Fragility of pulmonary capillaries

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Submitted 21 February 2013; accepted in final form 25 April 2013

West JB. Fragility of pulmonary capillaries. J Appl Physiol 115: 1–15, 2013. First published May 2, 2013; doi:10.1152/japplphysiol.00229.2013.—Although the pulmonary capillaries were discovered in 1661, the ultrastructure of the wall was not elucidated until 60 years ago. Electron micrographs then showed that only 0.2 μm of tissue separated the capillary endothelium from the alveolar space over much of the area. In retrospect this vanishingly small protective layer should have alerted physiologists to the potential fragility of the capillaries, but this was not appreciated until almost 40 years later. This predicament is unique to pulmonary capillaries. No other capillaries in the body are shielded from the outside environment by such a minute amount of tissue. Reasons why the fragility of the capillaries was not recognized earlier include an inappropriate comparison with the properties of systemic capillaries, the mistaken view that the pulmonary capillary pressure is always low, and a misleading use of the Laplace equation. Evidence for the fragility comes from physiological, pathological, and laboratory observations. As expected from evolutionary considerations, the fragility only becomes evident in the normal lung under exceptional conditions. These include elite human athletes at maximal exercise and animals that have developed the capacity for extreme aerobic activity. However, lung and heart diseases frequently cause capillary disruption. Remodeling of pulmonary capillaries occurs in humans in whom the capillary pressure rises over a long period. Neonatal capillaries are extremely fragile, presumably because they have never been exposed to increased transmural pressures. The capillaries conform to the general biological rule that tissue adapts its structure to carry out its required function.

blood-gas barrier; electron micrographs; pulmonary capillary pressure; type IV collagen; remodeling

THE DISCOVERY OF THE PULMONARY CAPILLARIES

The notion that blood found its way from the pulmonary arteries to the pulmonary veins in the lung by a route that could not be seen goes back a long way. William Harvey (1578–1657) certainly surmised the existence of small blood vessels. In Chapter 7 of De Motu Cordis (25) he referred to “the invisible porosities of the lungs and the minute cavities of their vessels” (polmonum caecas porositates et vasorum eius oscilla). In the same book Harvey cited the work of Galen (120–c. 200 AD) who asserted that blood passed from the right to the left ventricle through pores in the intraventricular septum. Many writers have emphasized this error. However, more recent research emphasizes that, by contrast, Galen apparently believed that most of the blood went through the lungs (18).

However, the fact that the pulmonary capillaries could not be seen by the naked eye stymied any further progress. The breakthrough came when Marcello Malpighi (1628–1694) exploited the newly discovered microscope (42, 77). Malpighi was an outstanding 17th Century Italian scientist who not only discovered the pulmonary capillaries and alveoli but also described the mode of respiration in insects. In addition he is often regarded as the father of embryology because of his work on the developing chicken embryo, and remarkably he is also recognized as one of the founders of plant anatomy (1).

Malpighi first looked at the lung of the living frog, but although he could see blood flowing through small vessels he could not identify the exact path. However, he then dried the lung and reported “The dried lung of a frog resolved my doubts. In a very small portion of it... there may be seen, with a perfect glass no broader than the eye, the points which are called Sagrino [dark spots on the surface of the lung of a frog] forming the membrane [wall of the alveolus], but mixed with looped vessels. 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. This network not only occupies the whole floor [of the alveolus] but is extended to the walls and adheres to the outgoing vessel, just as I could observe more abundantly, but with greater difficulty in the oblong lung of a tortoise... Here it lies revealed to the
senses that, as the blood passes out through these twisting divided vessels, it is not poured into spaces, but is always passed through tubules and is distributed by the many windings of the vessels” [Translation from (82)].

These statements were made in a letter (42) to Giovanni Borelli (1608–1679) who was an eminent mathematician and naturalist at the University of Pisa and a close friend. Malpighi himself spent most of his time at the University of Bologna but was also a professor in Pisa and Messina. Figure 1 shows drawings by Malpighi of what he saw. Figure I shows the alveoli on the right, which he also discovered, and the capillaries on the right. Figure II depicts the capillaries in more detail in an alveolus that has been diagrammatically opened up to show the floor and walls. In fact although Malpighi’s description of the pulmonary capillaries was a momentous discovery, his first description of the alveoli, again in the frog, was perhaps equally important. Until this time scientists regarded the lung as composed of solid material, and Harvey, for example, compared its substance to that of kidney or liver. Furthermore Malpighi not only described the alveoli but recognized that air that entered the lung through at the trachea was conducted through smaller and smaller airways to the alveoli. However, although he understood the juxtaposition of the air in the alveoli and the blood in capillaries, he never realized that the primary function of the lung was gas exchange.

CONTROVERSY ABOUT THE STRUCTURE OF THE WALL OF THE PULMONARY CAPILLARIES

Of course it was one thing to see the capillaries but quite another to elucidate their structure. Malpighi’s initial description of the frog capillaries was probably done using a hand lens but in many of his later studies he used a compound microscope, that is one with both an objective and ocular lens. As microscopes improved there was increasing interest in the structure of the capillary wall, but because the wall thickness, at least in its thin part, is less than 0.5 μm, it was essentially beyond the resolution of the light microscope.

Nevertheless a considerable literature developed on the structure of the blood-gas barrier. By the middle of the 19th Century there were two different schools of thought. One was that the capillaries were naked in the sense that there was nothing between the endothelium and the alveolar gas except possibly a little reticular or connective tissue. Proponents of this view included Zenker (86), Henle (27), Loosli et al. (37), and Policard (50). For example, Policard stated that “the respiratory surface is like the flesh of an open wound” (La surface respiratoire est assimable à une plaie à vif).

However, with the introduction of a new technique, some investigators believed that the pulmonary capillaries were either partly or wholly covered by epithelium. The new procedure consisted of staining the tissue with silver nitrate, which resulted in a network of black intercellular junctions that allowed the borders of the epithelial cells to be recognized. By using this technique Kölliker (34) described two types of alveolar epithelial cells that we now know as type I and type II cells. The type I cells covered a relatively wide area, whereas the type II cells were much more compact. However, these descriptions were essentially confined to a plan view of the cells and did not give accurate information about the thickness of the epithelial lining layer.

There was one intriguing finding in Kölliker’s description. He claimed that a large part of the squamous lining consisted of “non-nucleated plates” (“kernlose Platten”) of cytoplasm. This would not be consistent with modern views of cellular biology, because cells without nuclei such as mammalian red blood cells and platelets have such a limited life span. However, it is easy to see how Kölliker came to this conclusion because there are so few nuclei of the type I alveolar epithelial cells and the cytoplasm of these cells spreads over a wide area. Weibel (71) discussed Kölliker’s erroneous conclusion and pointed out that if the nucleus of a type I cell is at the junction of alveolar septa, it may send its cytoplasmatic extensions in two or three different directions and it is not at all clear that all of these extensions are connected to a nucleus.

At this time extensive studies of the possible existence and continuity of the alveolar epithelium were made in both normal lungs and those from patients with lung disease. Although the existence of both type I and type II alveolar epithelial cells was...
confirmed, there was still almost no information about the thickness of the epithelial cell layer and therefore of the total blood-gas barrier. The simple reason for this was that the investigators were trying to image structures that were at or beyond the limit of resolution of the light microscope.

**FIRST ELECTRON MICROGRAPHS OF THE STRUCTURE OF THE WALL OF THE CAPILLARIES**

The breakthrough came when it was possible to carry out electron microscopy of biological tissues. A key figure here was George Palade (1912–2008) who in 1974 was awarded the Nobel Prize in Physiology and Medicine because of his innovations in electron microscopy and associated discoveries in cell biology. A critical advance was demonstrating the possibility of fixing biological tissue for electron microscopy using buffered osmic acid (45).

Frank Low (1911–1998) has the distinction of revealing the ultrastructure of the pulmonary capillaries for the first time. He published two papers in 1952 and 1953 that revolutionized our knowledge of the blood-gas barrier (38, 39). These were outstanding contributions to the cellular biology of the lung, but strangely enough Low never received the accolades that he deserved. The first paper was limited to the rat lung, and the electron micrographs were of poor quality. Low appeared to be feeling his way with the revolutionary technique. It is interesting that although he was able to see the blood-gas barrier clearly, he did not emphasize its thinness. A major point in his discussion was that he was able to identify nuclei of the type I alveolar epithelial cells. This emphasis was in response to the description referred to earlier by Kölliker where he suggested that much of the epithelial lining consisted of nonnucleated plates.

However, in his second article (39) Low included the first electron micrographs of the human blood-gas barrier. One of these is shown in Fig. 2, and although the image does not have the extraordinary resolution of modern electron micrographs as shown in Fig. 3, most of the important features can be seen. Starting from the lower left we see a red blood cell (RBC), then the capillary lumen (CAP) and then the capillary endothelium labeled 2. Outside the endothelium we can clearly see the extracellular matrix labeled 3, although in the upper part of the image this appears to disappear at the point labeled 4. However, subsequent electron micrographs such as that shown in Fig. 3 show that the extracellular matrix is present over the whole of the length of the endothelium, and on one side of the capillary it enlarges to what is often called the interstitial space. To the right of the extracellular matrix layer is the epithelial cell labeled 1 with its large nucleus including the nucleolus labeled 5. Finally the alveolar space (ALV) is seen at the top right. It is said that a picture is worth a thousand words, and it could be argued that this one image resolved many of the issues raised by investigators over the previous 50 years or so.

In the context of fragility of pulmonary capillaries, this electron micrograph and its more modern equivalent shown in Fig. 3 make striking points. The scale at the top right of Fig. 2 shows that the total thickness of the blood-gas barrier in this image is $\sim 0.3 \, \mu m$ with the epithelial cell in some parts having a thickness of $\sim 0.1 \, \mu m$. The dimensions are seen even more clearly in Fig. 4, which is a very high power electron micro-
Graph. The clear message is that the pulmonary capillary is only separated from the alveolar space by a layer of extracellular matrix and an epithelial cytoplasm each \( \sim 0.1 \mu \text{m} \) thick. No other capillary in the body is protected by such a thin layer of tissue and the images should suggest that the pulmonary capillaries are vulnerable to failure.

If we look at the environment of other capillaries it is clear that none find themselves in the same predicament as the pulmonary capillaries. For example, the small intestine has a high concentration of capillaries that are involved with taking up nutrients from the intestinal lumen much as the pulmonary capillaries take up oxygen from the alveoli. However, the thickness of the epithelium of the gut is much greater than that in the lung. The same is true of the capillaries of the skin, which play an important role in losing heat from the body in hot environments and conserving heat in cold environments. Although the capillaries lie just under the epidermis, this is again orders of magnitude thicker than the epithelium of the blood-gas barrier.

Of course the reason why the distance between the pulmonary capillary blood and the alveolar gas is so small is that the transfer of the gases oxygen and carbon dioxide is by passive diffusion, and large volumes of these gases have to be transferred, particularly on exercise. There is therefore a strong selective pressure to maintain the extreme thinness of the covering of the pulmonary capillaries.

It is remarkable that evolution fixed on this tripartite structure of the blood-gas barrier, that is capillary endothelium, extracellular matrix, and epithelium, very early on and the structure has been highly conserved. For example, the extant lung fishes whose ancestors lived several hundred million years ago have basically the same structure, and this is preserved through the amphibia, reptiles, mammals, and birds (76). As we move from the amphibia to mammals and birds the barrier necessarily becomes thinner because of the increasing demands for oxygen consumption, but the basic structure of the barrier remains the same.

**WHY DID IT TAKE SO LONG TO RECOGNIZE THE FRAGILITY OF PULMONARY CAPILLARIES?**

Looking back, it seems extraordinary that the vulnerability of the pulmonary capillaries was not recognized for almost 40 years after Low published his electron micrographs. Images such as those in Figs. 2 and 3 leave no doubt that only \( \sim 0.2 \mu \text{m} \) thickness of tissue separates the capillaries from the alveolar gas space. Furthermore maintenance of integrity of this thin layer was clearly critical because otherwise the contents of the capillary would spill into the alveolar spaces with disastrous consequences for pulmonary gas exchange. Despite this there seems to be no discussion in the literature about the predicament of the pulmonary capillaries.

This is all the more surprising when there was abundant clinical and pathological data showing that blood entered the alveolar spaces in some diseases. A good example is mitral stenosis, which was a common disease well into the 1950s. For example, in 1954, the eminent cardiologist Paul Wood published a classical article in two parts on “An appreciation of mitral stenosis” (83, 84) in which he pointed out that hemoptysis was common and also that the lungs at autopsy frequently showed marked hemosiderosis. This was correctly attributed to “multiple recurrent hemorrhages,” but surprisingly the source was given as “the bronchopulmonary anastomoses in the mucosa of the terminal bronchioles.” This explanation for pulmonary hemosiderosis of cardiac origin had previously been suggested by Lendrum (35). In other words, the site of bleeding was considered to be the larger blood vessels, and in retrospect it is very puzzling that nobody suspected the bleeding would come from the capillaries. Perhaps part of the explanation was that these pathological studies were always carried out using light microscopy, and abnormalities of the structure of the capillaries could not be seen because of the limited resolution of the microscope. Incidentally the high pressures in the pulmonary capillaries were well known at this time because extensive measurements of pulmonary artery wedge pressure were included in Wood’s papers and this was shown to be increased.

So for some reason there was a blind spot about the fragility and vulnerability of pulmonary capillaries. How can this be explained? There are probably three reasons.

1) **Inappropriate use of the Laplace equation.** This equation relates the stress in the wall of a blood vessel to its transmural pressure (difference of pressure between the inside and outside), the radius of the vessel, and the thickness of its wall. The relationship is

\[
S = \frac{P}{t} = \frac{2}{R}
\]

where \( S \) is the wall stress, \( P \) is the transmural pressure, \( r \) is the radius, and \( t \) is the wall thickness.

On the assumption that damage to the capillary wall will only occur if the wall stress is very high, this equation shows that the smaller the radius of the vessel, the less is the wall stress, other things being equal. This equation has therefore been used to argue that in a capillary of radius \( \sim 3.5 \mu \text{m} \), the wall stress must be small.

However, this argument overlooks the fact that the wall thickness is extraordinarily small. As Figs. 2–4 show, the total thickness of parts of the wall of the human pulmonary capillary is \( \sim 0.3 \mu \text{m} \). In addition as we shall see below, there is evidence that the cellular layers themselves are not strong and that the strength of the capillary wall comes from the extracellular matrix. Furthermore it appears that only the layer of type IV collagen in the wall bears the load, and the thickness of this is only \( \sim 0.05 \mu \text{m} \) or 50 nm. This means that the thickness of the load-bearing tissue is extremely small, and therefore the stress can be high despite the fact that the capillary radius is small.

2) **Capillaries in the systemic circulation are not apparently vulnerable when the pressure inside them is increased.** It is true that capillaries in the systemic circulation, for example in the lower leg, can tolerate high pressures within them. For example, a person in the standing posture has a high pressure within the capillaries of the lower leg because of the substantial hydrostatic pressure difference down the body. The error here is assuming that the pressure inside the capillaries is the transcapillary pressure, whereas this is not the case. The pressure in the interstitium around the capillary must also increase along with the hydrostatic gradient, and the result is that the transcapillary pressure is little changed. It is true that the capillary endothelial layer in systemic capillaries appears to be similar to that in pulmonary capillaries, but in the systemic circulation the vessels are well-protected and supported by the tissue around them. This situation is very different from that in the lung where over most of the pulmonary capillary surface the only support is an extremely thin layer of alveolar epithe-
The pulmonary circulation is a low-pressure circulation compared with the systemic circulation. For example, the mean pressure in the human pulmonary artery under resting conditions is \(\sim 15\) mmHg, whereas the mean pressure in the human aorta is of the order of 100 mmHg. This has led many physiologists to assume that the pulmonary capillary pressure is always low, even during exercise, but there is evidence that this is incorrect. Admittedly it is not easy to measure the pressure in the pulmonary capillaries during exercise, and indeed the values in humans are somewhat controversial.

As we shall see below, very high values for left atrial pressure have been measured in galloping racehorses with values up to 70 mmHg. Some of these pressures have been measured with a catheter directly in the left atrium, and so there is no reason to doubt them. These very high pressures result from the fact that the cardiac output in the exercising horse is very high, and this results in very high end-diastolic filling pressures for the left ventricle. Humans of course are not capable of the extreme cardiac outputs of Thoroughbred racehorses, but nevertheless cardiac outputs on exercise increase very substantially and therefore it makes sense that left atrial pressures and therefore pulmonary capillary pressures will increase.

Several studies have reported high pulmonary venous pressures in humans during heavy exercise. The data come from pulmonary arterial wedge pressures, and these are prone to some artifacts during heavy exercise because of the large variations in intrathoracic pressure. Nevertheless in a study of normal human subjects exercising on a cycle ergometer, the mean pulmonary arterial wedge pressure was 21 mmHg, which indicates a substantial increase over the resting value of 7 mmHg (69). This increased wedge pressure was accompanied by a mean pulmonary arterial pressure of 37 mmHg and was seen when the subjects had a mean oxygen consumption of 3.7 l/min, which is a high level of exercise although not the maximal in these subjects. Other studies (23, 52) have shown similar results for pulmonary arterial and wedge pressures. Animal studies using micropuncture of their lungs have shown that capillary pressure is about halfway between pulmonary arterial and venous pressures (5). This would mean that at midlung the mean capillary pressure is 29 mmHg and, allowing for the hydrostatic pressure gradient in the lung, the capillary pressure at the lung base would be 36 mmHg. Therefore the assumption that the pressure in the pulmonary capillaries remains low under all conditions is clearly erroneous.

**EVIDENCE FOR THE FRAGILITY OF PULMONARY CAPILLARIES**

1) **Physiological.** Bleeding occurs from pulmonary capillaries under physiological conditions in the normal lung but only under special conditions. This is consistent with what would be expected from evolutionary considerations. In general, evolution provides us with structures that withstand all the usual physiological stresses, but if these are extreme failure may occur. These conditions are met by elite human athletes at maximum levels of exercise, for example. Bleeding from the pulmonary capillaries also occurs in animals that have developed the ability for extreme exercise. The best example is the Thoroughbred racehorse, and there is also some evidence that this also occurs in racing greyhounds.

It has been known since Elizabethan times that some racehorses bleed through their nose after galloping. This was ascribed to various causes such as moldy hay, but in 1981 it was found by bronchoscopy that some 70% of horses after a race had frank blood in their airways (47). Then in 1984, tracheal washings were recovered from Thoroughbreds in training and it was shown that all of these animals had hemosiderin-laden macrophages in their lungs (80). The upshot was that all Thoroughbred racehorses in training bleed into their lungs, an astonishing conclusion.

The mechanism for the bleeding was clarified when the pulmonary vascular pressures of these horses were measured while they were galloping on a treadmill (15, 32). Direct measurements of left atrial pressures with a catheter in the atrium showed pressures as high as 70 mmHg, and these were accompanied by pulmonary artery pressures as high as 120 mmHg. The systemic vascular pressures were also extremely high, with a mean arterial pressure up to 240 mmHg and a mean right atrial pressure of 40 mmHg.

Of course these Thoroughbreds have been selectively bred for hundreds of years to run very fast. They have maximal oxygen consumptions of up to 180 ml·min\(^{-1}\)·kg\(^{-1}\) and cardiac outputs as high as 750 ml·min\(^{-1}\)·kg\(^{-1}\). The result is that the filling pressures of the left ventricle are extremely high, and this accounts for the high left atrial, pulmonary venous, and pulmonary capillary pressures. With a left atrial pressure of 70 mmHg and a pulmonary arterial pressure of 120 mmHg, the capillary pressure must be \(\sim 100\) mmHg, and it is not surprising that the capillaries break under these conditions. When the...
lungs of these animals were examined by electron microscopy shortly after the animal had been galloping on a treadmill, breaks in the blood-gas barrier were seen (79). Horses that bleed repeatedly develop pathological changes in their lungs, mainly fibrosis. Veterinarians believe that the racing performance of horses is impaired.

It could be argued that Thoroughbred racehorses are at one end of the spectrum of aerobic activity. However, it may well be that other highly athletic animals break their pulmonary capillaries but no data are available. There is some evidence that racing greyhounds also bleed into their lung (51). It seems likely that other highly aerobic animals such as antelopes may break their capillaries, but the evidence such as bronchoscopy appearances after running or tracheal washings has not been sought.

The fact that highly aerobic racehorses break their pulmonary capillaries prompts the question of whether elite human athletes might do the same thing at extremely high levels of exercise. There is evidence that this is the case. In one study, elite cyclists sprinted uphill at maximal effort with a mean heart rate of 177 beats/min, and they then underwent bronchoalveolar lavage (BAL) shortly after the exercise. Control BAL was carried out on sedentary volunteers. It was found that the athletes had higher concentrations of red blood cells, total protein, albumin, and leukotriene B4 in their BAL fluid than the control subjects (28). This is strong evidence that elite athletes at maximal exercise develop changes in the blood-gas barrier consistent with failure of their capillaries. There are a number of additional reports of lung bleeding in other humans during high levels of exercise such as swimmers and runners (40, 74).

2) Pathological conditions. There are many pathological conditions in which the fragility of the capillaries can be demonstrated. The three main causes are a pathological increase in pulmonary capillary pressure, an increase in capillary wall stress caused by overinflation of the lung, and diseases where the strength of the capillary wall is impaired.

One of the most interesting pathological conditions is high altitude pulmonary edema (HAPE). In fact, this was the disease that first alerted physiologists to the fragility of capillaries. The pathogenesis of HAPE was a puzzle in the early 1980s. It was known to occur in some normal healthy people when they ascended to high altitude, but studies showed that the pulmonary arterial wedge pressure was normal and this ruled out left ventricular failure. However, it was found that there was a strong link between pulmonary hypertension and HAPE. Subjects who developed the disease had high pulmonary artery pressures, and in addition other people who were susceptible to HAPE had an increased hypoxic pulmonary vasoconstriction response. An important advance was the demonstration by bronchoalveolar lavage that the edema fluid in patients with HAPE had a large concentration of cells and high-molecular weight proteins, which showed that the walls of the pulmonary capillaries were damaged (24, 54). The conclusion was that in some way the high pulmonary arterial pressure was being transmitted to some capillaries.

However, hypoxic pulmonary vasoconstriction is known to occur mainly in the small arteries upstream of the capillaries, and so it was not clear how these could be damaged. But it had been suggested earlier that the hypoxic vasoconstriction might be uneven (31), with the result that those capillaries that are not protected by the constriction would be exposed to the high pressure and therefore fail. Subsequent animal experiments in which the pulmonary capillary pressure was increased and the lung examined by electron microscopy showed clear evidence of breaks in the capillary endothelium, alveolar epithelium, and in some cases the extracellular matrix as well (78, 66). This explanation for the pathogenesis of HAPE has now been confirmed by many studies.

A similar mechanism for damage to the pulmonary capillaries is seen in many patients with heart disease. For example, in left heart failure there is an increase in pulmonary capillary pressure. With small increases in pressure, pulmonary edema may occur, but this is a transudate explained by an imbalance of the Starling equilibrium. However, with higher pulmonary capillary pressures, the edema fluid has been shown to have a large concentration of high molecular weight proteins and therefore is of the high-permeability type (57, 67).

Overinflation of the lung is known to damage pulmonary capillaries if it is severe enough (13), and the explanation here is not an increase in pulmonary capillary pressure but another mechanism for the increase in capillary wall stress. At high lung volumes, the tension in the alveolar walls is high and much of this is transmitted to the capillary walls because the alveolar wall is basically composed of a string of pulmonary capillaries. This increased stress in the capillary wall then causes the vessels to disrupt. It has been shown in animal experiments that if the capillary transmural pressure is kept constant, but the lung is inflated to abnormally high volumes, damage to the capillaries can be seen by electron microscopy (20).

Capillary bleeding is also seen in the infant respiratory distress syndrome. Here the cause is a deficiency of pulmonary surfactant that results in an increased capillary transmural pressure. The capillary pressure itself is not raised but the pressure in the interstitium around the capillaries is reduced because of the rise in surface tension of the alveolar lining layer (48). This increases the retractive force of the alveoli leading to a reduced interstitial pressure.

Another pathological change causing increased fragility of the pulmonary capillaries is a disease such as Goodpasture’s syndrome in which the type IV collagen becomes abnormal (81). In the next section the importance of type IV collagen in the integrity of the pulmonary capillary is discussed.

3) Laboratory studies. To determine how much the pressure in the pulmonary capillaries needs to be increased before damage to their walls can be detected, experiments were carried out in an anesthetized rabbit preparation. The chest was opened, and catheters were placed in the pulmonary artery and left atrium so that the capillary transmural pressure was accurately known. The pressure was increased in small increments, the capillaries were fixed by infusion of intravascular glutaraldehyde, and the appearances were studied by electron microscopy (66, 78).

It was found that the first indications of ultrastructural changes were seen at a capillary transmural pressure of 24 mmHg. However, when the pressure was increased to 39 mmHg the number of breaks was much greater, and a further increase in number was seen at a pressure of 53 mmHg. It is interesting that some changes were seen at a pressure as low as 24 mmHg, because, as indicated earlier, the capillary transmural pressure at the bottom of the human lung during heavy
exercise is calculated to be as much as 36 mmHg. Of course it cannot be assumed that human pulmonary capillaries have the same characteristics as those in the rabbit. As described below experimental studies have shown that different transmural pressures are required to damage the capillaries in rabbit, dog, and horse lung (6). Disruptions are seen in the capillary endothelial cells, alveolar epithelial cells, and sometimes the extracellular matrix as well. Figure 6 shows examples of breaks in the capillary endothelium and alveolar epithelium.

An interesting feature of the cellular disruptions is that these are rapidly reversible when the capillary transmural pressure is reduced. This was demonstrated by first raising the pressure to a high level at which damage to the capillaries can be seen and then reducing the pressure to a low level and fixing the capillaries for electron microscopy. When this was done it was found that ~70% of both the endothelial and epithelial disruptions closed within a few minutes (14). A possible mechanism for this would be elastic deformation of the extracellular matrix, and this might be explained by an alteration in the shape of the type IV collagen matrix in response to stress as discussed below. The reversibility of the disruptions is also interesting in relation to the clinical features of HAPE. Typically these patients improve rapidly if they descend to a lower altitude, but this rapid improvement is not seen in other types of pulmonary edema such as that caused by left ventricular failure.

WHAT STRUCTURES IN THE WALL OF THE PULMONARY CAPILLARY ARE RESPONSIBLE FOR ITS STRENGTH?

Available evidence strongly suggests that the strength of the blood-gas barrier comes from the extracellular matrix. As Figs. 2–4 show the thin side of the barrier consists of only three layers, the capillary endothelium, extracellular matrix, and alveolar epithelium. However, it is unlikely that the two cellular layers confer much strength to the barrier. Some evidence for this is that in the experiments on animal preparations described above, disruptions of the endothelium and epithelium are frequently seen while the extracellular matrix remains intact.

Other studies show that the mechanical behavior of capillaries when the transcapillary pressure is raised is determined by the extracellular matrix. For example, the extent of the distension of capillaries in frog mesentery is consistent with the elastic properties of basement membrane (60). The critical role of the extracellular matrix was also shown in a study of isolated rabbit renal tubules, which are composed of only a single epithelial layer and its basement membrane. It was found that the relationship between the diameter of the renal tubule and its transmural pressure was the same whether or not the cellular layer was removed with detergent (75). Therefore in this preparation, the single layer of epithelial cells did not contribute to the mechanical properties. That study also provided strong evidence that the considerable strength of the renal tubule comes from the basement membrane.

Additional evidence suggesting that the basement membrane plays a critical role in the mechanical integrity of the capillary comes from the structure of the glomerulus. Glomerular capillaries withstand a high transmural pressure of the order of 35 to 40 mmHg (7) and they have thick basement membranes of ~350 to 400 nm in human kidney. This is three to four times greater than in pulmonary capillaries. Furthermore, in Goodpasture’s syndrome where antibodies attack the type IV collagen (81), bleeding occurs into both the glomerular and alveolar spaces. There is also a condition known as thin basement membrane nephropathy in which there is persistent glomerular bleeding in both children and adults (53).

The main components of the extracellular matrix include type IV collagen, laminin, intactin/nitogen, heparan sulfate proteoglycans, tenascin, and integrins and other anchoring fibers. The type IV collagen appears to be the most important constituent for the strength of the blood-gas barrier.

Type IV collagen has three peptide chains, two α1 (IV) with one α2 (IV), and is a triple helix. Each molecule is about 400 nm long and has a large COOH-terminal globular domain (NC1) at one end and a distinctive collagenous NH2-terminal at the other end (7S) that promote crosslinking. Two of the molecules link at the COOH terminus to give a doublet 800 nm long. Then four molecules link at the NH2 terminus to give a chicken wire type of structure as shown in Fig. 7.

An interesting feature of human type IV collagen is that there are regions that may allow bending of the molecule (61). This suggests that the matrix shown in Fig. 7B can lengthen under tension just as chicken wire does. This might explain the appearances in Fig. 6 where the extracellular matrix remains intact but both the epithelial and endothelial layers disrupt and separate.

Unfortunately there are only limited data on the mechanical strength of type IV collagen. The best study was carried out on basement membrane from the lens capsule of the cat, and this gave an ultimate tensile strength of 1.7 ± 0.16 × 106 N·m2 (17). Another study was carried out on the isolated rabbit renal tubule referred to earlier (75), and with some assumptions, this gave an ultimate tensile strength exceeding 5 × 106 N·m2. There is evidence that the type IV collagen is limited to the center of the extracellular matrix band, and it is probably indicated by the electron-dense layer in Fig. 4. This localiza-
tion of type IV collagen is supported by studies using anti-
human type IV collagen antibody that shows that the molecule is
predominantly located in the center of the extracellular matrix
(10). Therefore if we assume that the thickness of the type IV
collagen layer is $\sim 50$ nm and use a value of $1.7 \times 10^3$ N·m$^2$
for its ultimate tensile strength, the Laplace relationship sug-
gests that the capillaries will probably be damaged at a trans-
capillary pressure of $\sim 30$ mmHg, which fits with the animal
studies mentioned above. However, calculations like this make
a number of assumptions.

Because the layer of type IV collagen shown in Fig. 4 is only
$\sim 50$ nm thick and a doublet formed by two molecules is 800
nm long, it is clear that the sheet shown in Fig. 7B must lie
parallel to the capillary lumen. Several sheets could lie on top of
each other like sheets of chicken wire as in Fig. 7C. A collagen IV molecule is $\sim 1.5$ nm thick so there would be space
for $\sim 30$ sheets like those shown in Fig. 7B to be accommo-
dated.

SPECIES DIFFERENCES IN THE FRAGILITY OF PULMONARY
CAPILLARIES

The histological appearances of the lungs of most mammals
show many similarities. Indeed if one is shown a thin section
of the lung it is often difficult to identify the species from
which it came. One clue is the size of the alveoli. In general,
the smallest mammals with high metabolic rates have the
smallest alveoli. For example, the diameter of the alveoli in the
shrew is $\sim 12$ $\mu$m, whereas in the sloth the diameter is $\sim 700$
$\mu$m (63).

However, the ultrastructure of the blood-gas barrier reveals
important differences between species. For example, in one
study the thickness of the three components of the blood-gas
barrier, the capillary endothelium, extracellular matrix or in-
terstitium, and alveolar epithelium, were measured in rabbit,
dog, and horse (6). Figure 8 shows the cumulative relative
frequencies of the thicknesses of the three components of the
blood-gas barrier and the total thickness of the barrier in the
three species. (The cumulative relative frequency is the number
of measurements below a particular value and is a useful way
of comparing a series of measurements. For example, Fig. 8
shows that in the horse, 50% of the measurements of total
thickness were below 0.6 $\mu$m.)

Note that the total thickness in the horse was much greater
than in either the rabbit or dog. This ordering was also seen in
the thickness of the endothelium, interstitium, and epithelium.
However, the most striking difference was in the thickness of
the interstitium, which was much less in the rabbit than the dog
or horse. The values for the average thicknesses were 0.175,
0.318, and 0.390 $\mu$m for rabbit, dog, and horse, respectively.

As indicated earlier, the interstitium is the component of the
blood-gas barrier that is believed to confer its strength. There-
fore it is not surprising that higher pressures are needed to
disrupt components of the barrier when the thickness of the
interstitium is large. The pressures required for damage to the
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REMODELING OF PULMONARY CAPILLARIES

An important question is how is the blood-gas barrier main-
tained so exquisitely thin but just strong enough to withstand
all but the most extreme physiological stresses? A likely
possibility is that the capillary wall senses wall stress and
regulates its structure accordingly, presumably the most im-
portant response being the amount of the type IV collagen.
Evidence that this occurs in humans is in Fig. 9, which clearly
shows thickening of the basement membrane of pulmonary
capillaries in a patient with mitral stenosis (26). Other inves-
tigators (2, 9a, 33) have reported similar changes. In this
disease the gradual narrowing of the mitral valve results in a
progressive increase in pulmonary capillary pressure over
months and years.
It is well known that remodeling of the larger pulmonary blood vessels occurs in pulmonary hypertension. For example, thickening of the wall, including the smooth muscle and interstitium, occurs in experimental animals exposed to chronic hypoxia (59). Interestingly, remodeling occurs remarkably rapidly in these larger pulmonary blood vessels. In one study where mechanical tension was applied to explants of rings of rat pulmonary artery, it was shown that increases in collagen synthesis and elastin synthesis began within 4 h (65). A feature of that series of experiments was that the changes were dependent on the presence of the endothelium, because when this was removed the synthesis did not occur. Close inspection of Fig. 9 suggests that most of the thickening of the extracellular matrix in this patient with mitral stenosis seems to be associated with the capillary endothelial cell rather than the alveolar epithelial cell (see arrow). This would be consistent with the main role of the endothelium in remodeling.

Therefore a reasonable hypothesis is that some structure in the capillary wall is sensing the increase in wall stress. Of course this need not be the endothelial cell itself but could be some other cell such as the epithelium, fibroblast, or another cell in the wall. The sensing cell would then send a signal to the endothelial cell that would in turn increase the amount of basement membrane.

Attempts have been made to identify the factors that respond to increased stress in the capillary wall. These are difficult experiments partly because it is challenging to come up with a design that results in an increase in stress of the capillary walls without doing the same to the walls of the larger blood vessels. Also it is not easy to ensure that the signals are coming from the capillaries and not the larger vessels. One way to try to obviate this problem is to collect tissue only from the outer few millimeters of lung where larger blood vessels are not found.

In an experiment on an anesthetized rabbits, the chest was opened and the volume of one lung was increased while the other lung was ventilated at a normal volume (3). Control animals had both lungs ventilated at normal volumes. It was found that in the lung ventilated at a high volume, there was increased gene expression after 4 h for \( \alpha_1 \) (III) and \( \alpha_2 \) (IV) procollagens, fibronectin, basic fibroblast growth factor, and transforming growth factor beta 1 (TGF-\( \beta_1 \)). Unexpectedly, the changes in mRNA listed above were seen in both the overinflated lung with 9 cmH\(_2\)O PEEP and the normally inflated lung (1 cmH\(_2\)O PEEP). A possible explanation was that the overinflated lung sensed the increased tension, and the information was transferred via the circulation from the overinflated lung to the normally inflated lung.

In another experiment, capillary wall stress was raised by increasing the capillary transmural pressure (46). This was done by raising the venous pressure in isolated perfused rat lungs. The venous pressure was raised intermittently to avoid

![Fig. 8. Cumulative relative frequencies of the endothelium, interstitium, epithelium, and total blood-gas barrier in rabbit, dog, and horse. Note that the total thickness is smallest in the rabbit and also that the thickness of the interstitium is much less in this species. These morphometric data are consistent with the greater fragility of the capillaries in rabbits than in the other two species. [Borrowed with permission from (6).]]

![Fig. 9. Cumulative relative frequencies of the endothelium, interstitium, epithelium, and total blood-gas barrier in rabbit, dog, and horse. Note that the total thickness is smallest in the rabbit and also that the thickness of the interstitium is much less in this species. These morphometric data are consistent with the greater fragility of the capillaries in rabbits than in the other two species. [Borrowed with permission from (6).]]

![Fig. 9. Electron micrograph of a pulmonary capillary from a young patient with mitral stenosis. There is obvious thickening of the extracellular matrix, and the arrow shows that the thickening is mainly associated with the basement membrane of the capillary endothelial cell. [Courtesy of Sheila Haworth. Borrowed with permission from (76).]]
the development of pulmonary edema. The result was increases in gene expression for \( \alpha_1 \) (I) and \( \alpha_1 \) (III) procollagens, fibronectin, laminin, and TGF-\( \beta_1 \).

A further approach was to raise the capillary wall stress by giving the rat a low oxygen mixture to breathe (4). Here an assumption was that the hypoxic pulmonary vasoconstriction was uneven as discussed in the section on the pathogenesis of HAPE (2). Pathological conditions. Tissue was only removed from the peripheral region of the lung in an attempt to avoid the responses of the larger pulmonary blood vessels. It was found that levels of mRNA for various genes increased after a few hours of hypoxia, the increase was sustained for several days, and it then decreased. This pattern was seen for \( \alpha_2 \) (IV) procollagen, PDGF-B, \( \alpha_1 \) (I), and \( \alpha_2 \) (III) procollagens and fibronectin.

It can be seen from the above that no clear picture has yet emerged and more studies are needed. It is remarkable that so much is known about remodeling of the larger pulmonary blood vessels, whereas the capillaries have been largely ignored.

FRAGILITY OF PULMONARY CAPILLARIES IN SPECIAL SITUATIONS

1) Capillaries in neonatal animals. In mammals, considerable development of the lung takes place after birth. For example, in humans the number of alveoli at birth is only \( \sim 15 \) million, whereas in the adult it is nearly 500 million (11, 44). In addition, the morphology of the gas exchanging tissue changes markedly as the lung matures. Early in lung development there are no alveoli and the peripheral segments of the airway tree end in smooth-walled channels (transitory ducts) and in primitive saccules. These saccules are separated by thick septa that contain two capillary networks, one for each saccule. Figure 10 shows an electron micrograph of an immature primary septum in the early postnatal period in rat (8). Note that the capillary network is present on both sides of an interstitial layer richly endowed with cells. As the lung develops and the primary septum extends its length to ultimately become an alveolar wall, the capillaries are apparently pulled apart from each other and the single capillary layer that is seen in the adult lung is formed.

With these remarkable morphological changes taking place, it is perhaps not surprising that the fragility of the capillaries in neonates is different from that in the adult. Studies have been carried out on the fragility of pulmonary capillaries in newborn rabbits between 4 and 5 h after birth (21). After anesthesia, the chest was opened and catheters were placed in the main pulmonary artery and left atrium. A small clamp was placed on the ductus arteriosus, and the capillary pressure was increased in steps. The lung was then fixed with glutaraldehyde, and the capillaries were examined by electron micrographs. Figure 11 shows the number of breaks in the endothelium and epithelium plotted against the capillary transmural pressure in newborn and adult rabbits. Note that whereas in the adult rabbit, a capillary transmural pressure of 52.5 cmH\( \text{2} \)O was required before disruptions of the epithelium and capillary endothelium were seen, disruptions occurred in the neonates at a pressure of 15 cmH\( \text{2} \)O. It is clear that the pulmonary capillaries of the neonates are much more fragile, and this was particularly true for the capillary endothelium. However, the number of breaks in the epithelium at a capillary transmural pressure of 15 cmH\( \text{2} \)O was also statistically greater in the newborns than the adults.

There were interesting differences in the patterns of disruption between the neonates and adults. As Fig. 11 shows, the...
adult rabbits showed an approximately equal number of breaks in the epithelium and endothelium at a capillary transmural pressure of 52.5 cmH2O. However, in the neonates the number of endothelial breaks greatly exceeded the number of epithelial breaks, although the transmural pressure of the capillaries was much lower. Another feature of the disruptions in the newborn lungs was that most of the breaks in the epithelium and endothelium were associated with an intact basement membrane, whereas in the adult animals, approximately half of the epithelial and endothelial breaks were associated with disruptions of the basement membrane. In other words, the capillary and alveolar endothelial layers tended to be more easily disrupted in newborn lungs compared with their associated basement membranes.

An additional study was carried out to determine whether the increased fragility of the pulmonary capillaries in neonatal lungs was associated with differences of thickness of the three layers of the blood-gas barrier (22). Measurements were also made on animals that were removed from the uterus by Caesarean section before term. The normal gestation period of rabbits is 30 days, and the studies were made on premature animals of 27 days’ gestation, and comparisons were made with newborn (1 day old) rabbits and adults. In all three groups, the pulmonary capillaries were fixed by intravascular glutaraldehyde with an airway pressure of 10 cmH2O and a pulmonary artery pressure of 25 cmH2O. Thicknesses of the endothelial, interstitial, and epithelial layers were measured at right angles to the blood-gas barrier. Figure 12 shows the percentage of measurements of the thickness of the interstitium that were less than or equal to 0.1 μm in premature, 1-day-old, and adult rabbits. Note the high incidence of very small values in 1-day-old animals. [Borrowed with permission from (21).]

![Fig. 12. Frequency of measurements of the thickness of the interstitium that were less than or equal to 0.1 μm in premature, 1-day-old, and adult rabbits. Note the high incidence of very small values in 1-day-old animals.](http://jap.physiology.org/)

Compensatory growth processes have been studied in experimental animals, and under some conditions the neovalveolarization clearly involves the formation of new pulmonary capillaries. Most of these studies have been made by excising parts of the lung. For example, Fehrenbach et al. (16) performed left-sided pneumonectomy in adult mice and counted the number of alveoli in the remaining right lung using modern stereological methods. They found that by 20 days after the pneumonectomy, the number of alveoli had increased by ~50% compared with controls. This represented an increase in the number of alveoli in the lung from 645,000 to 925,000. Voswinckel et al. (68) also reported postpneumonectomy growth in adult mice.

There are considerable age and species differences in the abilities of animals to add additional tissue, including pulmonary capillaries after removal of part of the lung. For example in adult dogs, compensatory growth occurs only if more than half of the lung is removed (1a). No compensatory growth is seen if only 40% of the lung is removed (29, 30). In immature dogs, this compensatory process of alveolar growth can normalize gas exchange after pneumonectomy (62). Rats and mice retain the potential for compensatory growth into adulthood. This was shown by the study on mice cited above (16) and has also been demonstrated in rats (70).

An interesting issue is whether the new capillaries formed in the process of neovalveolarization have the same mechanical properties as the capillaries formed during normal maturation of the lung. For example, are they more fragile than normal alveoli? Information on this might be improved if we were able to understand the mechanism of the formation of the new capillaries during neovalveolarization. As was discussed earlier in the section on maturation of the lung, the adult alveoli with their single layer of capillaries are derived from the primitive saccules that are composed of thick septa containing two capillary networks (Fig. 10). The mechanism for the formation of adult alveoli with a single capillary network is thought to be elongation of the wall of the saccule by means of increasing tension in the fibers in its wall. This elongation would eventually result in a thin alveolar wall with a single layer of capillaries. Figure 13 illustrates diagrammatically how this could occur. One layer of the double-layered capillaries would slide over the other until there are two extended walls, now the alveolar walls, each with its single capillary layer.

Clearly this process cannot occur in the mature lung because this does not include primitive saccules with their double capillary networks. Indeed how the process of neovalveolarization comes about with compensatory growth in the adult lung is not certain. Burri (9) argued that a new secondary septum could be formed in the mature lung by pulling on a primary alveolar wall with the existing fiber network. He also suggested that additions to the capillary network could be made by the process of intussusceptive growth whereby single capillaries invaginate, eventually resulting in two daughter capillaries (9).
One interesting point about lung maturation is that postnatal growth of the parenchyma is most rapid at the periphery of the lung close to the pleura (43). This may be a clue to the processes involved in neoalveolarization, although the significance of the finding is not clear at the present time.

It is clear from the above that not enough is yet known about the process of neovascularization to make predictions about the properties of the new capillaries. Certainly there are no measurements that would help us to understand their fragility.

3) Capillaries formed from seeded endothelial cells in the process of bioengineering a lung. This last section is devoted to a topic that is only just emerging. There are no data on capillary fragility in this area, but it is interesting to consider some of the problems that might arise. The ultimate aim is to bioengineer a lung that could be transplanted into a patient with lung disease that would not be prone to antigenic rejection.

The general principles have been set out (49, 56). A human lung would be removed from a donor, and the whole organ would be decellularized to remove all antigenic material. This has been done in animal lungs by perfusing them with detergent via the pulmonary artery and the trachea, and presumably some variation of this process would be used. The absence of cells would be verified by microscopy. Next the scaffold remaining after decellularization would be scrutinized to make sure that the matrix of the airways, blood vessels, alveoli, and capillary network is intact. The blood vessels would then be seeded by perfusing them with cultured recipient endothelial cells via the pulmonary artery. The lung would be placed in a bioreactor that maintains it under normal physiological conditions, including temperature, pH, and blood-gas values.

Next the alveolar epithelium would be seeded by introducing cultured recipient epithelial cells via the airways. Possibly the cultured endothelial and epithelial cells would be provided by processing appropriate stem cells from the recipient. After seeding, the presence of healthy type I and type II alveolar epithelial cells and capillary endothelial cells would be verified by microscopy. The reseeding in the bioreactor might take several days based on animal experiments performed to date. At the end of this time the regenerated lung would be removed and its gas-exchange behavior and mechanical properties measured. Finally the lung would be transplanted into the recipient. Obviously this is an extremely ambitious bioengineering project. However, preliminary experiments in experimental animals have confirmed that parts at least of this complicated process are feasible (49, 56).

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The procedure for the whole lung that is described above has not yet been used in humans. However, there have been several successful tracheal and bronchial transplants since the original description by Macchiariini et al. (41). Naturally this is a much simpler problem and involves seeding epithelial rather than endothelial cells. However, the procedure has been shown to be successful without subsequent rejection.

Seeding of endothelial cells has also shown to be feasible in connection with cardiac stents (12, 19, 85). Here the main objective is an attempt to reduce thrombus formation and other complications associated with the use of stents. An interesting issue concerning seeded cells is that it has been found experimentally that their behavior is different depending on whether they have been seeded onto a surface (two-dimensional culture) or within a gel (three-dimensional culture) (55).

There is no information about the possible fragility of pulmonary capillaries resulting from these new techniques. Indeed there do not appear to be any published electron micrographs of the blood-gas barrier in the bioengineered capillaries as yet. However, the process of development of the blood-gas barrier in seeded lungs is so different from that occurring with normal maturation on the one hand and neovascularization on the other, that it would be remarkable if the fragility of the capillaries was the same. Figure 14 shows light micrographs of pulmonary capillaries after seeding of endothelial cells onto a scaffold in rat (49). Note that the alveoli spaces contain red blood cells, which might indicate increased fragility of the capillaries.

CONCLUSIONS ON THE FRAGILITY OF PULMONARY CAPILLARIES

The discussion of the fragility of pulmonary capillaries can be summarized as follows.

1) There is a strong selective pressure for the blood-gas barrier to be extremely thin because of the requirement for diffusive gas exchange. Other things being equal this tends to make the capillaries fragile.
2) The lungs from normal adult humans only show capillary fragility under exceptional conditions. However, increased fragility is common in lung and heart diseases.
3) Extreme exercise in elite human athletes can cause disruption of the capillaries, and this also occurs in highly aerobic animals such as racehorses.
4) The pulmonary capillaries of neonatal lungs are very fragile and the extracelluar matrix is very thin.
5) Histological evidence of remodeling of the blood-gas barrier is seen in patients with increased pulmonary capillary pressures over extended periods.
6) Animal experiments have shown genetic responses to increased capillary wall stress that could increase the strength of the blood-gas barrier.

A reasonable conclusion from these observations is that animals are born with thin and fragile blood-gas barriers because of the selective pressures for diffusional gas exchange. However, after birth, the stresses in the capillary wall associated with physical activity cause remodeling that reduces the fragility. A balance is achieved in normal human adults such that disruption of the capillary wall only occurs under exceptional conditions, and the blood-gas barrier is maintained extremely thin for adequate gas exchange. However, elite human athletes and highly aerobic animals can break their capillaries, and this often occurs in lung and heart diseases.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS

Author contributions: J.B.W. prepared figures; J.B.W. drafted manuscript; J.B.W. edited and revised manuscript; J.B.W. approved final version of manuscript.

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