special communication

How Does Lung Structure Affect Gas Exchange?*

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The lung is characterized morphologically by establishing a very large surface and an exceedingly thin barrier between air and blood. A model for relating these structural features to the lung's gas exchange function is first developed. It is then shown that DO2 estimated by morphometry is about two times larger than that estimated by physiology; there are possible reasons for this. Comparing animals of high activity (dog, horse) with corresponding species of lower activity (man, cow) reveals that DO2 is proportional to O2 needs. The mechanical properties of the lung are discussed which allow such a large surface with such a thin barrier to be maintained lifelong. Surfactant properties of the lining layer are important factors in stabilizing the alveolar surface. Repair processes are also essential and require metabolic activities of the cells lining the barrier. The case of adult respiratory distress syndrome is used to illustrate the consequences of severe damage to the cell linings of alveoli: the barrier is thickened, and a good part of the alveolar surface is flooded by edema fluid, so that gas exchange is severely impaired.

In recent years, there has been much emphasis on the fact that the lung can serve a multitude of metabolic functions. There is, however, only one vital function that is served exclusively through the lung, for which there is no alternative—this is the gas exchange between air and blood. It is therefore certainly justified to conjecture that the lung is specifically designed in view of efficient uptake of O2 and discharge of CO2.

Indeed, our needs for O2 uptake through the lung are large. Those among us who go jogging may use in their muscles up to 3 L O2 per minute, if they are well trained athletes even up to 5 L. The only way to get this O2 loaded into the blood is through the lung. How much does this depend on the lung's structural design?

In view of this question, a concept is developed by which we can test the hypothesis that the design features of the lung, as they are set up by lung structure, are important determinants of gas exchange between air and blood. A number of basic structural properties of the lung evidently favor gas exchange:

(1) The branching of the airway tree and the formation of a maze of densely packed alveoli around the terminal airway branches establish a very large internal surface nearly the size of a tennis court, and this in such a way that each unit of the surface can be easily ventilated.

(2) If the alveolar wall is viewed at higher power, it is seen as densely populated with red blood cells; they are contained in capillaries that extend as networks between pulmonary arteries and veins and can thus be easily perfused.

(3) At still higher power, the blood is found to be separated from the air by an exceedingly thin barrier which is made of at least two cell layers but still is about 50 times thinner than a single sheet of airmail stationery!

These design features are directly related to the lung's gas exchange function. There is evidence which shows that the airway tree is designed for nearly optimal, efficient ventilation of the alveoli, and the same holds for the blood vessels with respect to perfusion. Of note is the diffusion step in this process, ie, the step where O2 is transferred from the air to the blood across the barrier.1

This process is governed by the following three factors: in terms of function, the movement of O2 from one compartment to the other is governed by the PO2 gradient across the barrier which is established by ventilation and by perfusion, ie, by continuously exchanging the two media between which O2 is exchanged. In terms of design, the process is governed by the dimensions of the barrier: the larger the surface and the thinner the barrier, the more efficient gas exchange by diffusion.

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The Lung’s Diffusing Capacity: Relating Gas Exchange to Structure

It is customary to describe the functional gas exchange properties of the lung by its diffusing capacity, $D_{O_2}$, as introduced by Bohr in 1909. But since gas exchange is determined both by functional and by structural parameters, it should be possible to estimate the lung’s diffusing capacity by considering either the physiologic conditions, i.e., the driving force, or by looking at the design properties with a morphometric eye.

In physiology, $D_{O_2}$ is defined as the flow of $O_2$ per minute that occurs if the $P_{O_2}$ gradient is 1 mm Hg. Thus, if one can measure $O_2$ consumption, $V_{O_2}$, and the $P_{O_2}$ in alveolar air and capillary blood, one can estimate $D_{O_2}$ by Ohm’s equation:

$$D_{O_2} = \frac{V_{O_2}}{(P_{A_{O_2}} - P_{C_{O_2}})}$$

In this relation, $D_{O_2}$ is the diffusion conductance of the gas exchanger or the reciprocal of its diffusion resistance.

It is well known that the resistance or the conduc-
tance of any conductor, for example of an electrical wire, can also be calculated from its dimensions and its material properties. Thus, it is said that $D_{O_2}$ should be proportional to the barrier surface $S$ and inversely proportional to the barrier thickness $T$, this ratio multiplied by the permeability coefficient $K_{O_2}$:

$$D_{O_2} = K_{O_2} \cdot \frac{S}{T}$$

So in principle, if we can measure $V_{O_2}$ and the $P_{O_2}$ gradient, as well as $S$ and $T$, we have two approaches in hand with which to estimate $D_{O_2}$, one based on function, the other on structure, and this should allow us to approach the question how lung structure affects gas exchange in a quantitative way.

But before we can do that, we must examine our models a bit more closely. The conventional model for estimating $D_{O_2}$ by morphometry given above is too simple, because it really considers only the first step of $O_2$ uptake: the transfer of $O_2$ across the tissue barrier. However, the entire process involves, in reality, three steps (Fig 1): (1) the transfer of $O_2$ across the tissue barrier into plasma; (2) the diffusion of $O_2$ through the plasma; and (3) the binding of $O_2$ by hemoglobin within the red cells.

The more refined model shown in Figure 1 defines, for each of these steps, a conductance which is composed of a physical coefficient and some morphometric parameters, such as the alveolar and the capillary surface areas of the barrier, $S_A$ and $S_C$, the barrier thickness, $\tau$, for both tissue and plasma, and the volume of capillary blood, $V$, which binds $O_2$. It is a basic physical law that if three conductors are in series the sum of their resistances, $1/D$, is the total resistance, so that we derive $D_L$ from the sum of $1/D$. If we can make some reasonable assumptions for the physical coefficients, this model should allow us to estimate from morphometric data a value for $D_{O_2}$ which is directly comparable to the physiologic estimates because it comprises the entire pathway.$^{1,3}$

Some years ago, sets of lungs were collected from healthy young people ~20 to 40 years of age.$^4$ On histologic sections viewed with the electron microscope, the alveolar and capillary surface areas, the capillary volume, and the barrier thicknesses were measured by using stereologic methods. These are accurate methods based on statistical considerations.$^4$ The results of these measurements were as follows (Table 1):

(a) The gas exchange surfaces are on the order of 120 to

![Figure 1](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21351/ on 06/21/2017)
140 m²,
(b) the capillary blood volume amounts to 200 ml; when spread over the surface of a tennis court, this makes a very fine film of blood, less than one red blood cell thick so that each erythrocyte can become intensely and directly exposed to air.
(c) the barrier measures a bit more than ½ µm when its effective average thickness, the harmonic mean thickness, is considered.
Calculating DO₂ from these data necessitates assumptions about the physical coefficients of diffusion, K, and of O₂ binding to blood, 00. Using standard values, we estimate DO₂ at 200 ml O₂ • min⁻¹ • mm Hg⁻¹. It is possible that more refined but still speculative data on “effective 00,” may reduce this estimate to ~140, but not much further. This is evidently much higher than the 20 to 30 ml • min⁻¹ • mm Hg⁻¹ usually estimated by physiologic methods.

WHY THIS LARGE DIFFERENCE BETWEEN “MORPHOMETRIC” AND “PHYSIOLOGIC” DO₂?

Does it mean that the approach we have taken is not valid, that morphometric and physiologic DO₂ are not comparable? Or, if they are comparable, does it mean that lung design establishes a diffusing capacity that is vastly in excess of what is needed? In fact, this is the opinion of many physiologists who maintain that gas exchange is not limited by diffusion in the lung. This is quite certainly true at rest when one estimates that blood becomes equilibrated with alveolar air after ~½ of the path from artery to vein. So, clearly, the gas exchanger is too large.

However, the lung is hardly designed to just satisfy our O₂ needs at rest. It is likely that we exploit the lung’s diffusing capacity only in strenuous exercise, when the muscles operate at the limit of our work capacity. Under these conditions, we increase blood flow, ventilation, and O₂ consumption; the transit time is only about one third and we may well need the entire path length to load the larger amount of O₂ onto the blood.

Thus, we should compare the morphometric DO₂ data with physiologic data obtained in heavy exercise. Under these conditions, we find that O₂ consumption and ventilation increase by about tenfold, cardiac output 2.5 times, and the pulmonary diffusing capacity by a factor of 3.5 reaching values up to 100 ml • min⁻¹ • mm Hg⁻¹.

This physiologic estimate of DO₂ now compares reasonably with the morphometric estimates (Table 1). The remaining difference by a factor of 1.5-2 may partly be due to uncertainties in the assumed physical coefficients. Or it may reflect the fact that the body can perhaps not fully exploit the diffusing capacity of its lung because it cannot operate perfectly all the time. Because of this, the lung may need to have a certain safety factor built in, and safety factors of the order of 1.5 to 2 are well known for other systems.

One problem with this comparison is, however, that the physiologic and the morphometric estimates have not been obtained on the same individuals. To overcome this we have recently examined by morphometry, lungs of four species of Canidae, on which J. O’Neil and C. R. Taylor had estimated Dco by a single breath method. By morphometry, we found estimates that were consistently larger by a factor 2. Although the agreement between physiologic and morphometric estimates is not (yet) perfect, it still appears that the diffusing capacity of the lung, as determined by design properties, is proportional to the lung’s capacity to perform as a gas exchanger.

There is still another line of evidence in support of this. Remember that, physiologically, DO₂ is the ratio of O₂ consumption to driving force. Thus, one might speculate that DO₂ should be proportional to an animal’s O₂ needs. One could compare O₂ consumption and morphometric DO₂ in animals of similar size but different O₂ needs because of different activity patterns, and see whether this checks out (Fig 2). One
such pair could be man compared to the dog who uses twice as much $O_2$ per kilogram of body mass—for obvious behavioral reasons. And we find the dog's $Do_2$ to be twice that of man. Or we can compare horse and cow and obtain the same result: both $O_2$ consumption and $Do_2$ are more than twice as large in the horse. The $Do_2$ therefore seems to be proportional to the animal's $O_2$ needs.

The design features of the lung bear importantly on its functional performance as a gas exchanger, in the sense that the large surface and thin barrier are critical determinants of the pulmonary diffusing capacity.

**How Can a Thin Barrier of Such Large Surface Be Maintained?**

How does the lung succeed in maintaining such a large contact surface between air and blood, and how can it keep the barrier so exceedingly thin. Three things to note are the importance of the mechanical framework on which the capillaries are supported in air, the role of surfactant for keeping alveoli and capillaries open, and the basic features of the cell linings that allow the barrier to remain very thin.

The mechanical structure of the alveolar septum has a dense capillary network which weaves from one side to the other. On a section, one half of the barrier is extremely thin, made only of the two lining layers of endothelium and epithelium (Fig 3). On the other side, the interstitial space is widened and contains connective tissue fibers which are part of the lung's fibrous support scaffold. This picture is the result of a characteristic design property where the septum contains two interlaced networks, the capillaries weaving back and forth from one side to the other crisscrossing the network of connective tissue fibers (Fig 4). By this design, every capillary unit becomes directly supported on the fibrous framework but is attached to the fibers only on one side.

But fibers can serve a mechanical support function only if they are under tension. This means that the fibers in the alveolar walls must be anchored on both ends in such a way that they can be stretched or at least tensed by the respiratory movements of chest wall and diaphragm so as to spread out the capillary network in the air space. These two anchoring points are established by two coarser fiber systems: (1) the system of fibers that emanates from the pleura and penetrates into the lung in form of septa between segments, lobules; etc; and, (2) by the fibers that follow the wall of airways from the hilum out into the alveolar ducts where they form a network of strong fiber rings around the mouths of alveoli. A closer look at this region shows that the free edge of alveolar walls is indeed made of relatively strong fiber rings in which the thin fibers of the wall proper are anchored.

Thus, as the visceral pleura is pulled outwards by the negative intrapleural pressure, the peripheral fiber system distributes this distending force throughout lung parenchyma, and the alveolar walls can be spread out being pulled away from the axial fibers around the alveolar ducts (Fig 5). The result is the formation of a very fine froth made of small air bubbles, ∼.25 mm in diameter, which are all open to outside air through the alveolar duct and bronchial tree system, a structure with a rather large surface in a small volume.

Such a structure is, by its physical nature, unstable. Comparatively large forces are generated at the air-fluid surface which have the tendency to collapse the alveoli (Fig 5): on a hollow surface, the surface force is
5. Mechanical model for duct and surrounding forces in alveolar directed inwards, tending to shrink the bubble down, but over the free edge of alveolar walls, the force generated is directed outwards with a tendency to fold up the wall, enlarging the alveolar duct at the expense of alveoli. The question has long been debated whether the fiber system we have just discussed is strong enough to resist these collapsing forces, mainly by virtue of its continuous nature as a three-dimensional network; in other words, whether the large surface can be maintained simply because all alveoli are interdependent, so that a collapsing force acting on one alveolus would be counteracted by opposite forces in the surrounding alveoli.

Although this interdependence definitely plays a role, and even an important and essential one, it is not sufficient to stabilize the alveolar complex, and it does not have to be. Since the discovery of pulmonary surfactant, first in 1929 by von Neergard and then again by Pattle, and its functional characterization by Clements et al., we know that the forces generated at the alveolar surface are much smaller than one would expect.

Surfactant is a very thin film of phospholipids that is synthesized by the type 2 cells of the alveolar epithelium, stored in their lamellar bodies, and then secreted onto the alveolar surface where it spreads out on the surface of a liquid lining layer that forms little pools in pits and crevices between the capillaries (Fig 6). This surface lining layer reduces the surface forces in two ways: first by smoothing the surface irregularities and secondly, by the surface active nature of the phospholipid film which is rather unusual in the sense that the surface tension falls when the film is compressed, ie, as the alveoli become smaller.

How important is surfactant for stabilizing the architecture of the alveolar complex? This question has
recently been examined by Bachofen et al. by comparing normal rabbit lungs with lungs in which the surface lining layer had been washed away by lavaging the airways with a detergent. If one compares the overall mechanical properties of these lungs by recording pressure-volume curves (Fig 7), one finds, as is well known, that an intact lung has a wide hysteresis, i.e., on deflation the volume remains large even down to relatively low pressures. At a pressure of only 5 cm H₂O, the lung still retains about 60 percent of its total lung capacity. When lungs are fixed at this volume by vascular perfusion, one finds all alveoli to be evenly distended and open to the alveolar duct (Fig 8).

In detergent-rinsed lungs, however, a pressure of 15 cm H₂O was required to maintain 60 percent total inflation (Fig 7); thus, removing surfactant causes the retracting forces to be evidently much greater. And if such lungs are fixed by perfusion, one finds that the alveoli are collapsed (Fig 9). The alveolar walls are folded up because they have been pushed outward by the high surface forces acting on the free edge; this results in a widening of the alveolar ducts, with their strong fiber nets greatly distended.

This experiment shows very clearly that the architecture of the alveolar complex cannot be stabilized by the interdependent fiber system alone. If surfactant is removed, the air is contained in wide air spaces corresponding to overdistended alveolar ducts whereas all the surrounding alveoli are collapsed. The free surface area of these spaces is only about one third

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**Figure 7.** Pressure-volume diagram for normal (solid line) and detergent-rinsed lungs (broken line).

**Figure 8 (upper).** Lung fixed at 60 percent TLC in normal air-filled state. Note that alveoli are patent (A). **Figure 9 (lower).** Lung rinsed with detergent and then air-inflated. Alveoli (A) are collapsed, and axial fiber strands tensed (arrows). (Reprinted from Wilson and Bachofen.)

**Figure 10.** Scheme relating the forces that act on air-blood barrier.

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of that in a normal lung because the alveolar walls that contain the capillaries cannot be kept extended. Clearly, the gas exchange conditions must be rather poor under these circumstances.

The presence of a thin surface lining layer with surfactant has still another very important effect in that it allows the capillaries of the alveolar wall to be wide enough to be adequately perfused. Gas exchange between air and blood evidently depends on the amount of blood that can pass over the gas exchanging surface. But capillaries are greatly dependent on the balance of forces that act on the very thin air-blood barrier (Fig 10). If a capillary is patent, it will slightly bulge toward the air space and surface tension, then generate a force that pushes the air-blood barrier inward. It can remain patent only if this force is compensated by the local capillary blood pressure. Surfactant reduces the magnitude of the surface force, and the capillaries can remain open even though pulmonary capillary blood pressure is very low. By modifying the perfusion pressure, Bachofen et al. could recently show the importance of this balance of forces: as the pressure in the capillaries falls, they become slit-like narrow tubes. The amount of blood that can flow over the surface to pick up O\textsubscript{2} is evidently greatly reduced.

**HOW TIGHT IS THE BARRIER?**

Finally, noting the barrier between air and blood, adequate conditions for gas exchange can only be maintained if the barrier is structurally intact and thin. The essential function of the barrier is to keep fluid from leaking from the capillary into the alveolar air spaces, i.e., to keep the lung dry. This is achieved by setting up two uninterrupted cell sheets, one lining the capillary and the other the alveolus (Fig 3). We now know that these cell sheets, the endothelium and the epithelium, serve this sealing function very well not only because they can, to some extent, actively control the movement of fluids and solutes, but because they can assure the intactness of the lining from within the barrier itself, by self-repair of damages—an important difference to any man-made machine! To maintain the lifelong integrity of these linings, living cells are required that can continuously renew the cell constituents, that can replace, for example, membrane elements which may have become damaged or simply worn out. This property of the lining cells of the barrier depends essentially on their capability to synthesize proteins, lipids, etc, and this requires them to maintain an adequate metabolic machinery under the control of the cell nucleus.

Clearly, this maintenance function requires a certain cell mass, simply to house the nucleus and the organelles performing these functions. But gas exchange requires the barrier constituents to be as thin as possible. The lung is therefore faced with the problem of optimizing the structure of the barrier so as to have (1) enough cell mass to ensure the integrity of the barrier, but (2) as little as possible interference with the gas exchange pathway.

The solution to this problem is to confine the metabolic centers of these cells in very small regions around the nucleus and to allow very thin cytoplasmic leaflets to extend radially from these centers over very long distances (Fig 3). These cytoplasmic leaflets are made essentially of two plasma membranes with very little cytoplasmic ground substance in between, with no organelles except some vesicles engaged in fluid transport.

This structural design has the following two consequences of importance:

1. The barrier thickness is uneven. We find, as seen before, that about one half of the barrier surface is made only of the two extremely thin cell leaflets which are closely apposed, separated merely by a single fused...
basement membrane. The other half contains not only the fibers of the support system, but also the metabolic centers of the lining cells (Fig 3). It turns out that this uneven distribution of barrier thickness is most favorable for gas exchange. From the physical model for gas exchange set up before, we conclude that the $O_2$ flow rate through each unit of the barrier is inversely proportional to its thickness. For physical reasons, the overall conductance of this naturally irregular barrier is three times greater than if the same amount of tissue were used to make a barrier of even thickness! Thus, the lung has succeeded to optimize the design of its barrier so as to be effectively very thin in the interest of gas exchange, while still having a cell mass adequate to perform the metabolic functions required to maintain the barrier intact.

(2) The second point is that this design makes the barrier very vulnerable. Any severe damage to the thin but wide cytoplasmic extensions will be difficult to repair, and the barrier linings may disintegrate. Figure 11 shows an alveolar septum from a case of septicemia where both the endothelium and the epithelial lining are so severely damaged that the barrier can no longer serve its sealing function. Fluid rapidly leaves the plasma and floods the alveoli: gas exchange becomes severely impaired.

This type of tissue damage leading to acute respiratory failure is commonly found in the acute or exudative stage of ARDS, irrespective of the cause of the injury. One of the important structural determinants of pulmonary gas exchange, the very thin barrier for $O_2$ diffusion has been destroyed, and much of the large gas exchange surface is obliterated by alveolar edema. The difficulty with this disease is, however, that respiratory failure persists, even after alveolar edema has been resolved. The reason is found in a dramatic structural change in the barrier that is related to the repair process needed to rebuild an intact barrier. This process requires proliferation of cells to replace those which are destroyed, as well as the synthesis of a great amount of membrane material. As a consequence, the requirement for adequate metabolic centers of the cells lining the barrier must temporarily dominate the barrier design. Mainly, the epithelium in repair is seen to be characteristically made of thick cuboidal cells (Fig 12). These cells evidently introduce a large resistance for $O_2$ diffusion into the blood, even though alveolar edema may have been resorbed.

Respiratory failure will therefore persist until the barrier has been transformed, once again, into the exceedingly thin but well structured tissue sheet characteristic of the healthy lung. It will persist also until the large alveolar surface becomes, once again, freely exposed to air, and until this alveolar surface is again densely populated with patent, well perfused capillaries.

Conclusion

The case of ARDS is indeed a striking example with which to end this demonstration of how lung structure affects gas exchange. It does so, in the healthy lung, by maintaining, with great effort and cost, and at a high risk, a very large surface of contact between air and blood, as well as a barrier thick enough to serve as a tight fluid seal, but thin enough to allow easy diffusion of $O_2$ into the blood. It is a miracle, indeed, that this frail structure does not fail more often, that it allows us to breathe easily for most of our life.

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