Thorax 1982;37:713–717

Editorial

What forces keep the air spaces of the lung dry?

Alveolar oedema can be a serious clinical problem, but before discussing the natural forces available for its resolution we should consider the normal homeostatic mechanisms which must have been overcome for it to occur in the first place.

This is a controversial area of respiratory physiology, where most theories of pulmonary homeostasis are essentially variations of the original Starling hypothesis, according to which opposing vascular and osmotic pressures produce a net filtration of fluid into the interstitium.[1] The lymph drainage can accommodate this flow until there is roughly an eight-fold excess over normal.[2] This ratio is easily exceeded if the endothelium becomes more permeable to macromolecular plasma protein (*permeability* oedema) or capillary pressure is raised above a critical threshold of about 25 mm Hg[3] (*pressure* oedema). These categories may be differentiated on the basis of the concentration of colloidal protein in lymph collected as a reflection of interstitial fluid,[4] the accumulation of fluid in the lung often exceeding lymph drainage by a factor of 1000 or so.[5] Despite the general view that epithelium is of lower permeability than the endothelium,[4] the fluid escaping from the capillary does not remain interstitial for much of it soon invades the air spaces, taking a considerable amount of the protein with it. Some experiments have even shown alveolar and interstitial fluids to be identical[6] or to equilibrate in time,[7] while many others have shown no obvious correlation between the rate of alveolar flooding and the blood-alveolar osmotic pressure gradient.

The alveolar wall is the last barrier to entry of fluid into the airway system, and here there is a balance between forces rather than fluxes since there is no obvious counterpart of lymph drainage at the alveolar surface. On one side of the equation is the vascular pressure, represented by the interstitial pressure as the driving force; on the other side, the forces opposing alveolar flooding are much less obvious. If they were predominantly osmotic in nature, they would represent an essentially restorative force that would not come into effect until the fluid to be recovered had already escaped. Such a mechanism does not seem to reflect the all-or-none characteristics of alveolar oedema formation and the much slower rate of its resolution.[8] To accommodate these discrepancies and the lack of any consistant correlation between fluid fluxes and oncotic gradient, Staub has proposed that there is a sudden "unzipping" of intercellular junctions at the endothelium, permitting much protein and water to flow[4]; but this is more difficult to envisage at the epithelial surface, where intercellular junctions are believed to be very tight both morphologically[9] and physiologically.[10] Nevertheless, there have been many demonstrations that plasma proteins placed in fluid-filled alveoli can enter the circulation intact at a measurable rate,[4] indicating that sizable channels must exist even though in the normal lung there are no appreciable leaks.

These findings and the osmotic data referred to above have caused other groups to depart from the traditional emphasis on oncotic forces in the attempt to explain the threshold pressure which needs to be exceeded for alveolar flooding to be initiated. Guyton and his colleagues estimate that there is a "safety factor" of about 20 mm Hg which must be exceeded for fluid to break through into the alveoli.[3] The really vital question is what mechanism can provide a pressure threshold of this kind that must be exceeded for burst-through to occur when pressure is applied, with no flow under normal conditions despite the presence of sizable channels. Guyton *et al* proposed a negative interstitial pressure inherent in the parenchymal tissue,[3] but their attempts to measure it produced average values of only one-quarter of their estimated "safety factor."[11] Hence an alternative or additional mechanism is needed.

The need to retain fluid within a porous mechanical barrier without leaking through sizable channels is a problem encountered in many industrial contexts, including building and textile manufacture. As a previous editorial pointed out,[12] such water repellency—sufficient to withstand pressures of up to 35 lb/in^2 (1760 mm Hg)—can be induced in porous fabrics by treating them with cationic surfactants. Ironically, textile chemists often talk in terms of the "breathability" of special fabrics designed for exceptional comfort, by which they mean that gases—including water vapour—can pass freely in either direction and yet liquid water cannot penetrate.

Address for reprint requests: Professor Brian A Hills, Department of Anesthesiology, University of Texas Medical School at Houston, Houston, Texas 77030, USA.

Many of the cationic surfactants used for this purpose have two long hydrocarbon chains at one end of the molecule and a strongly positive quaternary ammonium ion at the other end, which is thus strongly adsorbed on to a negatively charged subphase to present a hydrophobic surface to any encroaching water. This is precisely the same combination of active terminal groups found in most pulmonary surfactants,[12] especially the predominant components—dipalmitoyl lecithin (DPL) and dipalmitoyl phosphatidyl ethanolamine (DPPE). We might argue that these are really "zwitterions" with a negative charge separating the quaternary ammonium ion from the two palmitic acid chains and, although the dipole is ideally orientated, it would not be so strongly adsorbed on to the negative charges inherent in all epithelium[13] as a pure cationic. When tested on porous cotton carboxylated to simulate these negative charges, however, lung surfactants were found[14] to impart water repellency with a penetration pressure well in excess of Guyton's "safety factor" of 20 mm Hg and to maintain it indefinitely, if left. It was found, moreover, that a drip could be started be wetting the low-pressure side, just as when one touches the inside of a tent in a rainstorm. This confirmed that the channels were open, yet surfactant inhibited flow by true water repellency, which would thus seem to offer a very simple mechanism for the pressure threshold for alveolar oedema formation and to satisfy the all-or-none nature of alveolar flooding with its much slower reversal. At least, this would fit the facts nicely if it were not for one major conflict with conventional respiratory theory.

Water repellency would be quite impossible if the low-pressure (alveolar) side of the blood-air barrier were lined with the continuous liquid layer that has been tacitly presumed to line the alveolus since the first mechanical studies of liquid-filled lungs were performed by von Neergaard in 1928.[15] Morphological studies have repeatedly failed to reveal such a lining[16] but show the surface fluid as confined to "pools" in the septal corners and other less regular areas—just as one would predict from pouring water on to a rough hydrophobic surface.[12] Many respiratory physiologists have dismissed electron micrographs as too prone to preparation artefact; but a few have devised experiments to detect the liquid lining layer. Their results have been positive,[17 18] but in each case the method required contact of a probe or foreign liquid with the surface and would naturally show fluid to be present since it was equivalent to "touching the tent in the rain," so invalidating any conclusion. Needless to say, we are pursuing non-tactile methods in this laboratory. My personal opinion is that the electron micrographs are probably correct, for when the authorities who showed mammalian lungs to be largely dry[16] use the same techniques on the lungs of animals—for example, frogs—which could derive a functional advantage from a continuous liquid lining to their lungs this is indeed what they find.[19] Creatures with these "wet" lungs also have a rate of fluid filtration through the pulmonary capillary walls that is 10–20 times that found in mammals,[20] which would be anticipated if flow in the pores were no longer inhibited by water repellency. The rapid acceleration of alveolar flooding which has been observed in dogs with prolonged pulmonary hypertension[5] can be attributed to wetting of the alveolar surface by the encroaching oedema, and hence wetting of the dry ends of those pores which had hitherto resisted the burst-through of fluid into the alveolus. Thus more pores are recruited to augment flow into the alveoli.

The popular concept of the bubble lining, as distinct from an essentially dry alveolus, is needed by conventional theory to provide the air-aqueous interface at which surfactants can be located as if they were simple detergents, and hence to explain their role as though their only property were their ability to modify surface tension. Once accepted, the bubble model becomes self-perpetuating in the hypothetical problems it generates. For instance, if we make the popular assumption that there is a *continuous* aqueous hypophase, we must then allow for the tendency of a bubble to shrink (see the Laplace equation below) and consequently explain why the larger bubbles do not grow and the smaller ones shrink—that is, why there is alveolar stability.[21] In the first lecture on pulmonary mechanics the student is often shown a picture of a large and a small bubble at either end of a closed tube and asked what would happen if the interconnecting valve were opened. He usually makes the wrong guess and is corrected by being told that the larger bubble grows at the expense of the smaller one (as in the equation below), thus demonstrating the alveolar instability which would occur if further surface tension characteristics were not attributed to the surfactant. This would never be a problem in the first place, however, if the normal alveolar surface were essentially dry. But when a powerful wetting agent (Tween 20) is instilled into the alveoli alveolar instability *is* introduced,[22] indicating that only when the dry surfaces become wet does the liquid lining become continuous and act as a bubble to introduce the problem of instability.

A further example that the traditional "bubble" approach to the alveolar lining is self-generating in theory is the textbook model of adjacent bubbles shrinking and thus pulling fluid into the intervening space as interstitial oedema.[21] Thus surfactant is claimed to exert a desirable effect by reducing surface

tension (γ) and hence the pressure ($\triangle P$) with which the adjacent bubbles of radius r are tending to collapse in accordance with the Laplace equation: $\triangle P = 2\gamma/r$.

The lowest values of the collapsing pressure ($\triangle P$) would occur for the least curvature ($r\uparrow$) corresponding to a spherical alveolus. For the minimum surface tension (γ) of 26 dyne/cm measured under physiological conditions,[23] and $r = 148$ μm for man,[24] the most conservative (lowest) value for $\triangle P$ would be 5·2 mm Hg in man. For small mammals such as the bat, however,where $r = 14{\cdot}5$ μm,[25] and the shrew ($r =$ 16 μm), the most conservative collapsing pressures are 27 mm Hg and 25 mm Hg respectively. These values are ridiculous not only because they exceed the safety factor for pulmonary oedema but because they represent an impossible inflation pressure for normal breathing. On the other hand, if mammalian lungs are essentially dry and there is no continuous liquid lining in the first place, then there would be no hypothetical bubbles and thus no collapsing pressure.

At the microscopic level the collapsing pressures must be the same for all points on a continuous liquid layer or fluid would flow along the surface until they were. Thus it is inconceivable that a "moonscape" such as the alveolar surface—with curvatures varying from strongly convex in some areas ($r << 0$) to gently concave ($r>0$) in others—could be in hydrodynamic continuity without the intervening spaces drying out or oedema collecting to a degree where the air space was reduced to a spherical core inconsistent with normal lung fluid content.

In making such a major divergence from standard textbook theory by proposing that the alveolar surface is normally dry[12]—which has the important advantage of offering the minimum resistance to the diffusion of oxygen and carbon dioxide across the blood-air barrier—we must look beyond homeostasis and briefly consider the mechanical aspects for which the bubble model was proposed in the first place.[15] The increased compliance imparted by liquid filling is as compatible with removal of the liquid "bracing" of the corners and wetting of a solid surface as it is with elimination of the air-aqueous interface provided by the bubble model. Solids possess surface energy just like liquids[26] but their surface tensions are only of interest when surface area changes as it does in the lung, so that a dry pulmonary epithelium could still provide the compliance changes observed on liquid filling.

To return to the conventional model of a continuous bubble lining, the collapsing pressure ($\triangle P$ in the Laplace equation) was estimated to be physiologically feasible in large mammals but much too high for small mammals—unless surfactants could reduce surface tension to below about 5 dyne/cm. Such values abound in published reports[27] but refer to measurements made at room temperature and ignore a large contact angle found under such conditions.[28] These apparently incorrect values have been emphasised as a means by which surfactants can "make breathing easy" by reducing the pressure needed to inflate the alveolus as though it were a bubble. This popular statement would be fine if we were to breathe with our lungs excised as in a laboratory experiment, but in vivo the lungs are encased in the chest wall, with which they exchange potential energy just as an elevator exchanges potential energy with its counterweight. The lung therefore needs the capacity to store potential energy as surface energy and thus a moderate surface tension. Calculations of the balance between chest wall and lung recoils indicate an optimal surface tension of about 26 dyne/cm[12]—just the value found experimentally when surface tension is measured under simultaneously simulated physiological conditions, including humidification at 37°C.[23] A lower value would be equivalent to reducing the counterweight on the elevator and so forcing the motor to work harder. A higher surface tension is also consistent with better water repellency[14] if accompanied by a contact angle such as that shown on tracheal epithelium.[29]

Having seen the compatibility of basic pulmonary mechanics and homeostasis with the concept of an essentially dry alveolar surface and hence water repellency as the mechanism for providing the pressure threshold for oedema formation, we may now consider pathological states. If the threshold is exceeded and the alveoli flood, then what natural forces would this model offer for eventually restoring homeostasis and how could these be aided?

When the pressure of fluid retained by any water repellent barrier is raised just above the retention pressure, spherical domes of fluid can be seen to emerge from the pores. The surface configuration is convex but the surface tension force resisting further exudation decreases as the drop is enlarged ($\triangle P\downarrow$ as $r\uparrow$ in the Laplace equation). At some point the drops then start to merge, which means that in the lung they would form a concave surface that would now tend to suck more fluid into the alveolus. In other words, the invading fluid would now form the bubble of the conventional model, greatly increasing the rate of flooding, introducing alveolar instability, and enhancing interstitial oedema formation—as observed in practice.[4 22] This is now a pathological state,however, rather than the normal physiological state to which the bubble approach is conventionally applied.

The question then arises of how such a condition can be reversed. If the vascular driving pressure is reduced below the critical capillary pressure, then the

fact that flooding continues[5] is probably due to the fact that the collapsing pressure in the equation is too negative owing to the small core of air and thus the small negative (concave) value of r. If the flooding is not extensive, then the surfactants remaining adsorbed on the alveolar wall can act as dewatering agents, similar to their industrial counterparts[12] in mobilising the supernatant fluid towards the corners. This would tend to restore the dry surface and hence water repellency. The phenomenon is similar to that observed in siphoning water out of a teflon-lined frying pan. The liquid layer does not reduce to an infinitely thin layer as it would on a hydrophilic surface but breaks up when it is about 1 mm thick to expose some dry surface. We have shown the same phenomenon with water over pulmonary surfactants adsorbed directly on to tissue. In the lung this "frying pan" phenomenon would be facilitated by positive end-expiratory pressure in expanding the lung to reduce the liquid layer to the point where it would break up and expose more gas-transfer surface. This would explain why the arterial oxygen tension rises immediately positive end-expiratory pressure is applied and long before there has been any opportunity to resolve the fluid.[30]

This argument would imply that adding a further hydrophobic coating to the dry surfaces would improve both water repellency and the dewatering capability once oedema had formed. This has been shown to some degree by Luisada and Cardi,[31] who found protection against pulmonary oedema afforded by antifoaming agents such as the silicones; but such compounds act by increasing contact angle and are also water repellents.

The final question is how to identify the forces which are available for resolving the fluid pushed into the corners by the natural dewatering capability of a hydrophobic surface, either acting alone or aided by positive end-expiratory pressure. Such a surface enables the pools to have an "edge" by allowing a contact angle, for which values as high as 67° have been obtained on pulmonary epithelial surfaces.[29] This means that fluid can be accumulated in the corners without the wetted area necessarily spreading. The liquid can now assume a convex profile with respect to the air and hence exert a *positive* force tending to return fluid to the interstitium. This force would be self-regulating since it would decrease as the oedema is resolved with the decrease in the curvature of the corner pool ($r\uparrow$ in the equation). These "corner pumps"[14] could thus provide a very simple yet effective means of resolving alveolar oedema.

Morphological evidence for their existence is provided in the electron micrograph of oedematous lungs taken by Kisch,[32] in which large contact angles can be seen at the boundary between the airway surface and adhering "droplets" of diameters less than 2 μm. If we substitute $r = 1$ μm and $\gamma = 26$ dyne/cm, the Laplace equation gives $\triangle P = 380$ mm Hg, indicating that the "corner pump" can exert a large force if needed. This might explain the remarkable finding of Matthay *et al*[33] that a 14% solution of macromolecular protein instilled into the lower airways can still be absorbed across the alveolar wall despite its theoretical oncotic pressure of 140 cm wg.

Thus the "corner pump" offers a particularly simple, effective, and self-regulating mechanism for the lung to resolve oedema—and one compatible with the basic physiology once we discard the conventional bubble model of the alveolus as relevant to any but the advanced pathological state of an oedematous lung.

BRIAN A HILLS
Department of Anesthiology
University of Texas Medical School at Houston
Houston, Texas

References

1 Starling EH. On the absorption of fluids from the connective tissue spaces. *J Physiol* 1896;**19**:312–26.
2 Erdmann JA, Vaughan TR, Brigham KL, Woolverton WC, Staub NC. Effect of increased vascular pressure on lung fluid balance inunanesthetized sheep. *Circ Res* 1975;**37**:271–84.
3 Guyton AC, Taylor AE, Drake RE, Parker JC. Dynamics of subatmospheric pressure in the pulmonary interstitial fluid. In: *Lung liquids.* Ciba Foundation Symposium 38. Amsterdam: Elsevier, 1976.
4 Staub NC. Pathways for fluid and solute fluxes in pulmonary edema. In: Fishman AP, Renkin EM, eds. *Pulmonary edema.* Washington: American Physiological Society, 1979:113–24.
5 Drake RE, Smith JH, Gabel JC. Estimation of filtration coefficient in intact dog lungs. *Am J Physiol* 1980;**238** *(Heart and Circulation Physiology No 7)*:H430–8.
6 Vreim CE, Snashall PD, Staub NC. Protein composition of lung fluids in anesthesized dogs. *Am J Physiol* 1976; **231**:1466–9.
7 Guyton AC, Parker JC, Taylor AE, Jackson TE, Moffatt DS. Forces governing water movement in the lung. In: Fishman AP, Renkin EM, eds. *Pulmonary edema.* Washington: American Physiological Society, 1979: 65–77.
8 Staub NC. Pulmonary edema. *Physiol Rev* 1974; **54**:678–811.
9 Pietra GG, Szidon JP, Leventhal MM, Fisman AP. Hemoglobin as a tracer in hemodynamic pulmonary edema. *Science* 1969;**166**:1643–6.
10 Taylor AE, Gaar KA. Estimation of equivalent pore radii of pulmonary capillary and alveolar membranes. *Am J Physiol* 1970;**218**:1133–40.
11 Meyer BJ, Meyer A, Guyton AC. Interstitial fluid pressure. V—Negative pressure in the lung. *Circ Res* 1968;**22**:263–71.

[12] Hills BA. What is the true role of surfactant in the lung? *Thorax* 1981;**36**:1–4.
[13] Idson B. Adsorption to skin and hair. *Journal of the Society of Cosmetic Chemists* 1967;**18**:91–103.
[14] Hills BA. Water repellency induced by pulmonary surfacants. *J Physiol* 1982;**325** (in press).
[15] Von Neergaard K. Neue Auffasungen über einen Grundbegriff der Atemmechanik die Retraktionskraft der Lunge, abhängig von der Oberflächenspannung in den Alveolen. *Z Ges Exp Med* 1929;**66**:373–94.
[16] Weibel ER, Bochofen H. Structural design of the alveolar septum and fluid exchange. In: Fishman AP, Renkin EM, eds. *Pulmonary edema.* Washington: American Physiological Society, 1979.
[17] Reifenrath R. Chemical analysis of the lung alveolar surfactant obtained by alveolar micropuncture. *Respir Physiol* 1973;**19**:35–46.
[18] Schürch S, McIver DJL. Surface tension at low lung volumes: dependence on time and alveolar size. *Biophys J* 1981;**33**:201A.
[19] Hughes GM, Weibel ER. Visualization of layers lining the lung of the South American lungfish *(Lepidosiren paradoxa)* and a comparison with the frog and rat. *Tissue and Cell* 1978;**10**:343–53.
[20] Burggren WW. Pulmonary blood plasma filtration in reptiles: a "wet" vertebrate lung? *Science* 1982;**215**: 76–7.
[21] West JB. *Respiratory physiology: the essentials.* 2nd ed. Baltimore: Williams and Wilkins, 1979.
[22] Nieman GF, Bredenberg CE, Clark WR, West NR. Alveolar function following surfactant deactivation. *J Appl Physiol: Respirat Environ Exercise Physiol* 1981; **51**:895–954.
[23] Barrow RE, Hills BA. Surface tension induced by dipalmitoyl lecithin in vitro under physiological conditions. *J Physiol* 1979;**297**:217–27.
[24] Dunnill MS. Postnatal growth of the lung. *Thorax* 1962;**17**:329–33.
[25] Tenney SM, Remmers JE. Comparative quantitative morphology of the mammalian lung. *Nature* 1963; **197**:54–6.
[26] Sumner CG. *The theory of emulsions and their technical treatment.* 5th ed. London: Churchill, 1954:287.
[27] Clements JA, Tierney DF. Alveolar instability associated with altered surface tension. In: Fenn WO, Rahn H, eds. *Handbook of physiology: Respiration.* Vol II. Washington: American Physiological Society, 1965:1565–83.
[28] Barrow RE, Hills BA. A critical assessment of the Wilhelmy method in studying lung surfactants. *J Physiol* 1979;**297**:217–27.
[29] Hills BA, Barrow RE. The contact angle induced by DPL at pulmonary epithelial surfaces. *Respir Physiol* 1979;**38**:173–83.
[30] Miller WC, Rice DL, Unger KM, Bradley BL.Effect of PEEP on lung water content in experimental non-cardiogenic pulmonary edema. *Crit Care Med* 1981; **9**:7–9.
[31] Luisada AA, Cardi L. Further studies with antifoaming agents in experimental pulmonary edema. *Circ Res* 1956;**3**:510–3.
[32] Kisch B. Electron microscopy of the lungs in acute pulmonary edema. *Exp Med Surg* 1958;**16**:17–28.
[33] Matthay MA, Landolt CC, Staub NC. Effect of 14% albumin in alveolar fluid on the rate of liquid removal from the air spaces of sheep. *Fed Proc* 1981;**40**:447.