Comparative physiology of the pulmonary blood-gas barrier: the unique avian solution

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West JB. Comparative physiology of the pulmonary blood-gas barrier: the unique avian solution. Am J Physiol Regul Integr Comp Physiol 297: R1625–R1634, 2009.—Two opposing selective pressures have shaped the evolution of the structure of the blood-gas barrier in air-breathing vertebrates. The first pressure, which has been recognized for 100 years, is to facilitate diffusive gas exchange. This requires the barrier to be extremely thin and have a large area. The second pressure, which has only recently been appreciated, is to maintain the mechanical integrity of the barrier in the face of its extreme thinness. The most important tensile stress comes from the pressure within the pulmonary capillaries, which results in a hoop stress. The strength of the barrier can be attributed to the type IV collagen in the extracellular matrix. In addition, the stress is minimized in mammals and birds by complete separation of the pulmonary and systemic circulations. Remarkably, the avian barrier is about 2.5 times thinner than that in mammals and also is much more uniform in thickness. These advantages for gas exchange come about because the avian pulmonary capillaries are unique among air breathers in being mechanically supported externally in addition to the strength that comes from the structure of their walls. This external support comes from epithelial plates that are part of the air capillaries, and the support is available because the terminal air spaces in the avian lung are extremely small due to the flow-through nature of ventilation in contrast to the reciprocating pattern in mammals.

The Two Selective Pressures Affecting the Blood-Gas Barrier

One of the most critical structures for efficient pulmonary gas exchange in air-breathing vertebrates is the blood-gas barrier. After it was realized some 100 years ago that oxygen and carbon dioxide move through this barrier by passive diffusion (15), it was clear that an important selective pressure was that the barrier be extremely thin and have a large surface area. These characteristics follow immediately from the Fick diffusion equation, which states that the amount of gas diffusing across the barrier is proportional to the area of the barrier and inversely proportional to its thickness.

However, a second selective pressure, which acts as a major constraint to the thinning of the gas-exchanging barrier, has only recently been recognized. This is because, in addition to the barrier being thin and having a large area, it must have sufficient strength to resist mechanical failure in the face of the large stresses developing within it (36). These stresses arise primarily because of the transmural pressure of the pulmonary capillaries that increases when the cardiac output rises as in severe exercise. An additional factor increasing the stress under some conditions is a high state of lung inflation, where the tension in the alveolar walls increases and part of the increased stress is transmitted to the capillary walls. Even with relatively small increases in capillary transmural pressure during exercise, the wall stress associated with these can be very high because of the extreme thinness of the wall. Thus we can see immediately that the strong selective pressure to have a thin blood-gas barrier inevitably results in a propensity to develop very high wall stresses.

The purpose of this review is to discuss the interaction between these two selective pressures and, in particular, to show how the avian lung evolved a solution for the blood-gas barrier that is radically different from that in all other air-breathing lungs.

Structure of the Blood-Gas Barrier

Figure 1A shows a diagram of the typical structure of the blood-gas barrier in air-breathing vertebrates. Although the structure is relatively simple, it beautifully conforms to the two selective pressures listed above; that is, it is extraordinary thin but remarkably strong. There are only three layers: epithelium, extracellular matrix (ECM), and endothelium. The epithelium is typically covered by a thin aqueous layer that has the function of reducing the surface tension.

The epithelial layer exists because this is the interface between the organism and the air of the environment. Lungs first evolved as an outgrowth from the primitive gut, which is lined by epithelium. The endothelial layer exists because the pulmonary blood vessels derive from endoderm, and all cap-
illaries are lined by endothelial cells. Both the epithelial and endothelial cellular layers are typically extremely thin, thus allowing efficient diffusive gas exchange.

The third layer, the ECM, is critically important for the second selective pressure, that is, maintaining the integrity of the blood-gas barrier in the face of large forces that would otherwise damage it. The cellular layers themselves are not strong. However, the basement membranes of the epithelial and endothelial cells contain type IV collagen, the fibers of which have a high ultimate tensile strength (6). The structure of type IV collagen is shown in Fig. 1B, and it is mainly confined to the center of the ECM layer, where it often shows as an electron-dense band in electron micrographs. The thickness of the type IV collagen layer is as little as 50 nm, thus combining extreme thinness with great strength. Despite its thinness, this layer is the lifeline that maintains the integrity of the blood-gas barrier and prevents the contents of the pulmonary capillaries from spilling into the air spaces.

The success of this simple design from an evolutionary point of view is seen when we compare the structure of the blood-gas barrier from the air-breathing vertebrates, including the air-breathing fishes, amphibia, reptiles, mammals, and, finally, birds. Examples are shown in Fig. 2. It is remarkable that the structure has remained so consistent over such an enormous evolutionary scale. Note that the three layers are clearly visible in all instances, and in several, the central electron-dense bands in the middle of the ECM can be identified.

The Selective Pressure to Facilitate Gas Diffusion Through the Blood-Gas Barrier

Thinness of the blood-gas barrier. We have seen that the first selective pressure for the blood-gas barrier is that it be very thin and have a large area. In keeping with this, Fig. 3 shows that the mean thickness of the barrier decreases from amphibians to reptiles to mammals and birds in keeping with the different gas exchange needs among the different classes of vertebrates. Only the mammals and birds are homeothermic endotherms with the capability of high sustained maximal oxygen consumption. Furthermore, some birds have a higher mass-specific maximal oxygen consumption than any mammals (31), and birds often have a higher aerobic scope, that is, the increase in oxygen consumption from resting to maximal values (3). Therefore, the marked decrease in mean thickness of the barrier is in keeping with the gas exchange needs.

The data plotted in Fig. 3 are from Table 1 of Maina and West (21), which includes 34 species of birds, 37 species of mammals, 16 species of reptiles, and 10 species of amphibians. The plots show the mean harmonic thickness because the investigators who collected these data were particularly interested in the diffusing capacity of the lung for oxygen, and the mean harmonic thickness is the appropriate measurement for this. The reason is that thickness is in the denominator of the diffusion equation. The mean harmonic thickness is determined by taking the reciprocal of the mean of the sum of the reciprocals of the measurements made perpendicular to the plane of the barrier. It is perhaps not surprising that reptiles have substantially thinner barriers than amphibians, because the latter class of vertebrates uses the skin for respiratory gas exchange in addition to the lung. The fact that the thickness of the barrier is further reduced in mammals and birds is expected, because these classes are capable of much higher sustained maximal oxygen consumptions. However, the marked difference between mammals and birds is perhaps unexpected. The values of the mean harmonic thickness are 0.47 and 0.19 μm, respectively, which means that the mean thickness in these two groups differs by a factor of 2.5. Even in members of the two classes that have small body sizes, there are large differences. For example, the thickness in the violet-earred hummingbird is 0.099 μm, whereas that in the shrew is 0.34 μm, a 3.4-fold difference (21). The extraordinary ability of birds to reduce the thickness of the blood-gas barrier is one of the main points of this review and is discussed below. All the mean values shown in Fig. 3 are significantly different from each other at the level of $P < 0.001$.

Although the differences between the mean values are so large, there are some substantial differences within each class of vertebrates. For example, within the birds, the ostrich has a mean thickness of 0.56 μm, and the value in the Humboldt penguin is 0.53 μm. However, all the values of the other birds in the group vary between 0.32 μm for the domestic fowl and 0.12 μm for the common gull. It has been suggested that the thicker blood-gas barrier in the diving birds such as penguins might help to prevent collapse of the air capillaries during dives. There also are differences within the mammals, with the domestic pig having the highest value at 0.72 μm and the ground mole rat having the lowest value at 0.20 μm. However, despite these appreciable differences within each class of vertebrates, the standard errors as shown by the bars are very small.
Surface area of the blood-gas barrier. In contrast to the highly conserved structure of the blood-gas barrier, as shown in Fig. 2, and the relatively small variation in the thickness of barrier within each vertebrate class, as shown in Fig. 3, the surface area of the barrier changes enormously between species (24). The surface area of the barrier is closely related to the size of the lung, and obviously this varies greatly both within and between classes of vertebrates. Gehrl et al. (11) documented the strong relationship between the surface area of the barrier and the body mass of mammals. For example, the surface area varies from \( \text{0.02 to over 1,000 m}^2 \) between the smallest shrew and the horse. It is this very large difference in surface area that enables the much higher maximal oxygen consumptions of the big mammals compared with the small ones. In other words, the enormous differences in maximal oxygen consumption between animals of different body size are made possible not by changes in the structure or thickness of the blood-gas barrier but by the large changes in surface area.

There also are differences between the classes of birds and mammals. Birds have about a 15% larger surface area of the blood-gas barrier compared with mammals of the same body mass despite the fact that the volume of the gas-exchanging tissue in the bird parabronchi is much smaller than that in the mammal (19). This is made possible by the tight packing of the pulmonary capillaries in the avian parabronchi. Reptiles and amphibia have relatively small surface areas of the blood-gas barrier, \( \text{10 cm}^2/\text{g body mass} \) within the range of \( 10–100 \text{g} \) (24). This is a factor of about 10 less than that in many mammals. These numbers are consistent with the fact that the lungs of reptiles and amphibia are less finely divided, and the air spaces are much larger than in mammals (28).

The Selective Pressure to Maintain the Mechanical Integrity of the Blood-Gas Barrier

Strength of the blood-gas barrier. So far we have considered the structure, thickness, and surface area of the blood-gas barrier, because these are the important factors for the first evolutionary pressure that allows adequate amounts of gas to diffuse between the air and blood. We now turn to the second...
selective pressure, that is, the features that allow the integrity of the barrier to be sustained in the face of large mechanical forces that would otherwise damage the barrier.

Available evidence indicates that the strength of the barrier comes from the ECM, particularly the type IV collagen within this, as shown in Fig. 1. For example, if the capillary transmural pressure is increased to high levels in experimental lung preparations, electron micrographs show disruptions in the epithelial and endothelial layer, but the ECM generally remains intact (36). Furthermore, it has been shown that the elastic properties of isolated rabbit renal tubules are determined by the ECM (35), and the same is true of the distensibility of capillaries in frog mesentery (26). In addition, the thickness of the ECM of capillaries in the systemic circulation increases down the body along with the transmural pressure, and this is particularly well seen in a giraffe (43). In all these examples, the ECM has a critical role.

The structure of type IV collagen is shown in Fig. 1B. The COOH-terminal end of the molecule has an EC1 globular domain that enables two of the 400-nm-long molecules to join to form a doublet. The NH2 terminus has a 7S domain that enables four doublet molecules to form a matrix configuration somewhat like chicken wire. The 7S domain links with integrins α1β1 and α2β1 (13). The total collagen IV layer, as shown in parts of Fig. 2, may have a thickness of only 50 nm, which means that the layers that look like chicken wire or chain-link fence are stacked above each other to give great strength combined with some porosity.

Few measurements of the ultimate tensile strength of type IV collagen fibers are available, but measurements of basement membrane from the lens capsule of cat (6) indicate an ultimate tensile strength of \(\sim 1-2 \times 10^6\) N/m², a very high value that approximates that of nonreinforced concrete. Extrapolation of measurements from isolated rabbit renal tubules gives values that are consistent with this finding (21, 35).

Stresses in the blood-gas barrier. Figure 4 is a diagram showing the two principle stresses to which the blood-gas barrier is potentially exposed. First, there is a hoop or circumferential stress that results from the difference of pressure between the inside and the outside of the capillary in accordance with the Laplace relationship. If the capillary is regarded as a thin-walled cylindrical tube, the stress \(S\) is given by \(Prt\), where \(P\) is the transmural pressure, \(r\) is the radius of the capillary, and \(t\) is the thickness of the load-bearing structure. Calculations of the tensile stress in the type IV collagen layer in the pulmonary capillaries of humans during intense exercise suggest that they approach the values for the ultimate tensile strength cited above (38).

A second cause of wall stress occurs if the lung is inflated to high volumes. The increased longitudinal tension of the alveolar wall is partly transmitted to the capillaries that basically make up the wall. It has been shown that for a given capillary transmural pressure, inflating the lung to the high volumes in experimental preparations causes ultrastructural damage to the wall (7). Because the parabronchial structures do not change volume during respiration, this potential cause of increased stress in the blood-gas barrier is avoided.

Stress failure of the blood-gas barrier. There is experimental evidence that if the transmural pressure of pulmonary capillaries is raised to high levels in mammalian preparations, ultrastructural changes in the blood-gas barrier occur. Typically, these are breaks in the alveolar epithelium and capillary endothelium, and less commonly, in the ECM itself. In experimental rabbit lungs, the first signs of stress failure are seen at a capillary transmural pressure of \(\sim 25 \text{ mmHg}\), and the number of breaks increases steadily up to a pressure of \(\sim 50 \text{ mmHg}\) (30). These pressures are in the same range as those calculated to occur in the human lung during heavy exercise (38).

Stress failure of the barrier is known to occur under some physiological conditions. The most striking example is so-called exercise-induced pulmonary hemorrhage in thoroughbred racehorses. Tracheal washings from these animals contain hemosiderin-laden macrophages, indicating that essentially all of these horses in training are bleeding into their lungs (41). The reason for the stress failure is that these animals have been selectively bred for high aerobic performance over hundreds of years, and their cardiac outputs are so high that the filling pressures of the left side of the heart are enormous. The result is that the pulmonary capillary pressure may approach 100 mmHg (37).

It is also known that elite human athletes lose the integrity of their blood-gas barriers during very high levels of exercise. For example, top-level cyclists who exercise close to their maximal oxygen consumption for a few minutes subsequently show a higher concentration of red blood cells in their alveoli than sedentary controls who do not exercise. The red cells are detected using bronchoalveolar lavage whereby small amounts of saline are injected into the alveolar spaces via bronchoscopy and subsequently recovered. The increased concentration of red blood cells is accompanied by abnormally high concentrations of total protein, albumin, and leukotriene \(B_4\) (12).

Many pathological conditions in humans cause stress failure of the blood-gas barrier when the pulmonary capillary pressure becomes abnormally high. These conditions include high-altitude pulmonary edema (27) and various cardiac diseases. There also is evidence of damage to the blood-gas barrier if the lung is inflated to high volumes in the intensive care unit (4) and also in diseases where the type IV collagen is weakened, such as Goodpasture’s syndrome (42).

Separation of the pulmonary circulation from the systemic circulation. So far in this discussion of the selective pressure to maintain the integrity of the blood-gas barrier, the emphasis has been on the strength of the barrier, including the stresses to which it is subjected and the consequences if these are too high. Another important evolutionary strategy has been to maintain a sufficiently low pressure in the pulmonary capillaries so that high hoop

![Fig. 4. Mechanisms for the mechanical stresses in the blood-gas barrier. The principal mechanism is the transmural pressure in the capillaries that results in a hoop stress (1). In addition, inflation of the lung to high volumes increases the stress in the alveolar wall (2), part of which is transmitted to the capillary wall.](http://ajpregu.physiology.org/ Downloaded from by 10.220.33.4 on November 19, 2017)
stresses could be avoided. This is thought to be one of the major reasons for the development of a separate pulmonary circulation.

*Phylogeny.* As vertebrates evolved from heterothermic ectotherms as in amphibia and reptiles to the homeothermic endothermic mammals and birds, not only did the maximum oxygen transfer by the lung increase, but the means of delivering the oxygenated blood to the peripheral tissues had to be greatly raised. The consequent high cardiac outputs inevitably result in increased pressures in the outflow tract from the heart. For example, the mean aortic pressure in many mammals is ~100 mmHg and is even higher in birds. Therefore, it became increasingly important to protect the pulmonary capillaries from the high pressures.

In fishes, where the heart is composed of a single atrium and single ventricle, blood is pumped to the gills via the ventral aorta, and from there it is distributed to the rest of the body by the dorsal aorta. In this arrangement the hydrostatic pressure in the gill capillaries must exceed that in the dorsal aorta. As an example, in the albacore tuna (*Thunnus alalunga*), the mean dorsal aortic pressure has been reported as high as 79 mmHg (1). Therefore, the pressure in the fish gills is much higher than can be tolerated without stress failure in some mammals. This necessitates a thicker capillary wall in tuna than in mammals.

In the evolutionary progression toward endothermy in mammals and birds, a gradual separation of the pulmonary circulation from the systemic circulation occurs (5). Complete separation is only seen in the mammals and birds, and as a result, these two classes of vertebrates are the only ones capable of sustained very high oxygen consumptions. In the modern amphibian, for example, the frog, the beginnings of the separation of the two circulations can be seen in that there are two atria but only one undivided ventricle. Nevertheless, there is some streaming of blood within the heart with the result that much of the better oxygenated blood from lungs finds its way into the aorta. This preferential distribution of blood from lungs to the peripheral tissues is another major benefit resulting from the two separate circulations. This benefit is in addition to the need to limit the hydrostatic pressure in the pulmonary capillaries.

Although this streaming of blood is advantageous in terms of oxygen delivery, the pulmonary capillaries are still exposed to a relatively high pressure because the ventricle is undivided. It is only because these ectothermic animals have relatively low maximum oxygen consumptions that the blood-gas barrier need not be as thin as it is in mammals and birds (Fig. 3). In addition, amphibia have the advantage that much of the gas exchange occurs through the skin, which is therefore a second gas-exchanging organ. In fact, in amphibia, the outflow from the undivided ventricle goes to a pulmocutaneous artery, which in some species allows the flow to be preferentially directed to either the lung or the skin.

Further separation of the two circulations is seen in the noncrocodilian reptiles such as snakes, where there are two atria and now the ventricle is partially divided. This arrangement improves the streaming of blood so that, from the point of view of gas exchange, there is now a rudimentary double circulation. However, the fact that the ventricles are undivided means that the pulmonary capillaries are exposed to the high pressures.

The monitor lizard (*Varanus exanthematicus*) provides an interesting variant. There is a ridge in the ventricle of this animal that separates the two outflow tracts to the lungs and the rest of the body during systole. The result is that the pressure in the pulmonary artery is lower than in the aorta because of the resistance to flow caused by the ridge (2). Pulmonary gas exchange is therefore facilitated, allowing unusually high oxygen consumptions, and the blood-gas barrier is protected from the high systemic pressures, which otherwise might cause stress failure.

Crocodilian reptiles differ from noncrocodilian in that they are the first animals in the evolutionary line that do not have a right-to-left communication in the heart. However, there is a shunt between the pulmonary artery and aorta with the result that the pressure in the pulmonary capillaries is normally the same as that in the systemic pressure. The shunt also allows diversion of the right ventricular output to the aorta, causing a shunt around the lung during diving (40).

The highest sustained maximal oxygen consumptions are seen in mammals and birds, and it is therefore necessary that the walls of the pulmonary capillaries be extremely thin (Fig. 3). This in turn means that the pressures in the capillaries need to be much lower than those in the systemic circulation to avoid stress failure of the blood-gas barrier. There is no other solution to providing an extremely thin blood-gas barrier than completely separating the pulmonary and systemic circulations.

*Ontogeny.* It is fascinating that intrauterine development of mammals shows some similarities with the progression of changes on an evolutionary scale as discussed above. In the human fetus, for example, the aorta and main pulmonary artery are connected by the large, short ductus arteriosus. This anatomy has similarities to that of amphibia and most noncrocodilian reptiles in that in the fetus, both ventricles discharge into what is essentially a common conduit. However, it is interesting that, as in amphibians and reptiles, some streaming of blood occurs within the fetal heart. It transpires that much of the best-oxygenated blood from the placenta that arrives in the heart from the inferior vena cava does not leave the heart through the pulmonary artery, but rather crosses the right atrium to the left atrium through the patent foramen ovale. From there, it is mainly distributed to the head and brain. By contrast, the more poorly oxygenated blood in the superior vena cava is mainly streamed to the right ventricle so that part of it reaches the lung whereas much enters the descending aorta.

Nevertheless, despite this streaming of blood that improves oxygenation of the brain, the pressure in the pulmonary artery is as high as that in the aorta because of the large shunt through the ductus arteriosus. It would be natural to expect this high pressure to cause stress failure of the walls of the pulmonary capillaries. This is avoided by having a high resistance in the small pulmonary arteries, which have large amounts of vascular smooth muscle. As a consequence of this high pulmonary vascular resistance, only about 15% of the cardiac output reaches the lungs, and the pressure in the pulmonary capillaries is kept low. Naturally, the blood flow to the lungs need not be high as in the adult, because all the gas exchange occurs through the placenta, and the only function of the pulmonary blood flow is to provide for nutrition to the developing lung.

At birth, radical changes occur in the circulation. Because the lung now replaces the placenta for gas exchange, it is necessary to provide a rapid increase in pulmonary blood flow. This is brought about by a large fall in pulmonary vascular resistance, mainly as a result of the release of hypoxic pulmo-
nary vasoconstriction when the newborn baby takes its first 
breathes. At the same time, the patent ductus arteriosus begins 
to close, thus reducing the amount of shunted blood. It is 
remarkable that this complicated series of events occurs so 
successfully in the majority of births. Incidentally, the vulner-
ability of the fetal pulmonary capillaries has been demonstrated 
by showing that the pulmonary capillaries in newborn rabbit 
lung are more fragile than in the adult and therefore more liable 
to stress failure (8, 9). A possible reason for the fragility of the 
capillaries is that they are exposed to such a low pressure 
during most of fetal life. It is known that the thickness, and 
therefore presumably the strength, of the blood-gas barrier 
undergoes remodeling in response to changes in capillary 
hydrostatic pressure (22).

The Unique Avian Solution for the Blood-Gas Barrier

Extreme thinness of the barrier. The extreme thinness of the 
blood-gas barrier in birds was discussed in relation to Fig. 3, 
where we showed that the mean harmonic thicknesses for a 
large group of birds and mammals differs by a factor of 2.5. 
Figure 5 shows electron micrographs from the lungs of chicken 
(Gallus gallus; A) and dog (Canis familiaris; B), and the much 
thinner barrier in the bird is immediately evident. Studies of the 
total thickness of the barrier and also the thicknesses of the 
endothelial, ECM, and epithelial layers have been carried out 
in our laboratory comparing chicken, rabbit, dog, and horse 
lungs (33). The total thickness of the avian blood-gas barrier 
is much less than that for mammals, as would be expected from 
Fig. 3, but in addition, the thicknesses of each of the three 
layers making up the barrier is also much less in the chicken. 
The most obvious differences are in the ECM thickness, where 
the values for chicken, rabbit, dog, and horse are 0.045 ± 0.02, 
0.174 ± 0.23, 0.319 ± 0.51, and 0.386 ± 0.64 μm, respecti-
vatively. In other words, the ECM is seven times thicker in the 
dog than in the chicken.

This finding of an extremely thin ECM layer in the bird is 
paradoxical because, as discussed earlier, there is strong evi-
dence that the strength of the blood-gas barrier comes from the 
ECM layer, and flying is a very energetic activity. For exam-
ple, Butler et al. (3) found that pigeons flying in a wind tunnel 
increased their oxygen consumption from 20.3 at rest to 200 
ml·kg⁻¹·min⁻¹, and this was accompanied by a rise in cardiac 
output from 555 to 2,410 ml·kg⁻¹·min⁻¹. Peters et al. (25) in 
similar studies reported an increase in oxygen consumption 
from 17.8 to 310 ml·kg⁻¹·min⁻¹, while cardiac output in-
creased from 303 to 2,244 ml·kg⁻¹·min⁻¹. Therefore, it is 
surprising that the integrity of the blood-gas barrier can be 
maintained with such a thin ECM layer in the face of a high 
pulmonary capillary pressures.

Uniform thickness of the blood-gas barrier. Further inspection 
of Fig. 5 shows another important difference between the 
blood-gas barriers of the chicken and dog. The blood-gas 
barrier in the chicken is extraordinarily uniform in thickness in 
addition to being very thin. By contrast, in the dog, there is 
considerable variability in the thickness of the blood-gas bar-
rier. It is well known that the pulmonary capillaries of mam-
malian lungs tend to be “polarized” in the sense that one side of 
the barrier is very thin but the other is much thicker. On the 
thin side, the barrier consists only of the alveolar epithelial cell, 
capillary endothelial cell, and the interstitial layer, the last 
being made up of the fusion of the two basement membranes. 
By contrast, on the thick side, the interstitium includes fibrils of 
type I collagen and even occasional cells, such as fibroblasts 
(34). We have documented the much smaller variation in the 
thickness of the blood-gas barrier in the chicken compared with 
that in rabbit, dog, and horse by calculating the coefficient of 
variation of the total thickness of the barrier (33). The mea-
surements show that the coefficient of variation in the chicken 
is less than one-half the value found in the dog, for example.

The fact that the pulmonary capillary of mammals is polar-
ized, that is, that one side is considerably thicker than the other, 
has important implications for the efficiency of diffusive gas 
exchange. Gehr et al. (10) reported that approximately one-half 
the total surface area of the blood-gas barrier in the human lung 
was located on the thick side of the pulmonary capillaries. This 
means that about 50% of the blood-gas barrier is inefficient for 
diffusion. Clearly, the arrangement in the bird is much more 
efficient.

What is the reason for the thick side of the pulmonary 
capillary in the mammalian lung when this is so deleterious for 
overall diffusive gas exchange? The answer is that a type I 
collagen cable extends all the way from one end of an alveolar 
wall to another, and in doing so, it must pass through one side 
of the capillaries that are strung out along the alveolar wall 
(34). This cable is apparently necessary to maintain the integ-
rity of the alveolar wall, and perhaps the capillaries themselves, 
and is shown diagrammatically in Fig. 6. The cable is a 
required mechanical support system for the delicate alveolar 
walls that extend over such a large distance.

External support of avian capillaries. A major difference 
between avian and mammalian lungs is the environment of the 
pulmonary capillaries. Figure 7 shows that whereas in mam-
wals the pulmonary capillaries are strung out along the alveolar 
wall, and are therefore essentially unsupported at right angles to 
the wall, in the avian lung the capillaries are nested in a honey-
comb-like structure of air capillaries. In other words, birds are 
unique among air-breathing vertebrates in that the capillaries are

Fig. 5. Electron micrographs of pulmonary capillaries in chicken (A) and dog lung (B). Note that the blood-gas barrier in the bird is much thinner and much more uniform in thickness than in the mammal. EPI, epithelium; F, fibrils of type I collagen; FB, fibroblasts. [A is modified from Maina (18); B is modified from Weibel (34).]
supported from the outside as well as by the intrinsic structure of their walls. The hypothesis is that these outside supports contribute to the mechanical integrity of the capillary and thus allow the blood-gas barrier to be much thinner and more uniform than in mammals.

**Nature of the external support of the pulmonary capillaries.**

As discussed above, the avian blood-gas barrier is very thin and uniform in thickness compared with that in mammals, and yet the exercise levels, and therefore presumably the pulmonary capillary pressures, in birds are high. This must mean that the barrier has additional mechanical support. However, the micromechanics of how the capillary walls are supported by their surrounding structures are unclear. Since the only tissue around the capillaries consists of the air capillaries (Figs. 5 and 7A), these seem to be the only candidates. The components of the air capillaries connected to the outside of the pulmonary capillaries are the epithelial bridges or plates that form the walls of the air capillaries. As Fig. 8A shows, these bridges are extraordinary thin, only ~50 nm in thickness in some places, and as Fig. 8B indicates, they consist of plates that connect with the walls of adjacent blood capillaries. A short Supplemental Video clarifies the structures shown in Fig. 8B. (Supplemental data for this article is available online at the American Journal of Physiology-Regulatory, Integrative and Comparative Physiology website).

At first sight it might seem unlikely that such thin structures could provide sufficient mechanical support. To resist outward displacement of the blood capillary wall by the transmural pressure, the bridges would have to be strong in compression. However, with a wall thickness of only ~50 nm, it seems unlikely that this could be the case. We would expect such thin sheets to buckle under a compressive load. On the other hand,
the geometrical arrangement of the epithelial plates is complicated, and there may be some sharing of the loads that is not apparent. Figure 9, A and B, contrasts the mechanical support of mammalian and avian pulmonary capillaries. In mammals, the capillaries are unsupported at right angles to the alveolar wall. By contrast, in birds, the capillaries are supported on the outside by epithelial plates that form part of the air capillaries. Perhaps the answer to how the blood-gas barrier is supported lies in the junction where the sheet makes its connection to the wall. Figures 5, 7, and 8, A and B, show an expansion of the bridges at the sites of connection to the capillary wall. If this tissue is strong in tension along the line of the junction, it would act as an additional support to prevent failure caused by hoop stress in the capillary wall. An analogy is a coarse net made of nylon that is wrapped around a rubber bulb containing a high gas pressure. The cords of nylon in the net support the wall of the rubber bulb, preventing it from expanding. In this way, the hoop stresses in the wall of the bulb are not allowed to increase. In effect, the high stresses are transferred to the nylon net. This arrangement would work best if the linear junctions between the plates and the capillary wall were numerous and also oriented in different directions like the net referred to above. We do not yet have enough information on the three-dimensional geometry at the electron microscopy level to know whether this is the case.

It should be pointed out that just because structures such as the epithelial plates, or their junctions with the capillary walls, are very thin does not necessarily mean that they cannot sustain substantial mechanical loads. It may be that the loads are shared in an efficient manner that we do not as yet understand. A possible analogy is the spokes of a bicycle wheel that individually are only a few millimeters in diameter but together can support a load on the wheel of perhaps 50 kg.

Another possible factor that might help to sustain the mechanical loads is the surface tension in the air capillaries. These surface tension forces could be very high, because the radius of curvature of the air capillaries is only \( \sim 5-10 \mu m \). It is easy to imagine that a network of such structures with a high surface tension could be very rigid, and in fact, the parabronchial tissue of duck lung has been shown to be very resistant to compression (16). We have almost no information on the possible role of surface tension, although it is known that bird lungs contain surfactant and also another trilaminar lipoprotein structure, the function of which is unclear (14, 23). The lipoprotein is located on the epithelial bridges (14).

Finally, it should be noted that in some places two blood capillaries, or even more, abut each other, as shown in Figs. 5 and 6A, and this will confer some mechanical support. However, this geometry also reduces the area of the blood-gas barrier available for gas exchange.

Reason for the small terminal air-spaces in the avian lung. The support to the pulmonary capillaries in the avian lung comes about because the terminal air spaces, that is, the air capillaries, are very much smaller than the terminal air spaces of the mammalian lung, that is, the alveoli. What is the reason for this? The answer is the flow-through pattern of ventilation in the avian lung in contrast to the reciprocating ventilation of the mammalian lung. Extensive reviews of the air flow system in birds are available (see, for example, Ref. 19). In the mammal, a small tidal volume of \( \sim 0.5 \) liter in humans is delivered into a large resting volume of the lung of perhaps 3.5 liters. Despite this small inspired volume, some of the fresh gas must travel to the periphery of the lung through a complicated process of convection and diffusion. This necessitates relatively large terminal air spaces that provide little resistance to flow. By contrast, the avian lung with its flow-through system means that the air can be pumped by the air sacs through the tiny air capillaries. This is the essential difference that contributes to the much more efficient blood-gas barrier in the avian lung.

Perspectives and Significance

The main purpose of this brief review is to elucidate the two separate selective pressures that have shaped the evolution of the structure of the blood-gas barrier in air-breathing vertebrates. The first pressure, which is that the barrier has to be extremely thin and have a large area, is well known and indeed was recognized 100 years ago. The review points out that the avian lung has been particularly successful in this respect in that the blood-gas barrier is generally much thinner than that in mammals. In addition, the thickness of the avian barrier is much more uniform than that in mammals, and these two characteristics are advantageous for gas exchange by passive diffusion.
The second selective pressure has only recently been recognized. This is the requirement to maintain the mechanical strength of the barrier in the face of its extreme thinness. The factors causing tensile stresses in the barrier are discussed, the most important of these being the hoop stress that arises because of the capillary transmural pressure. The primary material responsible for the strength of the barrier is believed to be the type IV collagen in the ECM between the alveolar epithelium and capillary endothelium. An important factor minimizing the hoop stress in the barrier in birds and mammals is the complete separation of the pulmonary and systemic circulations. Indeed, this separation is essential for the development of the high sustained oxygen consumptions seen in birds and mammals, where a very thin blood-gas barrier is mandatory.

A unique feature of the avian lung is that the pulmonary capillaries are supported by epithelial plates that are part of the air capillaries in the parabronchial tissue. The precise way in which the tissues surrounding the pulmonary capillaries allow the blood-gas barrier to be so thin and so uniform is not understood. Possible mechanisms include mechanical support by the epithelial plates themselves or mechanical support arising from the junctions of the epithelial plates with the capillary walls. These junctions show expansions of tissue that may reinforce the capillary wall like a nylon net around a rubber bulb and thus share the hoop stresses. It would be valuable to have more information on the three-dimensional microanatomy of the epithelial bridges and plates and their mode of junction with the walls of the capillaries.

Finally, it is pointed out that this unique support of the avian pulmonary capillaries that allows the blood-gas barrier to be so thin and uniform comes about because of the different modes of ventilation in avian and mammalian lungs. Because the avian lung has separated the gas-exchanging and ventilating functions, the air spaces surrounding the avian pulmonary capillaries are very small air capillaries that are available to supply mechanical support. This is in contrast to the situation in mammalian lungs, where the pulmonary capillaries are strung out along the alveolar walls and are unsupported at right angles to the walls. Nature has produced a more efficient respiratory system in birds than in mammals.

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