Role of the fragility of the pulmonary blood-gas barrier in the evolution of the pulmonary circulation

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West JB. Role of the fragility of the pulmonary blood-gas barrier in the evolution of the pulmonary circulation. Am J Physiol Regul Integr Comp Physiol 304: R171–R176, 2013. First published November 28, 2012; doi:10.1152/ajpregu.00444.2012.—In 1953 Frank Low published the first high-resolution electron micrographs of the human pulmonary blood-gas barrier. These showed that a structure only 0.3-μm thick separated the capillary blood from the alveolar gas, immediately suggesting that the barrier might be vulnerable to mechanical failure if the capillary pressure increased. However, it was 38 years before stress failure was recognized. Initially it was implicated in the pathogenesis of High Altitude Pulmonary Edema, but it was so clear that stress failure of pulmonary capillaries is common. The vulnerability of the blood-gas barrier is a key factor in the evolution of the pulmonary circulation. As evolution progressed from the ancestors of fishes to amphibians, reptiles, and finally birds and mammals, two factors challenged the integrity of the barrier. One was the requirement for the barrier to become increasingly thin because of the greater oxygen consumption. The other was the high pulmonary capillary pressures that were inevitable before there was complete separation of the pulmonary and systemic circulations.

pulmonary capillary; pulmonary vascular pressures; type IV collagen; extreme exercise; stress failure

MARCELLO MALPIGHI (1628–1694) has the distinction of discovering the pulmonary capillaries. He studied frog lungs using the recently invented light microscope and wrote to his friend, Giovanni Borelli (1608–1679), that he saw a series of small blood vessels connecting the arteries and veins. The existence of these had been surmised by William Harvey (1578–1657) to explain the circulation of the blood, but the capillaries could not be seen without a microscope. Malpighi stated “So great is the branching of these vessels, after they extend out hither and thither from the vein and artery, that no larger system of vessels will be served, but a network appears, formed by the offshoots of the two vessels.” Malpighi made drawings of the capillaries but of course was not able to visualize their walls clearly.

Over the next 200 years many investigators examined the walls of the pulmonary capillaries using improved microscopes, but the structure of the wall, which they realized was the blood-gas barrier, continued to be disputed. On the one hand, some investigators claimed that the capillaries were covered by “nonnucleated plaques.” This was understandable error because the nuclei of the alveolar epithelial cells are few and far between. However, in his second report, Low (13) showed excellent images. One is reproduced in Fig. 1 where we can see a red blood cell inside a capillary, the capillary endothelium labeled 2, the alveolar epithelium labeled 1, the nucleus of the epithelial cell with its nucleolus labeled 5, and the extracellular matrix labeled 3, though this is not visible at the location labeled 4. Note that the capillary endothelial and alveolar epithelial layers both have a thickness of about 0.15 μm, and that the total thickness of the blood-gas barrier is about 0.3 μm.
This micrograph from a human lung represents one of the most important advances in lung biology. Modern electron micrographs have greatly improved the resolution, and Fig. 2 shows that the layer of extracellular matrix, which was interrupted in Fig. 1, extends around the whole of the capillary. The micrograph also shows the nucleus of the type I alveolar epithelial cell (as indeed did Fig. 1) and also the nucleus of the capillary endothelial cell. It was remarkable to find a section showing both of these nuclei. Nevertheless, the basic ultrastructure of the blood-gas barrier was clearly shown by Low in 1953.

Slow Recognition of the Vulnerability of the Blood-Gas Barrier

It is remarkable that it took so long to recognize the vulnerability of this extremely thin blood-gas barrier. As we have seen, in 1953 Low clearly demonstrated that there was nothing separating the blood in the pulmonary capillary from the gas in the alveolar space except a structure that was only 0.3 μm thick. Furthermore, this structure consisted of only two very thin cells with a small amount of extracellular matrix sandwiched between them. This should have suggested that the blood-gas barrier was therefore vulnerable to increased stresses caused by any large increase in capillary pressure. However, the vulnerability of the capillaries was not recognized until 38 years later (28).

In fact, there was plenty of evidence in the clinical and pulmonary pathology literature to suggest that the capillaries were leaking red cells under some conditions which must mean that the walls were damaged. For example, it was well known that the patients with mitral stenosis who had an increased capillary pressure frequently developed hemoptysis and that their lungs contained large amounts of hemosiderin, which could only come from red blood cells. How did this get into the extravascular tissue? One explanation was that the bleeding occurred at the anastomoses between the pulmonary and bronchial arteries that were thought to be situated in the mucosa of the terminal bronchioles (10). This seems improbable because these blood vessels have substantially thicker walls than the capillaries. Of course it was known that the capillaries could leak fluid when the pressure inside them was increased, but this did not mean structural failure of the wall. It was explained by the imbalance of the Starling forces as was originally described in 1896 (22).

What was the reason for the slow recognition of the vulnerability of the pulmonary capillaries? Probably there were three factors. First, many investigators thought that pulmonary capillaries could withstand a high pressure inside them without failure because this was apparently the case with capillaries in
the systemic circulation. For example, the capillaries in the lower leg have a high pressure inside them because of the hydrostatic column of blood in the upright body. However, the fallacy here is that systemic capillaries are supported by the interstitial tissue around them. The pressure in the interstitium of the leg rises along with the pressure in the capillary lumen and therefore the transmural pressure of the capillaries is not necessarily increased. By contrast, pulmonary capillaries have no interstitial tissue to support them over much of their surface.

Another common misconception was that the pressure in the pulmonary capillaries was always relatively low. There is some excuse for this error because the pressures within the pulmonary circulation, particularly on the venous side, are difficult to measure. However, when physiologists started measuring the pulmonary artery pressure, and particularly the pulmonary arterial wedge pressure, in subjects during vigorous exercise, it was immediately appreciated that the pressure in the pulmonary capillaries could rise substantially. For example, in one study of normal human subjects in the upright position, it was shown that at an oxygen consumption of 3.7 l/min, which is a substantial level of exercise but not maximal, the mean pulmonary artery pressure was 37 mmHg and the mean pulmonary arterial wedge pressure was 21 mmHg (24). The wedge pressure reflects pulmonary venous pressure. Micropuncture studies of pulmonary blood vessels in animals have shown that the capillary pressure is about halfway between arterial and venous pressures (2). Based on this, the mean capillary pressure at mid-lung is about 29 mmHg, and at the bottom of the lung, because of hydrostatic pressure effects, the value would be about 36 mmHg. Other measurements of pulmonary vascular pressures in normal subjects during exercise have given similar results (5, 20).

A third reason why stress failure of the capillaries was not suspected was that physiologists invoked the Laplace equation. This states that the wall stress (\(S\)) is proportional to the transmural pressure (\(P\)) of a vessel and its radius (\(r\)) but inversely proportional to the thickness (\(t\)) of its wall. In symbols, \(S = P/rt\). The fact that the capillaries have a very small radius of the order of 3 \(\mu m\) clearly reduces wall stress. However, the wall is extremely thin, and furthermore only the type IV collagen layer in the wall is believed to be responsible for its strength. Calculations of the stress in this layer, which is only about 50 \(nm\) thick, indicate that with a capillary transmural pressure of 30 mmHg, the stress approaches the ultimate tensile stress of type IV collagen (26). Admittedly, these calculations are imprecise but they make the point that a small radius of curvature is not necessarily sufficient to avoid stress failure if the thickness of the wall is very small.

Recognition of Stress Failure of Pulmonary Capillaries

The recognition that stress failure can occur came from an unexpected source. In the 1970s, the pathogenesis of High Altitude Pulmonary Edema (HAPE) was a puzzle. It was known that there was a strong link between pulmonary hypertension and HAPE. For example, individuals who developed HAPE had high pulmonary arterial pressures, and people who were susceptible to the disease had an increased hypoxic pulmonary vasoconstriction response. However, the pulmonary arterial wedge pressure was found to be normal in the disease, and this ruled out left ventricular failure. A breakthrough came when it was shown by bronchoalveolar lavage that the edema fluid of HAPE had a large concentration of cells and high-molecular-weight proteins and therefore the edema was of the high permeability type (6, 21). This indicated that the edema must be associated with structural damage to the walls of the pulmonary capillaries. However, hypoxic pulmonary vasoconstriction occurs upstream of the capillaries and so it was not clear how the high pulmonary artery pressure could damage them. A possible mechanism had been suggested by Hultgren (8) when he argued that the vasoconstriction might be uneven. This would allow the high pressure to be transmitted to some of the capillaries. However, nobody previously had raised the pressure in pulmonary capillaries in experimental animals and examined the ultrastructure of their walls. When this was done in a rabbit preparation, there was clear evidence of breaks in the capillary endothelium, alveolar epithelium, and, in some cases, the extracellular matrix as well (28, 23). Figure 3 shows examples of electron micrographs showing stress failure.

Prevalence of Stress Failure in Pulmonary Capillaries

It soon became evident that stress failure of pulmonary capillaries occurred not only in HAPE but in many other conditions. For example, the experiments in the rabbit preparation showed that high states of lung inflation greatly increased the number of breaks in the capillary wall for a given capillary transmural pressure. This, therefore, explained, at least in part, the damage to the pulmonary capillaries that is seen in the intensive care unit when high levels of positive end-expiratory pressure are employed. One of the most dramatic examples of stress failure is seen in racehorses. For centuries, bleeding from the lung had been known to occur in these animals after galloping, and when the horses were examined by bronchoscopy, it was shown that bleeding was common. Eventually it was found that all racehorses in training have hemosiderin-laden macrophages in their tracheal washings, which meant that they are all bleeding into their alveolar spaces. Direct evidence of stress failure in the capillaries was shown by galloping thoroughbreds on a treadmill and examining their lungs by electron microscopy (29). The reason for the bleeding is that these animals develop extremely high pulmonary vascular pressures during exercise with mean pulmonary artery pressures up to 120 mmHg and left atrial pressures as high as 70 mmHg (4, 9). These high pressures result from the extremely high cardiac outputs during galloping and, of course, these animals have been selectively bred for speed over hundreds of years. Racing greyhounds also bleed into their lungs (18).

The fact that racehorses break their capillaries during exercise raised the question of whether this ever occurs in elite human athletes. This was studied in racing cyclists and, indeed, it was shown that after sprinting at levels near the maximum oxygen consumption there was an increase in the number of red blood cells in bronchoalveolar lavage fluid. The controls were cyclists who remained sedentary (7). Since this demonstration of the vulnerability of the blood-gas barrier in elite athletes at very high levels of exercise, there have been numerous reports of bleeding from the lungs in athletes under a variety of conditions (7).
Blood-Gas Barrier and the Evolution of the Pulmonary Circulation

The vulnerability of the blood-gas barrier is a key factor in the evolution of the pulmonary circulation. As evolution progressed from the ancestors of the fishes to amphibians, reptiles, and finally birds and mammals, two factors challenged the integrity of the barrier. One was the high pulmonary capillary pressures that existed before a complete separation between the pulmonary and systemic circulations developed. The other was the requirement for the barrier to become increasingly thin to allow the greater oxygen consumption of the amphibia and reptiles, and especially the endothermic birds and mammals.

The progression of the mean thickness of the blood-gas barrier from its highest value in amphibia to its lowest in birds is shown in Fig. 4. Note the very small thickness in birds that is made possible by the support of the blood capillaries by the surrounding air capillaries. Birds have a flow-through rather than reciprocating mode of ventilation as exists in mammals. The result is that birds have air capillaries with diameters of about 10–20 μm, much smaller than mammalian alveoli which, in the human lung, have a diameter of about 300 μm. This arrangement allows the walls of the blood capillaries to be supported by epithelial bridges that form the walls of the air capillaries. The situation is very different from that in the mammalian lung where the capillaries in the alveolar walls are essentially unsupported at right angles to the wall. The net result is that because of this additional support, the walls of avian lung capillaries can afford to have much thinner walls (30).

The evolutionary progression of the separation of the pulmonary from the systemic circulation is shown in Fig. 5. The first panel shows the arrangement of the circulation in fishes. The heart
has a single atrium and single ventricle. Blood is pumped to the gills where the gas exchange with the water occurs via the ventral aorta, and the effluent blood from the gills is transported by the dorsal aorta to the tissues of the body. As a consequence, the hydrostatic pressure in the capillaries of the gills must be greater than that in the dorsal aorta. The pressure in the dorsal aorta needs to be relatively high so that the blood can be distributed to all the tissues of the body. On the face of it this suggests that the gill capillaries would be liable to stress failure. However, this likelihood is reduced because the blood-water barrier is much thicker than the blood-gas barrier in mammals. The reason for the thicker barrier is that fishes are homeothermic (cold-blooded) with relatively low levels of maximal oxygen consumption, and therefore the diffusion characteristics of the blood-gas barrier are not as stringent as they are in mammals. Because the barrier is much thicker, it can be much stronger and thus stress failure is not an issue. Interestingly, there are some highly aerobic fishes such as the albacore tuna *Thunnus alalunga*, where the mean dorsal aortic pressure is as high as 79 mmHg. Such a high pressure would break the pulmonary capillaries of mammals, but because the blood-gas barrier is much thicker, this does not apparently occur.

It would be impossible to have the arrangement shown for fishes in Fig. 5 in the amphibians, reptiles, mammals, and birds. This is because as evolution proceeds, there is an increase in maximal oxygen consumption, reaching its peak in the mammals and birds, and this necessitates a thinner blood-gas barrier to allow the adequate diffusive gas exchange to occur (Fig. 4). Therefore, a gradual separation of the pulmonary circulation from the systemic circulation is critically important. This is the only way that it is possible to maintain a relatively low pressure in the lung capillaries while maintaining a high systemic arterial pressure to perfuse the tissues including the limbs that require a high blood flow.

Figure 5 shows that in modern amphibians, the beginnings of the separation between the pulmonary and systemic circulations occurs. Now there are two atria, one of which receives oxygenated blood from the lung, and the other the mixed venous blood from the tissues. However, the ventricle is undivided and so there is some mixing of blood from the two atria. Nevertheless, there is some streaming of blood within the heart with the result that much of the oxygenated blood from the lungs finds its way into the aorta. Note that because the ventricle is not divided, the lung capillaries are exposed to a relatively high pressure. However, again, these animals are exothermic and therefore have relatively low maximal oxygen consumptions, and so the blood-gas barrier can afford to be relatively thick (Fig. 4).

When we progress to the noncrocodilian reptiles, we see a further difference in the arrangement of the circulations. Now in addition to having two atria, the ventricle is partly divided. This means that the streaming that we saw in amphibians is improved with the result that more of the oxygenated blood returning from the lungs finds its way into the tissues. However, the fact that the ventricles are not completely divided means that the pulmonary capillaries are potentially exposed to the high systemic arterial pressure. There is an interesting exception to this in some reptiles such as the monitor lizard *Varanus exanthematicus*. In this case there is a ridge in the ventricle that allows the outflow tracts of the lungs and the dorsal aorta to be separated during systole. As a result, the pressure in the pulmonary artery is lower than that in the aorta (3).

Crocodilian reptiles differ from the noncrocodilian in that there is no communication between the two ventricles. As a consequence, the pressure in the pulmonary capillaries is potentially relatively low. However, these animals have a shunt between the pulmonary artery and aorta that allows them to divert variable amounts of blood flow to the lung or the systemic circulation. Under normal conditions the entire output of the right ventricle goes to the lung, but during diving apnea, pulmonary vascular resistance rises and the result is a shunt around the unventilated lung.

Mammals and birds are unique in this evolutionary development in that they are fully endothermic and capable of very high maximal oxygen consumptions. As a consequence the blood-gas barrier has to be extremely thin to allow the rapid diffusion of oxygen across it (Fig. 4). This in turn means that the capillaries are highly vulnerable to stress failure unless the pressure is kept relatively low by complete separation of the pulmonary and systemic circulations. Nevertheless, as we have seen, some mammals under some conditions of very high oxygen consumption raise the pressure in the pulmonary capillaries so high that stress failure occurs.

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Fig. 5. Diagram showing changes in the evolution of the pulmonary circulation. As evolution progresses from fishes to amphibians, reptiles, mammals, and birds, there is increasing separation of the pulmonary and systemic circulations.
Potential for Stress Failure in the Developing Fetus

It is fascinating that as the fetus develops in utero and finally emerges into the environment, the pulmonary and systemic circulations follow a pattern somewhat similar to that shown in Fig. 5. In the mammalian fetus, such as a human, the pulmonary artery and aorta are connected by a large patent ductus arteriosus. This anatomy is similar in some ways to that in amphibians and noncrocodilian reptiles in that in the human fetus, both ventricles discharge into what is essentially a common conduit. In fact in crocodilian reptiles, there is a shunt between the pulmonary artery and aorta similar to the ductus arteriosus. However, as in amphibians and reptiles, there is streaming in the fetal heart so that much of the well-oxygenated blood from the placenta crosses the right atrium to the left atrium through the patent foramen ovale and is distributed to the brain.

A feature of the shunt between the pulmonary artery and the aorta means that the pulmonary capillaries are potentially exposed to the relatively high pressure in the systemic circulation. In principle, this makes the pulmonary capillaries vulnerable to stress failure. Two factors lessen this outcome. One is that the fetal lung contains a large amount of vascular smooth muscle in the small pulmonary arteries that contracts as a result of hypoxic pulmonary vasoconstriction and thus decreases the pressure in the capillaries. In addition, the developing fetal lung has no need of thin-walled pulmonary capillaries because it is not involved in gas exchange. In fact, only about 15% of the cardiac output in the human fetus reaches the lung. This is sufficient for the development of the organ and, of course, a large blood flow through the lung is unnecessary because the placenta, not the lung, is responsible for gas exchange.

Dramatic changes occur at birth when the gas exchange has to change in a very short time from placental to pulmonary. Blood flow through the lung of the newborn increases greatly mainly as a result of the release of hypoxic pulmonary vasoconstriction, which is very effective because of the abundance of vascular smooth muscle. In addition, the patent ductus arteriosus gradually closes protecting the pulmonary circulation from the high systemic pressures. One of the triumphs of evolution is that the fall in pulmonary vascular resistance and closure of the ductus arteriosus are so well synchronized in the majority of births. Occasionally the ductus is slow to close and then the pulmonary capillaries are potentially exposed to a high pressure with resulting damage to their walls.

In summary, the fact that gas exchange across the blood-gas barrier occurs through passive diffusion necessitates a very thin barrier in highly aerobic vertebrates such as mammals and birds. This very thin barrier makes it vulnerable to stress failure especially at high levels of exercise when the capillary pressure rises. The gradual separation of the pulmonary and systemic circulations as evolution progresses from fishes to amphibians, reptiles, and finally birds and mammals is essential to protect the pulmonary capillaries from stress failure.

REFERENCES