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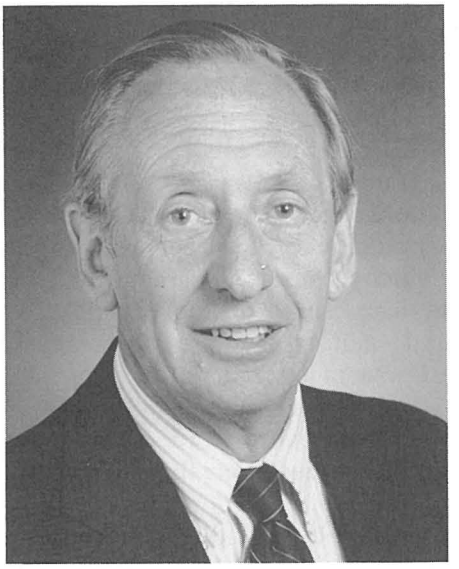
Strength and Failure of Pulmonary Capillaries



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I was fortunate to attend a good school in Adelaide, Australia, and was greatly influenced by a Mr. Ray Smith, who taught physics and chemistry in the last three years of high school. He had an infectious enthusiasm and a wonderful clarity of exposition that had an important bearing on how I learned to write and talk about physiology. In my last couple of years at school my great love was high energy physics, and I probably would have gone into that area were it not for the fact that both my father and mother had medical backgrounds and that in the education system that I was brought up in it was necessary to elect your field of study by the age of 16 or 17.

I found medical school very tedious partly because the material was taught in a descriptive, nonanalytical manner. These were the days before full-time academic appointments in the clinical departments at Adelaide University. In particular, I was taught physiology very badly, and this probably set back my interest in the topic by about ten years. Most of my university friends were outside the medical school, and I spent a good deal of my time studying music and other humanities. As a result, I barely scraped through in my final year.

After the required year of residency, I left for England on the first available boat (this was before long distance air travel was feasible) and started to put down roots in London, a city I still regard as the most stimulating city in the world. Fortunately I had a link with someone at the Postgrad-

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uate Medical School, Hammersmith Hospital (later to become the Royal Postgraduate Medical School), and after a year or so I was accepted there as an intern. At this stage I had very little idea of what area of medicine to pursue except that, being interested in physical phenomena such as pressures and flows, I considered cardiology or pulmonary diseases. It happened that the Postgraduate Medical School was soon to embark on a new program in clinical pulmonary physiology, and Dr. Charles Fletcher suggested that I spend a year at the Pneumoconiosis Research Unit near Cardiff, learn some pulmonary physiology, and then return to Hammersmith. While I was at Cardiff, Julius Comroe's green-covered book, *The Lung,* appeared and I devoured every word. That exceptional book persuaded me that I had found my niche.

When I returned to Hammersmith, two new technical developments determined my research program. The first was that Kemp Fowler had just built the first mass spectrometer designed specifically for pulmonary research. We used it to study the alveolar gas composition both in expired gas[58,59,61] and during bronchoscopy by passing the sampling tube of the mass spectrometer down the old, rigid bronchoscope.[28,60] The procedure we developed at that time for determining the amount of ventilation-perfusion inequality in the lung from measurements of the respiratory exchange ratio in expired gas was exploited on Spacelab SLS-1 in June 1991, when we found, to our surprise, that there was considerable ventilation-perfusion inequality present during space flight.

The second technical development was that the first cyclotron specifically for medical research was just coming on line, and, among the exotic radioisotopes it produced, the most remarkable was oxygen-15, with a half life of only 2 min. Together with Phillip Hugh-Jones and others, I studied the patterns obtained when a patient inhaled a single breath of this gas and counters were placed over different regions of the lung.[14,15] To our utter astonishment, the rate at which the radioactive oxygen was removed from the apex of the normal upright lung was much less than that at the base.[56,57]

It is difficult now to realize that at that time there was no notion that the distribution of blood flow in the lung was uneven. Admittedly, in retrospect, some early measurements using bronchospirometry and small catheters passed into the bronchi were consistent with uneven blood flow. But the significance of these observations had not been fully appreciated, and therefore the demonstration using oxygen-15 of the striking regional differences of blood flow was enormously exciting. Subsequently we found that if we labeled carbon dioxide with the same radioisotope, the rates of removal were faster and easier to measure. Figure 1 shows one of the early tracings made using ^{15}O-labeled carbon dioxide in 1958. Much of my research over the subsequent 10 years was devoted to the factors responsible for the inequality of blood flow and ventilation in the lung and their effects on regional and overall gas exchange.

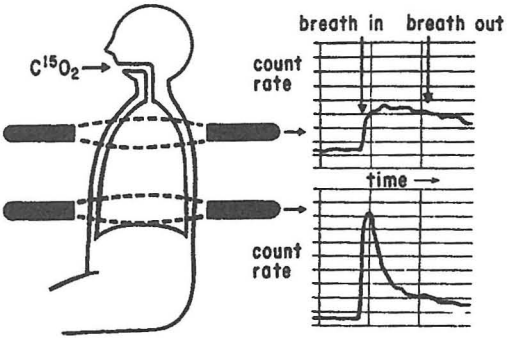

Figure 1. Early tracings obtained with ^{15}O-labeled carbon dioxide showing the striking difference in blood flow between the top and bottom of the upright lung. The subject took a single breath of the gas and held his breath for 15 s. Note the slow rate of removal of the gas at the apex of the lung compared with the pattern at the base of the lung.

I spent almost 15 years at the Postgraduate Medical School, with three interruptions. The first was to join Sir Edmund Hillary on a Himalayan high-altitude physiology expedition in 1960. This was followed by a year with Hermann Rahn in Buffalo and later a year at the NASA Ames Research Center at Moffett Field in California. I became interested in space physiology because I had spent a great deal of time thinking about the effects of gravity on the lung. While I was in California, the new medical school at the University of California, San Diego, was recruiting its first faculty members, and this seemed like a wonderful opportunity. It was, and I have spent the last 22 years very happily at UCSD. I have been away only for a period in 1981 during the American Medical Research Expedition to Everest.

I would now like to turn to the recent work on the strength and failure of pulmonary capillaries, carried out in collaboration with Dr. Odile Mathieu-Costello. It is well known that the blood-gas barrier is extremely thin. Indeed in the human lung, approximately half of the barrier has a thickness of only 0.2–0.4 μm.[20] However, the integrity of the blood-gas barrier must be maintained because otherwise plasma or even blood from the capillaries will leak into the alveolar spaces and interfere with gas exchange. Therefore the blood-gas barrier needs to be strong as well as thin. It is curious that physicians and physiologists have rarely asked the question: how strong is the blood-gas barrier?

We approached this problem by taking anesthetized rabbits, opening the chest, cannulating the pulmonary artery and left atrium, and perfusing the lung with the rabbit's own blood. After only 1 min of autologous blood perfusion, we washed the blood out with a saline/dextran mixture and followed with buffered glutaraldehyde to fix the lungs for electron microscopy. We used pulmonary arterial pressures of 20, 40, 60, and 80 cmH_2O. The pulmonary venous pressure was always set 5 cmH_2O below the arterial pressure, and the alveolar pressure was 5 cmH_2O. Therefore the capillary transmural pressures were at 12.5, 32.5, 52.5, and 72.5 ± 2.5 cmH_2O.[52,64]

Two interesting findings emerged. The first was that at the high pressures the capillaries bulged into the alveolar spaces (Fig. 2). This was not surprising because Glazier and coworkers[22] had shown a similar appearance in an entirely different preparation, where dog lung capillaries had been rapidly frozen during perfusion with their own blood. In addition, a similar appearance was reported by Gil and coworkers[21] in rabbit lungs.

The second finding was more surprising. At capillary transmural pressures of 52.5 cmH_2O and above we saw ultrastructural damage to the blood-gas barrier, including disruption of the capillary endothelial cells, alveolar epithelial cells, and sometimes all layers of the barrier. An

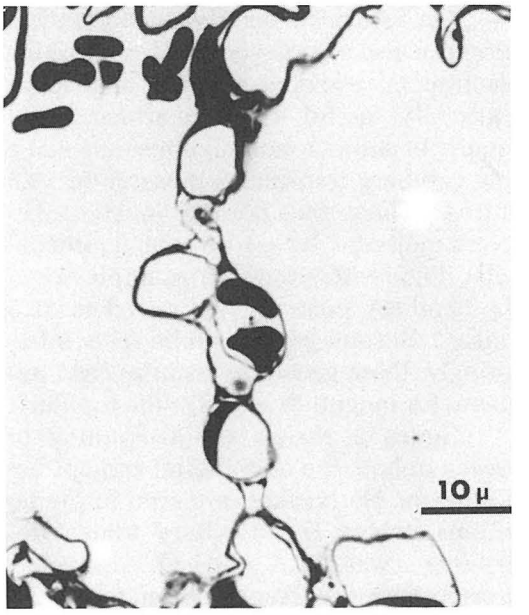

Figure 2. Photomicrograph of pulmonary capillaries of rabbit at a transpulmonary pressure of 52.5 cmH_2O. Note that the capillaries bulge into the alveolar spaces and that their average diameter is about 10 μm. (Reproduced with permission from reference 64.)

example is shown in Figure 3a, where the capillary endothelial layer shows disruption while its basement membrane remains intact, as does the basement membrane of the alveolar epithelial cell and the alveolar epithelium itself. Figure 3b shows another example. Here the alveolar epithelial lining is disrupted, and if you look carefully you can see that the capillary endothelial layer is also broken, with a red cell very close to the exposed endothelial basement membrane. A further example is shown in Figure 3c, where the alveolar epithelial layer is broken on one side of the capillary while the endothelial layer is disrupted on the other. Note the platelet apparently adhering to the exposed basement membrane. A final example is shown in Figure 3d, where all layers of the blood-gas barrier are broken and a red cell can be seen apparently moving out of the capillary lumen. Note also the appearance of "blebbing" in the alveolar epithelium near the break.

The breaks in the alveolar epithelial layer can also be seen very well by scanning electron microscopy. Here we had to be especially careful to avoid artifacts, and Figure 4a shows a normal appearance at a low capillary transmural pressure of 12.5 cmH_2O. The arrows point to junctions between adjacent type I alveolar epithelial cells. Figure 4b shows an example when the capillary pressure was raised to 52.5 cmH_2O. Several breaks can be seen. Interestingly, these generally occur at right angles to the longitudinal axis of the capillary.

Figure 5 shows the frequency of breaks in both the endothelial and epithelial layers. No breaks were seen in preparations, where the capillary transmural pressure was 12.5 cmH_2O. However, breaks were consistently seen when the pressure was raised to 52.5 cmH_2O or above. A few breaks were seen at a transmural pressure of 32.5 cmH_2O, although most of these were in one preparation, which could have been abnormal.

The three principal forces acting on the capillary wall are shown in Figure 6. The first is the hoop or circumferential tension caused by the capillary transmural pressure acting across a curved surface and calculated from the Laplace relationship. At a capillary transmural pressure of 50 cmH_2O (that is, at failure), the hoop tension is not particularly high, being about 25 dyn/cm (or 25 mN/m). The very small radius of curvature of the capillaries is an important factor in keeping this tension low. The second force is the surface tension of the alveolar lining layer. Because the capillaries bulge into the alveolar spaces at the high pressures (Fig. 2), we have argued that the surface tension will support the capillaries much as iron hoops support a barrel of beer. At normal lung volumes, the surface tension is believed to be 1–10 dyn/cm. It therefore represents a significant support to the bulging capillaries. At high lung volumes, where the surface tension might rise to 50 dyn/cm because of the behavior of surfactant, the support is predicted to be much greater. The third force is the longitudinal tension in the alveolar wall associated with lung inflation. This is probably very small at normal lung volumes but can rise to high levels at large lung volumes. We shall see later that the frequency of stress failure increases greatly at high lung volumes for the same capillary transmural pressure.

As indicated above, the hoop tension of the capillary wall at failure is relatively small. However, whether the wall gives way depends not on the tension but on the stress, that is, the tension divided by wall thickness. Figure 7 shows the calculation of wall stress for a capillary transmural pressure of 40 mmHg (= 54 cmH_2O), radius of curvature of 5 μm, and wall thickness of 0.3 μm. The calculated stress is 9×10^5 dyn/cm^2 (or 9×10^4 N/m^2, which is astonishingly high. Indeed this is approximately the same as the wall stress of the normal aorta, which is armored by substantial amounts of collagen and elastin. By contrast, the thin side of the

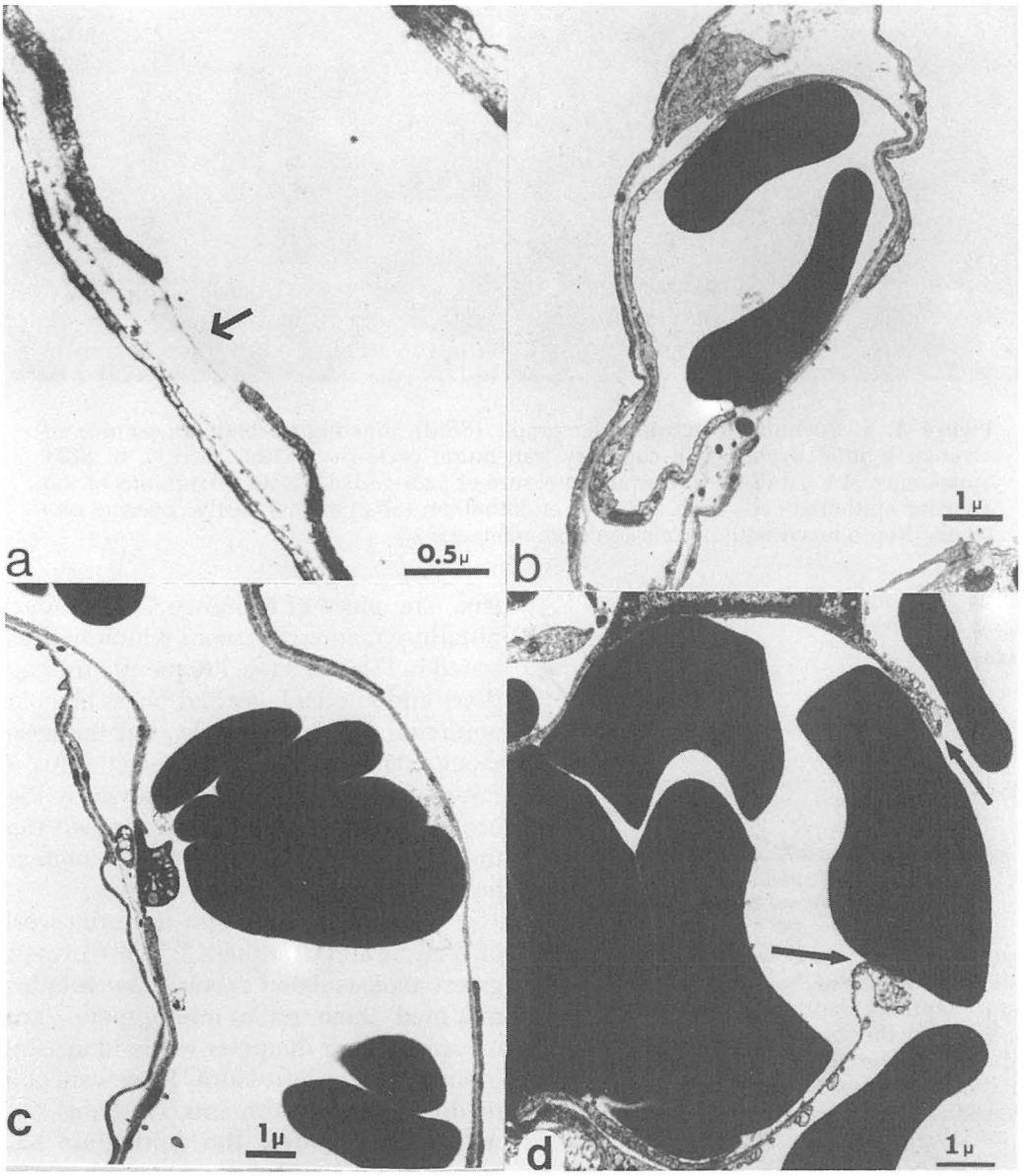

Figure 3. Electron micrographs showing stress failure in pulmonary capillaries. a. The capillary endothelium is disrupted, but the alveolar epithelium and the two basement membranes are intact. Capillary transmural pressure was 52.5 cmH_2O. b. Both the alveolar epithelium and capillary endothelium are disrupted, but the basement membrane is intact. Note the red blood cell closely applied to the exposed intact basement membrane. The capillary transmural pressure was 72.5 cmH_2O. c. The alveolar epithelial layer (right) and capillary endothelial layer (left) are disrupted. Note the platelet closely applied to the exposed basement membrane (left). The capillary transmural pressure was 52.5 cmH_2O. d. Disruption of all layers of the blood-gas barrier with red blood cell passing through the opening. Note "blebbing" of the alveolar epithelium. The capillary pressure was 72.5 cmH_2O. (a, b, c reproduced with permission from reference 64. d. reproduced with permission from reference 52.)

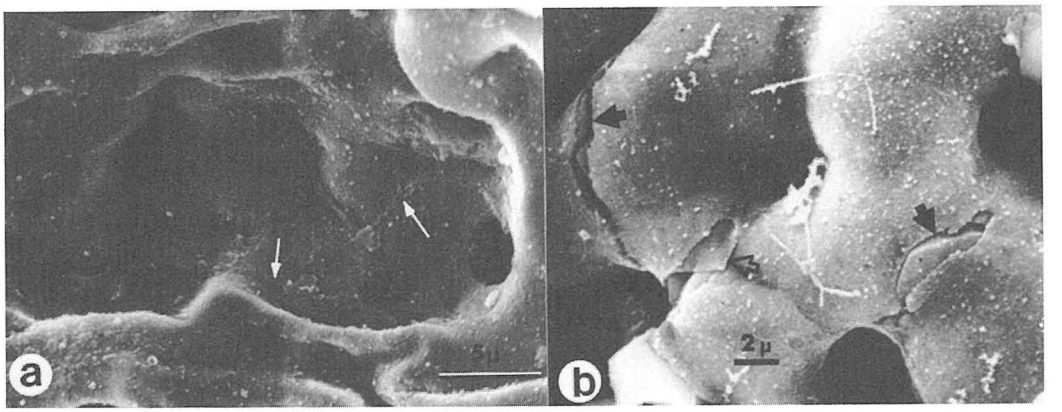

Figure 4. a. Scanning electron micrograph (SEM) showing normal appearance of alveolar epithelial cells at a capillary transmural pressure of 12.5 cmH_2O. b. SEM appearance at a capillary transmural pressure of 52.5 cmH_2O. Note disruptions of the alveolar epithelial cells with a flap of endothelium (open arrow) partly covering one break. (Reproduced with permission from reference 7.)

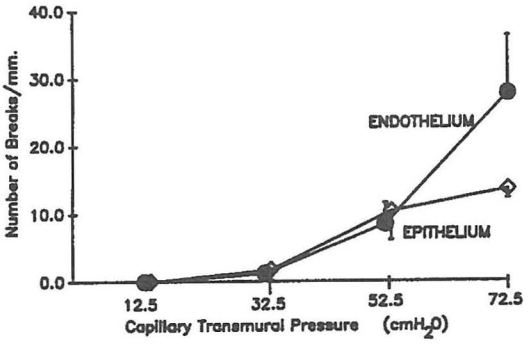

Figure 5. Number of breaks per mm of endothelial and epithelial boundary length plotted against capillary transmural pressure. Means ± SE. Very few breaks were seen at 32.5 cmH_2O, and the pressure had to be raised to 52.5 cmH_2O before breaks were consistently seen. (Reproduced with permission from reference 52.)

blood-gas barrier has half of its thickness made up of endothelial and epithelial cell layers, which presumably contribute relatively little strength. What is remarkable is not that the capillaries fail at high pressures, but that they do not fail more often.

We have given a great deal of thought to what is responsible for the strength of the blood-gas barrier. Several pieces of evidence suggest that most of the strength can be attributed to the extracellular matrix. One piece of evidence is the pattern of failure commonly seen, which is illustrated in Figures 3a–c. Frequently the capillary endothelial layer and/or the alveolar epithelial cell layer breaks, but the basement membranes remain intact. This is not a universal finding, as shown by Figure 3d, but it is common and suggests that the strongest component of the blood-gas barrier is the extracellular matrix.

More evidence comes from the work of Welling and Grantham.[55] These investigators took isolated rabbit renal tubules, mounted them on a micropipette, and measured their diameter while increasing their transmural pressure. They were able to do this both with intact tubules and with tubules where the epithelium had been removed with detergent so that only the basement membrane remained. They found that the mechanical properties of the tubules in extension were the same, regardless of whether the epithelium was present. This ingenious experiment strongly suggested that the mechanical behavior of the isolated tubules was essentially determined by the extracellular matrix.

Further evidence comes from the work of Williamson et al.,[67] who showed

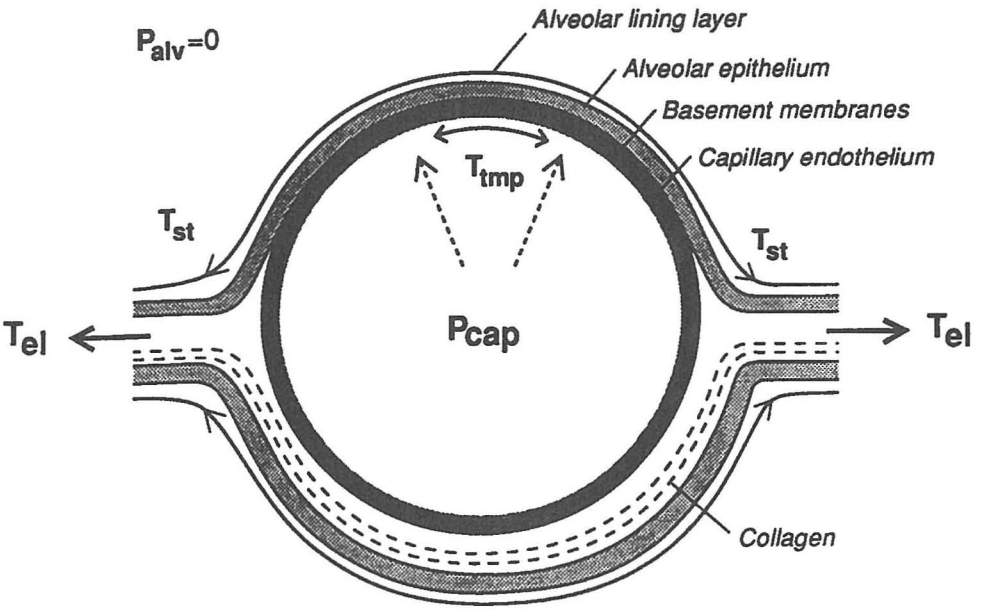

Figure 6. Diagram showing the three principal forces acting on the blood–gas barrier. These are the hoop or circumferential tension (T_{tmp}), surface tension of the alveolar lining layer (T_{st}), and longitudinal tension in the alveolar wall associated with lung inflation (T_{el}). (Reproduced with permission from reference 64.)

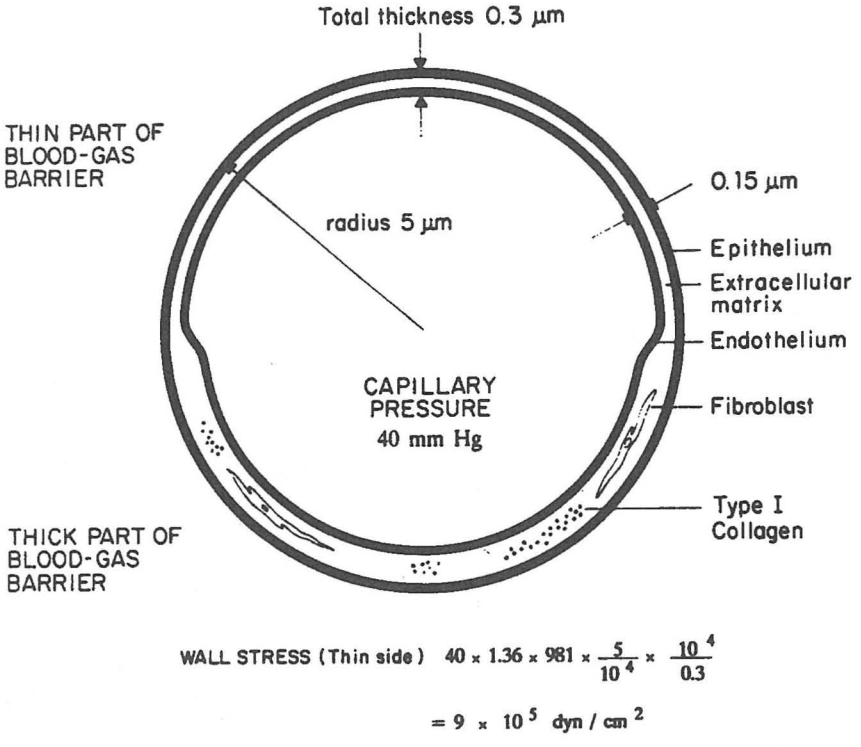

Figure 7. Diagram showing the calculation of capillary wall stress at a capillary transmural pressure of 40 mmHg. Radius of curvature is 5 μm and the thickness of the blood–gas barrier on the thin side is 0.3 μm.

that the width of the basement membrane in systemic capillaries down the human body from the abdomen to the calf increased along with the hydrostatic pressure. These authors were enterprising enough to show the same thing in the giraffe where the height is greatly increased! It is also well known that the basement membrane of pulmonary capillaries is thickened in patients with mitral stenosis who have a raised capillary pressure over months or years.[25,36] It has also been shown that the distensibility of systemic capillaries can be explained by the mechanical properties of basement membrane.[50] Finally, we know that glomerular capillaries, which normally maintain a hydrostatic gradient across them of about 40 mmHg, have a considerably thicker basement membrane than do pulmonary capillaries. All of these observations taken together strongly suggest that the extracellular matrix of pulmonary capillaries is responsible for most of their strength.

The extracellular matrix of the thin side of the blood-gas barrier is composed of the basement membranes of the two overlying cell layers, the capillary endothelium and alveolar epithelium. Alveolar wall basement membranes contain four main molecules: type IV collagen, which is believed to play a structural role; laminin, which is involved in linking the basement membrane with overlying cells; heparan sulfate proteoglycans, which form a charge shield and probably affect capillary permeability; and entactin (or nidogen), which is thought to bind laminin and type IV collagen. The most likely candidate for the great strength of extracellular matrix is the type IV collagen, which has an interesting configuration.[51,69] The molecules are approximately 400 nm long, and two join at the C terminal end. Then four molecules join at the N terminal end to give a matrix configuration similar to chicken wire. This apparently combines great strength with porosity. Measurements show that the tensile strength of basement membranes approaches that of type I collagen.[18,55,64]

There is evidence that the type IV collagen is not uniformly distributed throughout the extracellular matrix. Vaccarro and Brody[53] have shown that the extracellular matrix has a central lamina densa with a lamina rara on either side (Fig. 8). In addition, antibodies to type IV collagen track the lamina densa as it is formed by the fusion of the basement membranes of the capillary endothelial and alveolar epithelial cells.[8] The lamina rara on either side of the lamina densa apparently predominantly contain molecules such as laminin, which link the type IV collagen to the overlying cells, and the heparan sulfate proteoglycans, which are responsible for the charge barrier. Thus the great strength of the thin part of the blood-gas barrier apparently comes from

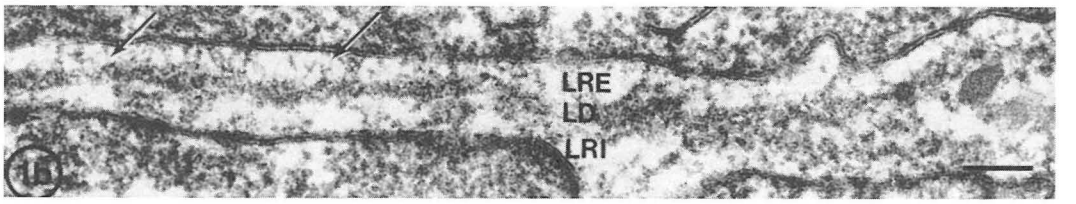

Figure 8. Ultrastructure of the thin part of the blood–gas barrier in rat. The alveolar epithelial cell is at the top and the capillary endothelial cell at the bottom. Note that the extracellular matrix has a central lamina densa (LD) with a lamina rara externa (LRE) and lamina rara interna (LRI) on each side. Most of the type IV collagen which is believed to be responsible for the strength of the blood-gas barrier is located in the lamina densa. Bar 0.1 μm. (Reproduced with permission from reference 53.)

an extremely thin layer of type IV collagen, only about 50-nm thick, which is sandwiched in the middle of the extracellular matrix.[62]

We have seen that in the rabbit lung, stress failure occurs at a capillary transmural pressure of about 52 cmH_2O, that is, about 40 mmHg. Is this such a high pressure that it is of little physiological or pathophysiological interest? The answer is no, because there is good evidence that in the human lung during maximal exercise the pulmonary capillary pressure rises above 30 mmHg. For example, Wagner et al.[54] exercised normal volunteers on a bicycle ergometer at an oxygen consumption of 3.7 L/m, that is, about 80% of their $\dot{V}O_2$ max. The mean pulmonary arterial pressure, measured with a Swan–Ganz catheter, was 37 mmHg, and the pulmonary arterial wedge pressure had a mean value of 21 mmHg. It is not known for certain where pulmonary capillary pressure lies in relation to arterial and venous pressure. However, Bhattacharya et al.[2] have shown by micropuncture that capillary pressure is about halfway between arterial and venous pressure, and Younes et al.[68] have obtained data suggesting that the capillary pressure is nearer to arterial pressure at high pulmonary blood flows. Therefore we can state that the capillary pressure at mid-lung is at least 29 mmHg. Because the bottom of the lung is some 10 cm below mid-lung, adding the hydrostatic gradient gives a capillary pressure there that exceeds 36 mmHg. Other studies on exercising normal subjects have provided similar data.[23,45]

Initially, we were very surprised to find that the capillary pressure during maximal exercise apparently rises to values close to those at which failure is seen. However, we now realize that this makes sense because of the dual role of the blood-gas barrier. Of course we cannot assume that stress failure occurs at the same pressures in the rabbit and human lung, and indeed we have recently obtained evidence in the dog lung that failure occurs at higher pressures than in the rabbit.

We can now summarize the events that occur as the pulmonary capillary pressure is gradually raised from low normal values to high values. Initially, as the Starling equilibrium is disturbed, fluid will move from the capillary lumen into the alveolar wall interstitium and possibly into the alveolar spaces. Nothing that we have said here goes against the Starling hypothesis. The result will be interstitial and perhaps alveolar edema. Then, as the pressure is raised to higher levels, we may see the phenomenon known as "pore stretching." This is somewhat controversial, but Pietra et al.[43] showed that when the pulmonary capillary pressure was increased, large tracer molecules such as hemoglobin moved between capillary endothelial cells into the interstitium of the alveolar wall. Finally, at even higher pressures, stress failure occurs with disruption of the capillary endothelial layer, alveolar epithelial layer, or sometimes all layers of the blood-gas barrier. The result will be a high permeability type of edema. Thus, as the capillary pressure is gradually raised from normal to high levels, the first stage is a low permeability, hydrostatic form of pulmonary edema, but this is later followed by a high permeability type of edema.

We can now turn to the pathophysiological conditions apparently associated with stress failure of pulmonary capillaries; these are listed in Table 1. The first group includes diseases in which an increased capillary pressure is associated with a high permeability type of pulmonary edema. Examples are neurogenic pulmonary edema, high altitude pulmonary edema, and possibly some cases of the adult respiratory distress syndrome.

There is strong evidence that neurogenic pulmonary edema is caused by stress failure of pulmonary capillaries. First, experimental models of this disease showed that both high pulmonary arterial

Table 1
Possible Conditions Involving Stress Failure

1. Increased pressure causing edema
   a. Neurogenic pulmonary edema
   b. High altitude pulmonary edema
   c. ? some cases of ARDS
2. Increased pressure causing hemorrhage
   a. EIPH in racehorses
   b. EIPH in greyhounds
   c. Bleeding in humans
3. Increased pressure causing edema and hemorrhage
   a. Chronic venous hypertension, e.g., mitral stenosis
4. Overinflation of lung
5. Abnormal extracellular matrix
   a. Goodpasture's syndrome
   b. Alpha-1 antitrypsin deficiency
   c. Emphysema

ARDS = adult respiratory distress syndrome;
EIPH = exercised-induced pulmonary hemorrhage.

and wedge pressures occur[47] and that these are associated with very high catecholamine levels in the blood. The exact mechanism by which this "sympathetic storm" causes elevated pulmonary vascular pressures is still debated, but it is probably acute left ventricular failure caused by systemic hypertension coupled with impaired myocardial relaxation. Next, Cameron and De showed that the edema is of the high permeability type with a large concentration of high molecular weight proteins and cells.[4] Finally, Minnear and his collaborators[38,39] showed ultrastructural damage to the blood-gas barrier that is essentially identical to the patterns that we have seen in the rabbit. They described both disruption of capillary endothelial cells[39] and breaks in alveolar epithelial cells,[38] although they did not recognize the mechanism. Thus the evidence that neurogenic pulmonary edema is caused by stress failure of pulmonary capillaries is extremely strong.

It is also probable that high-altitude pulmonary edema is caused by stress failure. First, it is now known that there is a strong association between the occurrence of high-altitude pulmonary edema and very high pulmonary arterial pressures caused by hypoxic pulmonary vasoconstriction.[30,41] Thus the edema presumably has a hydrostatic basis. However, recently Hackett et al.[24] and Schoene et al.[48] have shown that the alveolar edema is of the high permeability type with a large concentration of high molecular weight proteins and cells. Indeed one study showed that the protein concentration of the alveolar fluid in severe high-altitude pulmonary edema exceeded that in many cases of the adult respiratory distress syndrome.[48] Thus the problem is how to reconcile the occurrence of a high permeability type of edema with a presumed hydrostatic basis, which was what led us to begin this project on stress failure.

Other features of high-altitude pulmonary edema are also consistent with the stress failure mechanism. For example, postmortem studies often show vascular thrombi and fibrin clots in the lung.[1] These can be attributed to the exposed basement membranes caused by capillary endothelial cell distribution, which are highly reactive and cause adhesion of platelets, white cells, and red cells (Figures 3b and 3c). In addition, exercise at high altitude has been shown to be a provocative factor in high-altitude pulmonary edema.[27] It presumably acts by raising the pulmonary arterial pressure. The explanation of how hypoxic vasoconstriction can raise pulmonary capillary pressure is probably that given by Hultgren[29] some twenty years ago, that is, that the vasoconstriction is uneven, with the result that those capillaries not protected by arterial constriction see the high pressure. This would explain the patchy distribution of high-altitude pulmonary edema described both at autopsy and in chest radiographs.[31] Proof that stress failure of pulmonary capillaries is the mechanism of high-altitude pulmonary edema requires that the characteristic ultrastructural

changes be demonstrated at autopsy, and this has not yet been done.

Some cases of the adult respiratory distress syndrome may have their origin in a transient large rise in pulmonary capillary pressure, which exposes endothelial basement membranes and leads to adhesion and activation of platelets and white blood cells. This could then initiate a biochemical cascade with the liberation of platelet activating factor, kallikrein, bradykinin, and other injurious substances. Such a sequence of events might occur in a patient who is involved in an automobile accident where the blood catecholamine levels are transiently greatly increased. This situation would be like an early subclinical type of neurogenic pulmonary edema.

The second category of conditions attributable to stress failure of pulmonary capillaries is where the increased pressure causes frank hemorrhage (Table 1). The best example of this is the remarkable condition of exercise-induced pulmonary hemorrhage, which is seen in thoroughbred racehorses. This is extremely common. Tracheobronchial washings carried out by bronchoscopy in thoroughbreds in training show that essentially 100% have evidence of alveolar bleeding,[65] although less than 5% of horses have epistaxis. The condition has apparently been recognized since Elizabethan times[37] and exercise-induced pulmonary hemorrhage is an enormous problem for thoroughbred veterinarians, but the cause has not been identified. We believe that there is strong evidence that the condition is caused by stress failure of pulmonary capillaries.

These horses develop enormously high pulmonary arterial pressures while galloping. Direct measurements made on a treadmill show that the mean pulmonary arterial pressures are 80–100 mmHg.[17] There are also reports of left ventricular end diastolic pressures in ponies exceeding 50 mmHg.[46] Therefore the pulmonary capillary pressures must be extremely high. Thoroughbreds have enormous maximal oxygen consumptions, of up to 180 ml/min/kg (compare the elite human athlete at 70–80 ml/min/kg). These high levels of aerobic activity are associated with very high cardiac outputs, which exceed 250 L/min.

Because these animals have been selectively bred for racing for over 400 years,[9] their cardiovascular systems have developed to the point that the pulmonary vascular pressures are so high that the capillaries fail because of the high wall stress. Exercise-induced pulmonary hemorrhage has also been described in racing greyhound dogs,[34] indicating that the condition is not confined to the thoroughbred but occurs in at least one other selectively bred, highly aerobic mammal. The fact that the pathological consequence is bleeding rather than the high permeability edema, which is seen both in neurogenic and high-altitude pulmonary edema, can be explained by the abrupt rise in pulmonary capillary pressure. There is evidence that exercise-induced pulmonary hemorrhage may occur in elite human athletes.[63]

Not everyone accepts that this is the mechanism for exercise-induced pulmonary hemorrhage. In an extensive autopsy study of horses with exercise-induced pulmonary hemorrhage, O'Callaghan et al.[40] concluded that the bleeding probably came from the bronchial circulation. Certainly enlarged bronchial vessels are seen at the sites of old bleeding, and these are associated with mild inflammatory changes of the small airways. However, it is likely that these changes constitute a reaction to the blood in the alveoli and small airways.

Another objection to the stress failure hypothesis is that the bleeding is chiefly seen in the dorsal-caudal regions of the lung. At first sight this suggests that the capillary hydrostatic pressure is not a major factor because one would expect the pressure to be greatest at the bottom of the lung. However, the important pressure for

stress failure is the capillary transmural pressure, and it may well be that the alveolar pressure falls transiently to very low values in the dorsal-caudal region. We know that esophageal pressure falls by up to 30 mmHg during rapid inspiration during galloping,[17] and therefore substantial falls in alveolar pressure will occur at the same time. The dorsal-caudal regions of the lung are the furthest from the nares, and the changes in alveolar pressure are therefore likely to be particularly marked in these areas. In addition, these regions of the lung are close to the diaphragm, which has a very oblique orientation in the horse. Downward movements of the abdominal contents during galloping may cause large transient falls in alveolar pressure. Another factor may be the distended alveoli in the upper regions of the lung as a result of distortion of the lung by its weight. As we shall see below, stress failure of pulmonary capillaries is much increased at high lung volumes. We are presently collaborating with James Jones, John Pascoe, and Walter Tyler at the University of California, Davis, to obtain more data on this fascinating problem.

Chronic increases in pulmonary capillary pressure may give rise to a combination of pulmonary edema and hemorrhage. A good example is the patient with mitral stenosis (Table 1). Hemoptysis is a common symptom in severe disease, and autopsy studies have shown large amounts of hemosiderin in the lung. Pulmonary edema can also occur. An interesting ultrastructural feature is that type II alveolar epithelial cells are sometimes seen lining parts of the epithelium.[36] These may develop in response to damage to the type I epithelial cells as a result of stress failure (Figures 3b–3d). As pointed out earlier, marked thickening of the basement membrane is commonly seen in mitral stenosis, presumably in response to the chronically increased capillary pressure.[25,36]

Overinflation of the lung is an important contributing factor to stress failure of pulmonary capillaries (Table 1). We have studied this in the anesthetized rabbit preparation by increasing the transpulmonary pressure from 5 to 20 cmH_2O while keeping the capillary transmural pressure constant at 32.5 or 52.5 cmH_2O.[19] Figure 9 shows the striking increase in the number of breaks per mm cell boundary layer length for both endothelium and epithelium for a capillary transmural pressure of 32.5 cmH_2O. At this moderate capillary pressure there were almost no breaks in the endothelium or epithelium at a normal lung volume. However, when the transpulmonary pressure was increased to 20 cmH_2O when the lung volume was close to total lung capacity, there was a large increase in the number of breaks. The differences were statistically significant at the

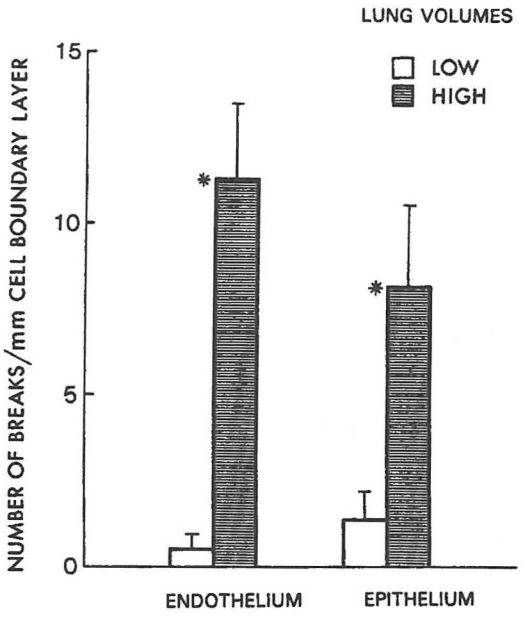

Figure 9. Effect of increasing lung volume on the frequency of stress failure. The transpulmonary pressure at the low lung volume was 5 cmH_2O and 20 cmH_2O at the high lung volume (that is, close to total lung capacity). In both instances, the capillary transmural pressure was 32.5 cmH_2O. Note the large increase in frequency of stress failure when the lung volume was increased. This provides a mechanism for the increased capillary permeability caused by overinflation.

5% level. A large increase in breaks was also seen when the capillary transmural pressure was kept at 52.5 cmH_2O and lung volume was increased.

These results provide a physiological mechanism for the increase in capillary permeability at high lung volumes that has been described by many investigators.[5,12,13,16,35,42] It is known that the increased permeability is due to the high lung volume rather than the high alveolar pressure because banding the chest prevents the increased permeability.[26] Ultrastructural evidence of damaged alveolar epithelium at high lung volumes has also been reported.[12,33]

As pointed out by others, this potential cause of damage to pulmonary capillaries at high states of lung inflation is particularly important in the intensive-care setting. It is often necessary to apply high airway pressures and substantial levels of positive end-expiratory pressure to obtain sufficiently high levels of PO_2 in the arterial blood. Often these diseased lungs have nonuniform mechanical properties, and it is difficult to avoid overexpanding some regions while preventing atelectasis in others. Barotrauma, as it is sometimes referred to, has emerged as one of the most challenging problems of intensive-care management.

This last group of conditions in which stress failure of pulmonary capillaries may play a role is when there is an abnormality of the extracellular matrix (Table 1). The first of these is Goodpasture's syndrome, where it has been shown that autoantibodies attack the NC1 globular domain of type IV collagen.[66] Because the type IV collagen apparently plays a critical role in maintaining the integrity of the blood-gas barrier, it is not surprising that bleeding occurs into the alveolar spaces. Donald et al. published ultrastructural evidence of breaches in the basement membrane in Goodpasture's syndrome.[11] As pointed out earlier, the glomerular capillaries are exposed to a high hydrostatic gradient of about 40 mmHg, and it is not surprising that damage to the basement membrane of these capillaries results in bleeding into the kidney.

It is also possible that stress failure of pulmonary capillaries is one of the earliest pathophysiological events in the development of the emphysema of alpha-1 antitrypsin deficiency. The basis for this disease is presumably an imbalance in the protease-antiprotease system as a result of the congenital lack of alpha-1 antitrypsin. Indeed many investigators believe that this imbalance is at the root of the more common types of emphysema, where the imbalance is associated with cigarette smoking.[32,49] It has been shown that neutrophil elastase attacks elastin in the alveolar wall, and it has been suggested that this is the initiating event in the breakdown of the wall. However, neutrophil elastase is known to cause degradation of type IV collagen,[44] and if this molecule plays the critical role in the integrity of the capillary wall that we have suggested, then the earliest destructive changes of emphysema may occur here. A possible scenario is stress failure of a pulmonary capillary at normal vascular pressures because of weakening of the wall, with the production of a small hole or fenestra.[3,6] That alveolar bleeding is not a feature of emphysema can be explained by the gradual development of the destructive changes over many years. Note, however, that pathologists have occasionally remarked on the presence of red blood cells on the alveolar surface in emphysema[3] and certainly alveolar hemorrhage is a prominent feature of animal models of emphysema produced by instilling neutrophil elastase into the lungs.[49]

Finally, I have emphasized those conditions in which the walls of the pulmonary capillaries fail because of exposure to high stresses or weakening of the walls by disease. However, it should not be concluded that the normal pulmonary blood-gas barrier is weak. On the contrary it is

immensely strong. However, the lung has a basic bioengineering dilemma, as is shown in Figure 10. The blood-gas barrier must be extremely thin because gases pass through it by passive diffusion and the resistance that the barrier offers is proportional to its thickness (Fick's law). We know that the blood-gas barrier cannot afford to be any thicker because at maximal oxygen uptakes some elite human athletes show diffusion-limitation of oxygen transfer in the lung.[10,54] The extreme thinness of the barrier therefore confers a clear evolutionary advantage.

On the other hand, the blood-gas barrier needs to be extremely strong because it also forms the walls of the pulmonary capillaries, which are exposed to very high stresses when the pulmonary vascular pressures rise during maximal exercise. Indeed there is evidence that the capillary pressures during maximal exercise approach those at which stress failure occurs. In other words, the blood-gas barrier has evolved to be as thin as possible for maximum efficiency of gas exchange, with just enough strength to maintain its integrity under the most challenging conditions. Apparently in thoroughbred racehorses, which have been selectively bred for high aerobic levels over hundreds of years, the balance between the development of the cardiovascular system and the lung capillaries has been disturbed, and as a result all of these animals bleed into their lungs. It also follows that if the barrier is weakened by disease, alveolar edema or hemorrhage is inevitable. Stress failure in pulmonary capillaries is a hitherto overlooked factor of basic biological importance and a mechanism that apparently plays a role in many types of lung disease.

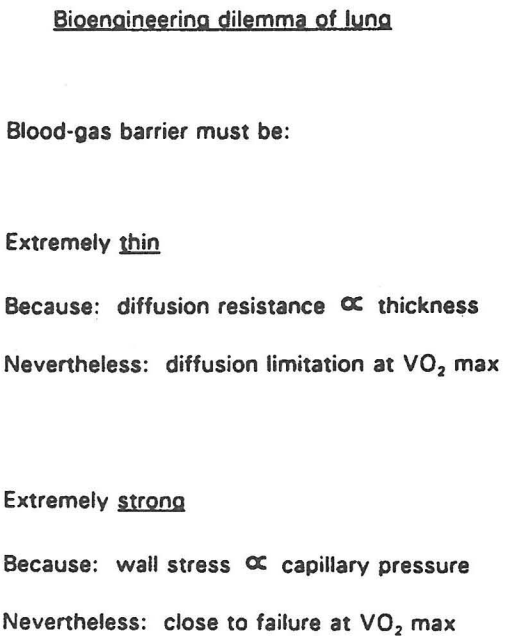

Figure 10. Basic bioengineering dilemma of the lung. The blood-gas barrier has to be both extremely thin and immensely strong.

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