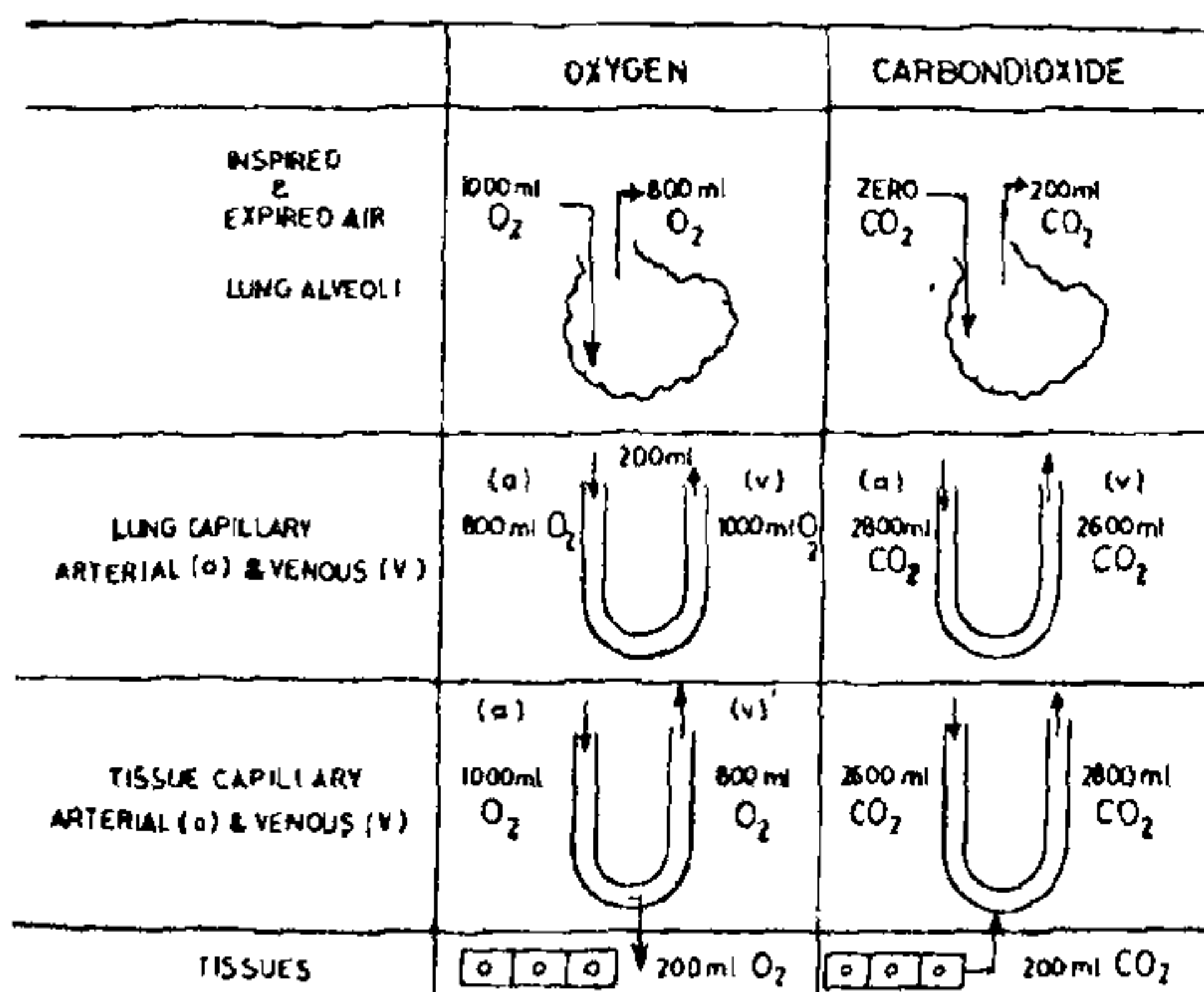
The resting requirements for oxygen in man amounts to 200 ml/min which may increase thirtyfold during exercise. Equivalent amounts of carbon dioxide which results from cell metabolism are simultaneously eliminated. The mechanisms of oxygen and carbon dioxide exchange between body cells and external environment sequentially involves exchange of air between the atmosphere and alveoli in the lung, exchange of oxygen and carbon dioxide between alveolar air and lung capillaries, transportation of oxygen and carbon dioxide by the blood and exchange of oxygen and carbon dioxide between the blood and tissues of the body. At rest, the air we

breathe or pulmonary ventilation amounts to 5 litres/min which contains 1 litre of oxygen. Of this inspired oxygen, 200 ml cross the lung alveoli into the pulmonary capillaries and the remainder is exhaled. The 200 ml of oxygen get added to the venous blood during its oxygenation in the lung and a corresponding amount of oxygen leaves the blood during its deoxygenation in the tissues. A similar movement of carbon dioxide by diffusion takes place in the opposite direction from tissues to the alveolar air (figure 1).

The force which induces the net movement of oxygen and carbon dioxide molecules across alveolar, capillary and cell membranes is passive diffusion which was demonstrated in the historic experiments of Krogh.

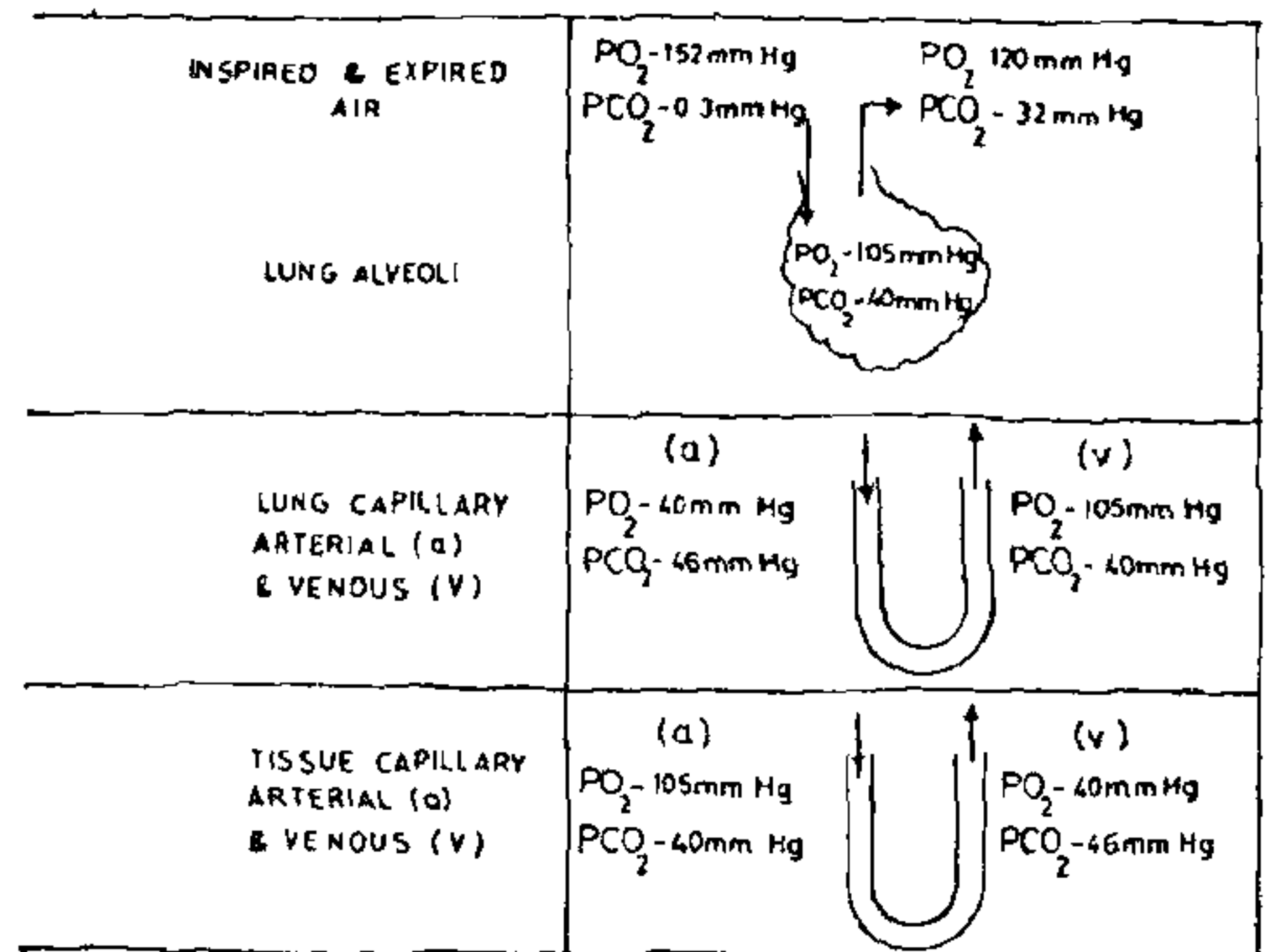
Net transport of gas molecules by diffusion can occur only when a concentration gradient exists. The partial pressures of oxygen and carbon dioxide at different sites of the respiratory cycle are therefore of utmost importance (figure 2).

At sea level, the PO_2 , is 152 mm Hg and pCO_2 0.3 mm Hg of inspired air whereas the corresponding figures for expired air are 120 mm Hg and 32 mm Hg respectively. In contrast, the alveolar gas partial pressures are relatively constant throughout the respiratory cycle because a



(PULMONARY VENTILATION 5 litres)
- RESPIRATORY QUOTIENT 1
- DOWNWARD & UPWARD ARROWS INDICATE INSPIRATORY AND EXPIRATORY EXCHANGES

Figure 1. Oxygen and carbon dioxide exchanges during respiration.



DOWNWARD AND UPWARD ARROWS INDICATE INSPIRATORY AND EXPIRATORY EXCHANGES
Fig 2 - PARTIAL PRESSURES OF OXYGEN AND CARBONDIOXIDE DURING RESPIRATORY EXCHANGE IN LUNG AND TISSUES

Figure 2. Partial pressures of oxygen and carbon dioxide during respiratory exchange.

large volume of oxygen and carbon-dioxide is left in the lung at the end of expiration and the new inspired air does no more than mix with the pre-existing air lowering its pCO_2 and raising its pO_2 by negligible quantities.

The venous blood reaching the lung with a high pCO_2 and low pO_2 is separated from the alveolar air only by a layer of less than one micron thickness. The difference in the partial pressures of oxygen and carbon dioxide on the two sides of this thin alveolar-capillary layer promotes the net diffusion of oxygen into blood and carbon dioxide into the alveoli until gas partial pressures on either side of the alveolar-capillary membrane equilibrate. The process of diffusion takes place rapidly because of the difference in gas partial pressures between the alveoli and capillaries, natural affinity of haemoglobin for oxygen and the large area of 100 sq. metres provided by the alveolar-capillary 'pathway' in a normal lung.

3. OXYGENATION SANS LUNG

While the human lung provides a highly efficient mechanism for blood oxygenation and release of carbon dioxide, the need for its substitution arises in clinical and pathologic conditions

where normal lung function is suspended or destroyed. The commonest example for the suspension of lung function is open heart surgery where an artificial circulation bypasses the heart and lungs of patients. In contrast to the relatively short period of heart-lung bypass which seldom exceeds four hours, blood oxygenation sans lung may be necessary for much longer periods when lungs are seriously damaged by trauma, viral pneumonia and several other pathologic conditions. Devices which provide artificial gas exchange during the suspension or absence of lung function are known as oxygenators even though they perform more than mere oxygenation. Originally introduced by Gibbon for open heart surgery in 1953², oxygenator technology grew rapidly in subsequent years and drew as much upon the biology of respiration as on gas-liquid mass transfer and the biocompatibility of materials.

4. BLOOD OXYGENATORS

While blood oxygenators cannot equal the performance of lung as outlined earlier, they are expected to fulfil stringent functional criteria which cover gas transfer, damage to blood constituents, nontoxicity of component materials, durability of function and test animal survival³.

The three basic types of oxygenators which have been in clinical use over the years provide a large surface of equilibration between blood and gas by the dispersion of blood in gas (film oxygenator), dispersion of gas in blood (bubble oxygenator) or the interposition of a permeable membrane between the liquid and gaseous phases (membrane oxygenators) figure 3.

They are briefly discussed below:

4.1. Film Oxygenators

The maintenance of a film of blood in a gaseous atmosphere calls for a support which could be stationary or moving. Apart from blood trauma induced by various forms of mechanical support, the initial problem in this approach related to the barrier posed by the superficial

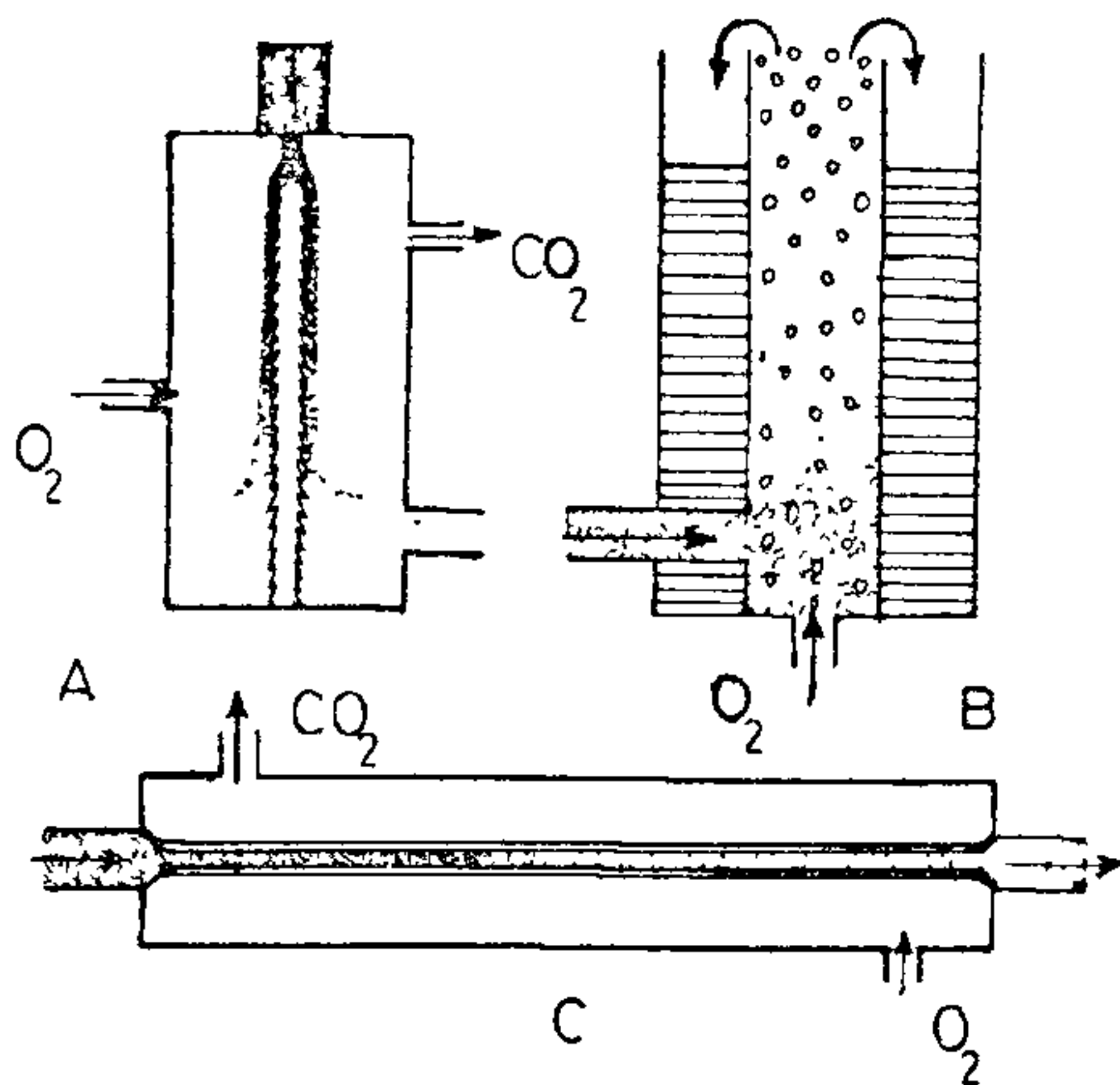


Figure 3. Oxygenators A. Film type, B. Bubble type and C. Membrane type.

layers of the blood film which became oxygenated quickly and hampered the oxygenation of the deeper layers. This difficulty was not overcome until Gibbon introduced a stationary screen with an irregular surface which created a gentle turbulence in the blood film. It may be interesting to note here that one of the earliest stationary screen oxygenators was developed by Charles Lindberg of trans-Atlantic flight fame during his partnership with Alexis Carrel for organ perfusion experiments⁴. Stationary screen oxygenators consisting of six screens, each 45 mm high and 30 cm wide, soon gave way to rotating disc oxygenators which provided a thinner blood film and made the apparatus less bulky⁵. The disc oxygenators featured a glass cylinder in which 60 or more stainless discs, 0.4 mm thick and 12.2 cm in diameter, were mounted 0.5 mm apart by means of spacers on a central shaft. Venous blood introduced at one end of the cylinder emerged at the bottom of the opposite end in the fully oxygenated state. While the static area of the blood film in these oxygenators was around 0.84 m², the dynamic area at 120 rpm could reach 110 m² per minute and arterialise blood at a flow rate of 2 l/min. The rotating disc oxygenator was extensively used for

over a decade until they were gradually replaced by disposable bubble oxygenators in the nineteen seventies.

4.2 Bubble oxygenators

The old knowledge that a large gas-liquid interface could be created by simply bubbling gas through a small volume of the liquid could not find clinical application until Clark, Gollan and Gupta introduced silicones as defoaming agents⁶. In bubble oxygenators, oxygen is dispersed into the venous blood through small holes in a distributing manifold located at the bottom of the bubble chimney. Small bubbles while highly efficient for oxygenation are inefficient for carbon dioxide removal and are difficult to remove. Large bubbles, on the other hand, are less efficient for oxygenation but are easily removed and are highly conducive to carbon dioxide removal. In practice, a coarse and fine porosity hybrid manifold is used in bubble oxygenators. The theoretic aspects of gas bubble formation has been discussed by Jackson^{7,8}.

The bubble oxygenators consist of chambers for bubbling, defoaming and settling which are arranged sequentially^{9,10}. Even though sequential bubble oxygenators continue to be in current clinical use because of their efficiency, disposability and relatively low cost, concentric bubble oxygenators have currently claimed wider acceptance despite higher cost in view of their compactness, lower priming volume and ready integration of a heat exchanger in their design. They consist of a central column through which venous blood mixed with oxygen climbs and a surrounding chamber of antifoam-coated substrate through which the oxygenated blood descends to the bottom of the unit. They also contain an integral metal coil for the circulation of cold or warm water for cooling or warming of blood during extracorporeal gas exchange. A recent model of a bubble oxygenator of concentric design which also incorporates a chamber for collecting blood from cardiac suction is shown in figure 4.

The present generation of bubble oxygenators have, in general, a priming volume of 1.2 litres



Figure 4. Chitra variflow oxygenator.

and provide excellent oxygenation at gas: blood flow ratios of 1:1 or less for several hours with little damage to blood constituents.

4.3. Membrane Oxygenators

The film and bubble oxygenators are unphysiologic in so far as they demand direct contact between blood and ambient gas. A return to the biologic design where a semi-permeable membrane separates capillary blood from the alveolar gas was achieved by membrane oxygenators which date back to the observation of Kolff that dark venous blood entering the top of the cellophane tube of his artificial kidney brightened during its transit. As polymer films were known to be permeable to gases and vapours through diffusion, polyethylene, sili-

cone, teflon and many other plastic films were initially employed in the development of membrane oxygenators. The transfer of gases across membranes is determined by several factors including the thickness of the film, degree of hydration of the membrane, nature of the gas and the gas tension difference between the two sides of the membrane. In the pressure conditions of the membrane lung where pure oxygen is used in the gas phase, carbon dioxide transfer has been more difficult than oxygenation. Broadly stated, CO_2 release is governed by the surface area of the membrane whereas O_2 transfer is dependent upon the thickness of the blood film.

Membrane oxygenator research initially took diverse paths. Some investigators attempted to develop liquid-liquid exchangers by employing liquid fluorocarbons which have a high coefficient of solubility for oxygen and carbon dioxide. Since the fluorocarbons are immiscible with blood, they could flow in direct contact with blood, the interface between the two liquids acting as a virtual membrane across which gas transport would take place. This approach however required an accessory bubble oxygenator to charge the fluorocarbon with oxygen and extract its load of carbon dioxide. It also left unanswered questions regarding the longterm biological effects of fluorocarbons. Another interesting approach was the use of catalytic membranes across which blood was exposed to an oxygen-rich liquid such as hydrogen peroxide and a carbon dioxide absorber like bicarbonate of sodium. The membrane itself consisted of cellulose with a transition metal oxide (*e. g.* ruthenium oxide) deposited in the mesh. While the catalytic membrane was effective, it could not prevent small leakages of hydrogen peroxide into the blood phase or the progressive loss of calcium, magnesium and phosphates from blood consequent on the chemical binding of carbon dioxide as carbonates. A third method sought to minimise the blood boundary layer which limited oxygen transport by promoting convective transport within the blood phase in the form of 'secondary flow'. While all the three approaches excelled in gas transport efficiency in the labora-

tory, they have not yet graduated into regular clinical application.

The currently popular models of membrane oxygenators are, in fact, constructed from microporous polypropylene membrane or hollow fibres. The membrane with a pore size of $1-2 \mu\text{m}$ is folded upon itself with plastic mesh spacers and encased in a plastic jacket. In this design, the thickness of the blood film is regulated by the gas column between the plastic jacket and the membrane stack which provides a static surface area of diffusion of $1.5-2.5 \text{ m}^2$. In the hollow fibre membrane model, fibres of $200 \mu\text{m}$ ID X $250 \mu\text{m}$ OD and pore size of $0.07 \mu\text{m}$ are fixed at each end in a polyurethane base and encased in a plastic jacket. Gas ports are moulded into the jacket which also contains an integral heat exchanger. The fibre lengths of 13 cm and 14 cm which are commonly used, provide static surface areas of 1.6 m^2 and 3.3 m^2 respectively.

As mentioned earlier, efforts have been made to improve gas transfer efficiency in membrane oxygenators by the application of secondary flow which is created by the interdigitation of blood and gas channels and the introduction of bilevel and intermixing fibres. These innovations have achieved transfer rates for oxygen and carbon-dioxide as high as $140 \text{ ml/m}^2/\text{min}$ and $125 \text{ ml/m}^2/\text{min}$ respectively at 6l flows with a priming volume as low as 600 ml^{12} . The advances in membrane oxygenation in terms of materials, design and the fluid mechanics of blood and gases have generally followed the direction of the microstructure and function of the mammalian lung.

Membrane oxygenators have found wider use in recent years despite their higher cost.

5. LONG TERM BLOOD OXYGENATION SANS LUNG

While bubble oxygenators largely meet the demand for blood oxygenation during open heart surgery, they cause unacceptable damage to blood in terms of cellular disruption and protein denaturation beyond four or five hours of perfusion. When long term blood oxygenation is sought for several days during which period

lungs severely damaged by trauma and viral or chemical pneumonia might recover, membrane oxygenators have been employed with reasonable success in recent years. Extracorporeal membrane oxygenation (ECMO) is still in its infancy and has among its major problems the accumulation of water in the gas phase and 'plasma weeping' from the membrane which inhibit gas transfer rate over long periods. There is little doubt however that ECMO will sooner or later pave the way for semi-permanent or permanent lung substitutes which would offer a new life to patients with severe lung disease and pulmonary insufficiency. This would call for continued improvements in the microporous membrane and the possible incorporation of the nonrespiratory functions of the normal lung in the membrane system by techniques such as the grafting of appropriate cells and molecular groups.

ACKNOWLEDGEMENT

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NEWS

NEW THERAPY FOR ULCERS

... "A synthetic prostaglandin that stands up to histamine H₂ receptor antagonists in ulcer treatment and also protects gastric mucosa has been approved for use in Mexico. The prostaglandin E₁ derivative, misoprostol (Cytotec, Searle), is as effective as cimetidine (Tagamet, Smith Kline & French) and has few side effects, according to Stephen J. Sontag [Veterans Admin. Hosp., Hines, Ill]. 'Also, it protects mucosal tissue from irritants and may prevent blood loss caused by ulcers or nonsteroidal anti-inflammatory agents,' Sontag said. ... 'Furthermore, the cytoprotective effect may not be limited to the stomach and duodenum. The prostaglandin derivative may prove

useful for treating pancreatitis, asthma, or liver cirrhosis,' he added. So far, Mexico is the only country to approve Cytotec for treatment of gastric and duodenal ulcers, but Searle has requested approval in at least 30 countries."

[(In *Medical World News* 8 Apr 85, p. 63-4 (See also: E. Garfield. All about ulcers, antacids, and how little we know. *Essays of an information scientist*. Philadelphia: ISI Press, 1981. Vol. 4, p. 666-73.) [p. 2604j]*). Reproduced with permission from Press Digest, *Current Contents*®, No. 26, July 1, 1985, p. 9. (Published by the Institute for Scientific Information®, Philadelphia, PA, USA)]