Pulmonary Alveolar Blood Flow

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ABSTRACT

Explicit results concerning blood flow, alveolar blood volume, regional differences, and transit time distribution are derived from the sheet-flow theory and compared with experimental evidence available in the literature. A general consistency is indicated. The theory exhibits in a simple form the effects on flow of the arterial, alveolar, and venous pressures, the alveolar area, the mean path length between arterioles and venules, and the tension in the alveolar membrane, both elastic and surface tension; thus the theory provides a quantitative understanding of a large number of factors.

KEY WORDS

- microcirculation
- resistance
- pulmonary circulation
- blood volume
- distensibility
- transit time
- recruitment
- regional difference

The concept of sheet flow in the pulmonary alveoli is based on morphological evidences (1). Quantitative analyses (2–6) and model experiments (7, 4) have established the fluid mechanical basis for the theory. In the initial development of the theory, it was reasoned that the alveolar membranes were so highly stressed in their own planes because of the inflation of the lung that their response to transmural pressure would be linear. Furthermore, the two alveolar-capillary membranes (see terminology used in ref. 6) are locally connected by densely spaced posts so that the elastic deflection in response to the transmural pressure is localized. Accordingly a linear sheet thickness-pressure relationship was assumed (2). This assumption was verified recently by Sobin et al. (8) for the pulmonary alveoli of the cat within a physiological range of perfusion pressure. Further confirmation can be drawn from earlier results of Glazier et al. (9). In addition, Fung and Sobin (6) pointed out that their morphometric data imply that as far as elastic extension in the plane of the alveolar sheet is concerned the sheet may be regarded as elastically homogeneous. On these bases, Fung and Sobin (6) presented a detailed analysis of the deflection pattern of the alveolar-capillary membrane, thus relating the sheet thickness-pressure relationship to physical parameters such as the tension in the membrane and geometric parameters such as the post diameter, interpost distance, and the vascular space-tissue ratio.

The basic theory provides a means to analyze pressure, velocity, thickness, and streamline distributions in each alveolar sheet. Indirectly we can also deduce the distribution of red blood cells, the transit time, and other details. Such detailed information can be obtained, however, only if we can specify the geometric boundaries of the sheets, the locations of the arterioles and venules, and the pressures at the arterioles and venules. Since these boundary conditions are unknown, it appears that we have too elaborate a tool to be useful. For practical applications, therefore, further approximation is necessary. One direction for such a simplification is shown by Fung and Sobin (6). It consists of averaging...
the flow along a streamline and then averaging all streamlines over a sheet. By comparing the theoretical results with the experimental data of Roos et al. (10), we have shown that the theory and experiment are consistent as far as flow and resistance are concerned.

When such approximations are accepted we can derive a number of further results. In this article, the results concerning regional differences, blood volume, and transit time will be presented and compared with published experimental results. It will be shown that the theory and experiments are in general agreement.

In the following, we shall first consider the sheet thickness-pressure relationship at the lower end of transmural pressure. Then we shall discuss the venule exit condition. On the basis of the small Reynolds number of capillary blood flow we conclude that flutter is impossible. Without flutter the steady-state solution of Stokes’s equation determines the pressure distribution throughout the alveolar sheet. We shall show that we should not see a demarcation between zone 2 and zone 3 with respect to sheet thickness distribution. Then the effect of gravitation will be presented. The analysis concludes with the alveolar blood volume and the transit time distribution, first in a single alveolar sheet, then in the whole lung.

Comparison with available experimental data will be discussed. All the symbols have the same significance as they do in references 2 and 6. In particular, unless stated otherwise, all pressures refer to transmural pressure, i.e., the alveolar gas pressure is used as the gauge standard, \( p_{\text{atv}} = 0 \).

SHEET THICKNESS AT LOW PRESSURE

What is the theoretical form of the thickness-pressure relationship as the transmural pressure, \( \Delta p \), tends to zero or negative? According to the sheet model, each post has a natural length—the length of the tissue as it is grown under atmospheric pressure, \( \Delta p = 0 \). When \( \Delta p > 0 \), the posts are subjected to longitudinal tension; when \( \Delta p < 0 \), they are subjected to compression. (If the alveolar-capillary membranes were “spot welded” at the “posts,” the natural length of the posts would be zero.) Since the lung tissue behaves like other soft tissues, the stress is approximately an exponential function of the strain (11). The post will be very compliant at \( \Delta p = 0 \), but increasingly more rigid as |\( \Delta p \)| increases.

At finite transmural pressures the deflection of the alveolar-capillary membrane will remain a linear function of the pressure if our major hypothesis holds that the inflation of the lung accounts for the principal part of the tension in the alveolar membrane. Then the expected thickness-pressure relationship is shown as the dotted curve in Figure 1 of reference 6. In the neighborhood of \( \Delta p = 0 \), the thickness varies exponentially with \( \Delta p \) because of the elasticity of the posts. At larger \( |\Delta p| \), the thickness change is due mainly to the membrane deflection and tends to vary linearly with the load.

A preliminary experimental confirmation of this relationship is shown in Figure 1. A cat lung in vertical position within an opened chest was perfused with silicone elastomer in the manner described in reference 1, with alveolar pressure = 15 cm H2O, pleural pres-

\[ \text{FIGURE 1} \]

Measured alveolar sheet thickness, \( h \), of the lung of a healthy male mongrel cat (4.0 kg) in the range where the transmural pressure, \( \Delta p \), was small. Each point represents a sheet. The mean pressure head for each thickness range is marked by a square.
sure = 0, i.e., atmospheric. After catalization and solidification, slides were made from vertical sections of the lung. Measurements were made in the following manner. A specific range of thickness was selected, say, 5.0-5.49μ. The heights of all sheets whose thickness fell within this range were recorded by noting the position of the slide on the microscope stage. These heights were converted to transmural pressure by designating that particular height at which the fluid pressure (perfusion pressure plus hydrostatic pressure head) equaled alveolar pressure as zero. In Figure 1, the obvious gap in sheet-thickness data points between 0 and 2.5μ is representative of the real absence of an open microvascular sheet below a thickness of 2.5μ.

The scatter of these data is very large for at least two reasons: (1) the data are unclassified, no distinction was made with regard to lobe and location; (2) intrinsic random variation of the natural length and elasticity of the posts. For so complex a living tissue, uniformity in size and material distribution cannot be expected. The effects of these nonuniformities are magnified in the low stress range in which the compliance is the greatest. In terms of general trend the theoretical thickness-pressure relationship is verified.

**THE SEIZURE PRESSURE**

Since the red cells have finite dimensions, the blood vessel must have a minimum size to let the blood flow through. If an alveolar sheet becomes too thin, the flow would stop. Gregersen et al. (12) have shown that the critical size of circular cylindrical pores through which human red cells can be forced is about 2.4 μm. The sheet thickness for "seizure" of red cells in the alveolar sheet has not been determined. Let us call the pressure below which blood flow stops the seizure pressure and designate it by p<sub>S</sub>. Let p<sub>art</sub> be the local blood pressure in the sheet at the arteriole inlet, then if p<sub>art</sub> - p<sub>ven</sub> < p<sub>S</sub>, there will be no flow in the sheet.

In view of the wide scatter of data at low pressure, it seems justifiable to assume that p<sub>S</sub> = 0 for ordinary purposes. The experimental collection of data on p<sub>S</sub>, however, could have clinical significance.

**EXIT CONDITION OF THE SHEET**

To discuss the regional difference of pulmonary blood flow with precision, it is necessary to elaborate on the evaluation of p<sub>art</sub> and p<sub>ven</sub>. We recall that p<sub>art</sub> and p<sub>ven</sub> denote, respectively, the pressure in the flowing blood at the points of arteriolar entry into a sheet and venular exit from the sheet. In each sheet the pressure, p, lies between p<sub>art</sub> and p<sub>ven</sub>. The sheet-flow theory enables us to compute p anywhere in the sheet if p<sub>art</sub> and p<sub>ven</sub> are known.

Undoubtedly, p<sub>art</sub> and p<sub>ven</sub> are related to the pressures at the pulmonary artery, p<sub>PA</sub>, and at the left atrium, p<sub>LA</sub>. They differ because of the hydrostatic pressure head and the hemodynamic resistance. Let the pulmonary artery be located at the level z<sub>0</sub>. Let z (or z<sub>LA</sub>) be the height of an alveolar sheet (or the left atrium) above z = z<sub>0</sub>. Then we have

\[ p_{\text{art}} = p_{\text{PA}} - \rho g z - \sum (\Delta p_i)_{p, \text{arteriole}} \]  
\[ p_{\text{ven}} = p_{\text{LA}} - \rho g (z - z_{\text{LA}}) + \sum (\Delta p_i)_{p, \text{ven}} \]

where \( \rho \) is the density of the blood, \( g \) is the gravitational acceleration, \( (\Delta p_i)_{p} \) is the pressure drop in the \( i \)th generation of the arteries, \( (\Delta p_i)_{v} \) is that in the \( i \)th vein. \( (\Delta p_i)_{p} \) is equal to the product of the flow in the \( i \)th vessel and the resistance in that vessel, which, for an elastic vessel, is itself pressure dependent. Therefore, to calculate p<sub>ven</sub> from p<sub>PA</sub> one would have to account for the flow.

Because of the last term in Eq. 1b, one must not conclude that p<sub>ven</sub> ≤ 0 whenever p<sub>LA</sub> - \( \rho g (z - z_{\text{LA}}) \) ≤ 0. This is an important point if one wishes to understand the connection between the sheet flow and the "waterfall" of Permutt et al. (13) or "sluicing" of Bannister and Torrance (14).

Let us consider a collapsible sheet under the conditions p<sub>art</sub> > 0, whereas p<sub>LA</sub> - \( \rho g (z - z_{\text{LA}}) \) < 0, and follow Permutt et al. (13) to examine p<sub>ven</sub> from the side of the sheet. If p<sub>ven</sub> is lower than the alveolar pressure the vessel will collapse. But if it were closed the...
arteriole pressure will prevail in the entire sheet and the vessel will be opened again. Permutt et al. (13) indicated that a flutter condition occurs. We would like to point out, however, that flutter is possible only for flows in larger tubes with finite Reynolds numbers, for which the inertia force is large compared with the elastic, pressure, and viscous forces. In contrast to large tubes, the Reynolds number in pulmonary microcirculation lies in the range of $10^{-4}$ to $10^{-1}$; hence the inertia force is so small compared with the elastic, pressure, and viscous forces that flutter will be impossible. The mechanical condition is analogous to a vibration system in which the mass is infinitesimal. Such a system deforms instantly under changing external loads without dynamic overshoot. Mathematically, this corresponds to the fact that the equation of motion of the fluid reduces to the quasi-steady equation of Stokes at small Reynolds numbers. When the equation of motion is combined with the equations of continuity (describing the law of conservation of mass) and the constitutive equation of the sheet (describing the elasticity or the thickness-pressure relationship), the final equation describing the dynamics of the alveolar sheet (and capillary blood vessels in general) turns out to be a nonlinear diffusion equation. The mathematical behavior of such an equation is very different from the wave equation which describes the propagation of waves in arteries, veins, and large Starling resistors. In particular, although flutter is possible in large vessels it would not be possible in capillaries, in which any small accidental perturbations would be dissipated. Details of this argument are presented in Appendix A.

A model experiment was carried out to verify this point. We repeated the experiment on Starling resistors of finite diameters. When water flowed in such a collapsible tube at large Reynolds number under the condition that the exit pressure in the tube was smaller than the static pressure outside the tube, flutter occurred. When a silicone fluid of high viscosity was used as the flowing medium so that the Reynolds number was so small as to be comparable with that in a normal pulmonary alveolar sheet, no motion of the tube wall was detected over a period of several hours, during which the external conditions were maintained constant. Flutter did not occur. The experimental details and interpretation are given in Appendix D.

Thus flutter cannot arise. Therefore we need to consider only steady-state solutions. Let us continue to consider the case $p_{LA} - pg (z - z_{LA}) < 0 < p_{art}$. If all veins are collapsed under this condition, then there will be no flow and no further consideration is needed. For a significant discussion let us assume that some veins will remain open because of their intrinsic stiffness. Consider the smallest vein that can remain open under the external pressure. Figure 2 illustrates such a vein whose right segment ($x>0$) is patent while the left segment ($x<0$) is collapsible under negative transmural pressure. Then for a flow to the right, we shall show that in a cylindrical tube the station $x=0$ marks the minimal cross section.

FIGURE 2
Illustration of possible locations where a small vein will remain open under a negative transmural pressure, $p_{LA} - pg < 0$. 

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To demonstrate this, let us assume that in the collapsible segment the lumen will be reduced to zero whenever
$$p_i(x) - p_o < 0,$$
where the subscripts “i” and “o” refer to “inside” and “outside” respectively, and $p_o$ is assumed constant. If we assume that the tube is collapsed at a section $x_o < 0$, then the flow is stopped, and the pressure in the segment to the left will be the arterial pressure, which is greater than $p_0$, and a contradiction will be obtained. It follows that nowhere to the left of $x = 0$ could be collapsed. Since neither can the tube collapse to the right nor can it flutter, therefore the point of collapse, if any, must be at $x = 0$.

Now for a Stokes flow the pressure gradient is always positive toward downstream. Hence the internal pressure, $p_i(x)$, decreases monotonically. For a patent elastic tube, the elastic modulus is always positive; therefore the elastic distention of the tube decreases monotonically toward $x = 0$. If the tube cross section is uniform in the natural state, then the minimum cross section will be located exactly at $x = 0$, QED.

The size of the minimum cross section of an alveolar sheet at the exit depends on the flow. From Eq. 27 of reference 6, we have the flow per alveolar sheet

$$Q = \frac{1}{C} \left[ (h_0 + \alpha \Delta p_{art})^4 - (h_0 + \alpha \Delta p_{ven})^4 \right].$$

Solving for the venule pressure, we obtain

$$\Delta p_{ven} = \frac{1}{\alpha} \left[ (h_0 + \alpha \Delta p_{art})^4 - CQ \right]^{1/4} - \frac{h_0}{\alpha}.$$  (2)

For a fixed $\Delta p_{art}$, the minimum value $\Delta p_{ven}$ can have is reached when $Q$ reaches the maximum value

$$Q_{\text{max}} = \frac{1}{C} (h_0 + \alpha \Delta p_{art})^4,$$  (4)

which corresponds to $h_e \to 0$. For a flow smaller than $Q_{\text{max}}$, the exit section of the alveolar sheet remains open with a finite thickness even though $p_{LA} - \rho g (z - z_{LA}) < 0$.

In the pulmonary sheet the flow adjusts itself so that $\Delta p_{ven} > 0$ and the venous exit remains open. No flow greater than $Q_{\text{max}}$ is possible. For a given $\Delta p_{ven}$, the maximum flow, $Q_{\text{max}}$, is achieved when the sucking force from the left atrium is so great that the sheet becomes cusplike at the exit section where the minimum gap, $h_e$, tends to zero. That the sheet becomes cusplike at the exit section under this condition has been demonstrated in the examples shown in reference 2, but the clearest indication of this cusplike behavior is perhaps furnished by Eq. C6 of reference 6, Appendix C, which refers to a two-dimensional example and shows that $h \to 0$ as $x \to 0$ in the manner of $h = x^4$. Therefore the resistance at the cusp is a mathematically integrable singularity, and the integrated resistance across the cusp remains small. In other words, the length of the segment where $h_e \to 0$ is so vanishingly small that its effect on flow is negligible.

This mathematical device is, of course, merely an idealization of reality. Theoretically and practically, the cusp can be rounded off without substantial effect. However, it is obviously convenient to speak of $h_e \to 0$ in association with $Q \to Q_{\text{max}}$, in spite of the fact that the cusp may be rounded off.

Incidentally, as discussed before, $h_e$ becomes a nonlinear function of the transmural pressure when $p_{ven} \to 0$. For practical purposes, as is shown in Figure 1, we may assume that the linear relationship $h_e = h_0 + \alpha \Delta p_{ven}$ holds when $\Delta p_{ven} > 0$ and that $h_e = 0$ when $\Delta p_{ven} \leq 0$.

Thus we learn that when $p_{art} > 0$ we must have $h_e \geq 0$: the inequality sign holds if the flow, $Q$, is not maximal; but when $Q$ is maximal we must have $h_e = 0$. Further, if $p_{LA} - \rho g (z - z_{LA}) < 0$, the flow can be maximal if and only if the immediate postcapillary venule can remain patent under the negative pressure. Otherwise the smallest section will move further downstream to the beginning of the smallest vein that can remain patent. If the venule is sufficiently rigid, further reduction of $p_{LA} - \rho g (z - z_{LA})$ will not affect the flow.
REGIONAL DIFFERENCES—SMOOTH MERGING OF ZONE 2 AND ZONE 3

West (16, p 24) has emphasized the regional difference in pulmonary flow. Expressed in terms of local pressures, he writes

- **Zone 1**: \( p_a > p_o > p_v \)
- **Zone 2**: \( p_o > p_a > p_v \)
- **Zone 3**: \( p_o > p_v > p_a \)

where the subscripts \( A, a, \) and \( v \) stand for alveolar, arterial, and venous, respectively.

In West’s discussion of these zonal differences, \( p_o \) and \( p_v \) are computed statically so that \( P_a = P_{PA} - \rho g z \) and \( p_v = P_{LA} - \rho g z \).

Hence his \( p_v \) is not the real pressure at the venule. If \( p_o \) and \( p_v \) were interpreted as port \( p_{art} \) and \( p_{ven} \) then the condition for zone 2 given above is untenable, because as we have shown in the preceding section, as long as there is flow \( p_{ven} = p_{art} \) cannot be negative. Therefore the condition for zone 2 should be simply \( p_{art} < p_{ven} \) without an auxiliary statement about \( p_{ven} \).

However, if this were the case, then how can we distinguish zone 2 from zone 3? The answer is that we cannot: these zones will merge into each other smoothly. The reason is as follows. As it is shown in the previous section, the alveolar thickness at the venule exit remains finite in zone 2 as long as the flow \( Q \) is not maximal. Therefore no sudden change in sheet configuration occurs at the junction between zone 2 and zone 3. The exceptional case arises when \( h_v = 0 \). But if \( h_v = h_a + \alpha \Delta \) then at one level, say \( z_1 \), the flow in the entire zone 2 above \( z_1 \) will be maximal. In other words, \( h_v = 0 \) throughout. If this happens at the juncture of zone 2 and zone 3, then \( h_v = 0 \) also marks the highest level of zone 3, and the two zones again merge smoothly.

Thus it appears that there exists a level \( z = z_m \) which distinguishes whether \( Q \) is maximal or not in West’s zone 2 and zone 3 disappears on further consideration. In heuristic terms, one might explain the existence of a dividing level \( z = z_m \) by saying that below \( z = z_m \) the suction of the left atrium pressure is not enough to make \( h_v \) tend to zero as a cusp, whereas above \( z = z_m \) the suction is strong enough to make the flow maximal.

Hughes et al. (17) have compared the rate of increase of blood flow down a vertical lung under zone-2 and zone-3 conditions. Six comparisons were made at transpulmonary pressure (TPP) of 10 cm H\(_2\)O and three comparisons at TPP of 20 cm H\(_2\)O; the results at both pressures showed that the difference between the means of the ratio was not significant. They showed that the changes in the slope of increasing blood flow when they did occur were not closely related to the junction between the zones. These results are consistent with the prediction of the sheet-flow theory.

EFFECT OF GRAVITY ON BLOOD FLOW

The effect of gravity on the inflow and outflow pressures of a sheet, \( p_{art} \) and \( p_{ven} \), has been exhibited in Eqs. 1a and 1b. By substituting \( p_{art} \) and \( p_{ven} \) into Eqs. 27-33 of reference 6, the flow and resistance at level \( z \) can be obtained. The total flow is

\[
\text{Total flow} = \int_{z_b}^{z_a} N(z) \frac{C(z)}{h_a^4(z) - h_v^4(z)} \, dz
\]  

(5)

where \( z_a \) is the height at the apex, \( z_b \) is the height at the base, and \( N(z) \) is the number of sheets per unit height at level \( z \).

Eq. 5 is valid for the entire lung. However, if we wish to show further details, we may note that in zone 1, \( h_v = h_o = 0 \). In zone 2, \( h_v = 0 \) if flow is maximal, whereas \( h_v > 0 \) if flow is not maximal. In zone 3, \( h_v > 0 \) and \( h_o > 0 \). Let the heights limiting these zones be \( z_a \) (Fig. 3):

- **Zone 1**: (no flow)
- **Zone 2a** (\( Q \) is maximal): \( z_a = z_m \)
- **Zones 2b and 3** (\( Q < Q_{max} \)): \( z_m - z_b \)
where $a = \text{apex}$; $S = \text{seizure level}$; $m = \text{flow maximal}$; $b = \text{base}$. Then

$$\text{Total flow} = \int_{z_b}^{z_m} N(z) \left[ h_s^a(z) - h_s^s(z) \right] dz + \int_{z_m}^{z_a} N(z) h_s^a(z) dz. \quad (6)$$

ALVEOLAR BLOOD VOLUME

By integrating the volume over the alveolar sheets, we can obtain the alveolar blood volume. Since volume is equal to thickness at times area, the result for each alveolar sheet can be written in the form

$$\text{Alveolar blood vol/sheet} = S' h_s f(h_v/h_a)$$

$$= S' \left[ h_o + \alpha (p_{\text{art}} - p_{\text{alv}}) \right] f \left( \frac{h_v}{h_a} \right), \quad (8)$$

The formula applies when the points $z_o, z_s, z_m$ and $z_a$ are located as shown in Figure 3. If the zonal distribution is such that $z_a$ lies beyond $z_o$, then one should replace $z_a$ by $z_o$. If $z_m$ also lies beyond $z_o$, then the whole lung is in zone 3, and we should replace both $z_m$ and $z_s$ by $z_o$ in the formula above.

Alveolar blood vol/sheet $= S' h_s[0.93 + 0.07 (h_v/h_a)^2]$. \quad (9)

Translated into an expression in terms of pressures, this becomes

$$\text{Alveolar blood vol/sheet} = S' \left[ h_o + \alpha (p_{\text{art}} - p_{\text{alv}}) \right]$$

$$\times \left\{ 0.93 + 0.07 \left[ h_o + \alpha (p_{\text{ven}} - p_{\text{alv}}) \right]^2 \right\}$$

In Appendix B, a qualitative discussion of the variation of $C(z)$ and $Q(z)$ due to gravity is presented.
suggested in the experimental results on dogs of Glazier et al. (18) (see Discussion in ref. 6), then the theoretical results given by Eq. 10 can be shown in Figure 5. It is seen that the pulmonary alveolar blood volume is primarily a function of the arterial pressure. The effect of venous pressure on the alveolar blood volume is minor. For example, a variation of venous pressure from 5 to 30 cm H₂O changes the blood volume by less than 7%.

The results shown in Figure 5 refer to an example in which the arterial supply enters an alveolar sheet in a precapillary that forms a ring at the margins of the sheet, and the postcapillary drains the blood at the center in a single opening. One may wish to know how much of the general feature is due to this special geometry. To illustrate this point, let us consider an extreme case, illustrated in Figure 6, in which the precapillary and postcapillary are parallel and supply a sheet continuously and uniformly along the whole length. This is the simplified case discussed in Appendix C of reference 6. The exact solution is given in Eqs. C5 and C6 of reference 6. By integrating \( h(x) \) from \( x = 0 \) to \( x = L \), we obtain the volume per unit length which can be reduced to the following form:

\[
\text{Alveolar vol/sheet} = \frac{4}{5} S' h_a \left[ \frac{1 - (h_v/h_a)^5}{1 - (h_v/h_a)^4} \right].
\]  

This represents an upper bound of possible effect of venous pressure on alveolar blood volume.

Permutt et al. (20) have examined pulmonary blood volume extensively. A typical example of their results is shown in Figure 7. If a comparison is made between Figures 5 and 6.
Theoretical relationship between the pulmonary alveolar blood volume and the arterial and venous pressures. Ordinate is the pulmonary blood volume per unit area of the sheet. Abscissa is the transmembrane pressure at the arteriole end of the sheet. The transmembrane pressure at the venule end is seen to have only a minor effect on the blood volume. Data correspond to Figure 4.

and 7, we should remember that (1) $p_{\text{art}}$ is smaller than $p_{\text{PA}}$ according to Eq. 1, and (2) integration of Eq. 10 is needed to obtain the total alveolar blood flow in the lung. The general trend is in agreement, although the slope is steeper in Figure 7 than in Figure 5. We may remark further that (1) if the natural length of the posts, $h_0$, is smaller than the assumed value, 2.5 $\mu$m, then the curves of Figure 5 would be closer to the origin when $p_{\text{art}} - p_{\text{alv}} \to 0$; (2) according to reference 6, the larger the transpulmonary pressure used in inflating the lung, the smaller is the slope, $\alpha$, of the curves. The TPP used by Glazier et al. (18) corresponding to the value $\alpha = 0.122 \mu$m/cm H$_2$O adopted in Figure 5 was 10 cm H$_2$O. The same reference yields a smaller value of $\alpha = 0.079 \mu$m/cm H$_2$O when the TPP was increased to 25 cm H$_2$O. The value of TPP used by Permutt et al. (20), whose results are quoted in Figure 7, was smaller: it had an end expiration pressure of 5 cm H$_2$O. Thus the slope, $\alpha$, is expected to be larger in the case of Permutt et al. A correction of these effects would bring the theoretical results closer to the experimental ones. (In Appendix C, we estimate this to be $\alpha = 0.172 \mu$m/cm H$_2$O if $h_0 = 2.5\mu$.)

Permutt et al. (20) showed further that there was little difference in the relationship between pulmonary alveolar blood volume and inflow pressure whether the perfusion was forward or backward and whether the lungs were in zone 2 or zone 3. Both of these features are in agreement with the sheet-flow theory.
Experimental results of Permutt et al. showing the relationship between pulmonary blood volume and pulmonary artery pressure in one dog at a variety of left atrial pressures (from Figure 8 of reference 20). If this figure is compared with Figure 5, one should remember the possible difference in physical constants as discussed in the text and in Appendix B.

DISTRIBUTION OF TRANSIT TIME IN AN ALVEOLAR SHEET
Since the velocity distribution is given by the sheet-flow theory, we can derive a theoretical transit-time distribution for blood in the pulmonary alveoli. As an example, let us consider the case illustrated in Figure 3a of Reference 2, whose solution is given in Figures 10 and 11 of that reference. In this case, we have \( h = \text{constant} \), and the velocity along any streamline, \( \psi = \text{constant} = c \), is \( \frac{\partial \psi}{\partial n} \), where \( n \) is the distance perpendicular to the streamline. Let \( s \) be the distance measured along the streamline, then the transit time, \( t \), for a particle along that streamline is

\[
t = \int \frac{ds}{\text{velocity}} = \int \frac{ds}{\partial \psi/\partial n}. \quad (12)
\]

If we consider two neighboring streamlines, \( \psi = \text{constant} = c \) and \( \psi = c + \Delta \psi \), and let the distance between these two streamlines be \( \Delta n \), then the transit time along these streamlines is

\[
t = \frac{1}{\Delta \psi} \int \frac{\Delta n \, ds}{\psi = c} = \int \frac{\Delta n \, ds}{\psi = c}. \quad (13)
\]

If \( f(t) \) is the frequency function of the transit time, then by definition \( f(t) \, dt \) equals the fraction of the fluid that enters an alveolar sheet whose transit time lies between \( t \) and \( t + dt \). But \( \Delta \psi \) is by definition equal to the quantity of flow between the streamlines \( \psi = c \) and \( c + \Delta \psi \). Hence if \( \Delta \psi \) is kept constant throughout the field of flow, then the frequency function, \( f(t) \), would be inversely proportional to \( dt = f_{\psi=c} + \Delta \psi - f_{\psi=c} \).

With these relations we can determine the frequency function for the present example as follows. The area between successive streamlines in the sheet shown in Figure 10 of reference 2 is determined with a planimeter. Each of the areas represents 10% of the flow. The inverse of the difference between successive areas is proportional to the frequency. The result is shown by the histogram of Figure 8, which can be represented approximately by the empirical formula

\[
f(t) = \frac{1}{20} \delta(t - 1) + 1.678 e^{-2(t-1)} + \frac{1}{45} e^{-0.2(t-1)} \quad (14)
\]

for \( t \geq 1 \), while \( f(t) = 0 \) for \( t < 1 \). Here \( \tau = \text{(transit time)} / (\text{minimum transit time}) \) and \( \delta = \text{unit impulse function} \). If we return to physical units with \( t \) in seconds and let \( t_{\text{min}} \) denote the minimum transit time, then

\[
f(t) = \frac{1}{t_{\text{min}}} f(\tau) = \frac{1}{t_{\text{min}}} f \left( \frac{t}{t_{\text{min}}} \right) \quad (15)
\]

The mean transit time, denoted by \( \bar{t} \), is

\[
\bar{t} = \int_0^\infty tf(\tau) \, d\tau = t_{\text{min}} \int_1^\infty \tau f(\tau) \, d\tau. \quad (16)
\]

For the empirical formula given above, we have

\[
f(\tau) \to \frac{1}{t_{\text{min}}} f(\tau) \to \frac{1}{t_{\text{min}}} \delta(t - 1) + 1.678 e^{-2(t-1)} + \frac{1}{45} e^{-0.2(t-1)} \quad (17)
\]
The theoretical transit time distribution for blood flow in an alveolar sheet which is illustrated in Figure 3a of reference 2. Computation gives the histogram which is fitted by a curve $f(T)$. $T$ is the ratio of transit time to the minimum transit time through the sheet.

$$\bar{t} = 1.475 t_{\text{min}}.$$  \hspace{1cm} (17)

We can relate the mean transit time to the physical parameters of the alveolar sheet. By a process entirely analogous to that employed in deriving Eq. 25 of reference 6, we obtain the mean velocity of flow in an alveolar sheet:

$$\overline{U} = \frac{1}{3\mu \alpha L} \left[ h_0^3 - h_v^3 \right],$$  \hspace{1cm} (18)

where $L$ is the mean path length of the streamlines between the arteriole and venule:

$$\frac{1}{L} = \frac{1}{(\psi_2 - \psi_1)} \int_{\psi_1}^{\psi_2} \frac{1}{L(\psi)} \, d\psi.$$  \hspace{1cm} (19)

Then

$$\bar{t} = \frac{\overline{L}}{\overline{U}} = \frac{3\mu \alpha L^2}{h_0^3 - h_v^3}. \hspace{1cm} (20)$$

It is obvious that $\bar{t}$ should be proportional to the coefficient of viscosity, $\mu$, and the friction factor, $\alpha$, and increase with increasing length of the path, $L$; but the reason for $\bar{t}$ to depend directly on the square of the mean path length between the arteriole and venule, $L^2$, and inversely on the cube of the pulmonary arterial pressure (or more precisely, on $h_0^3 - h_v^3 = [h_0 + \alpha \Delta p_{\text{art}}]^3 - [h_0 + \alpha \Delta p_{\text{res}}]^3$) is more subtle, and requires some thinking for its assimilation. The way the arteriole and venule pressures affect $\bar{t}$, as shown in Figure 9, is most impressive.

The formulas above are derived for a sheet of uniform thickness. If the sheet thickness is variable, a stream function can be defined (Eq. 26, ref. 2) so that

$$hU = \frac{\partial \psi}{\partial y}, \quad hV = \frac{\partial \psi}{\partial x}.$$  \hspace{1cm} (21)

Then the transit time along a streamline, $\psi=c$, is given by

$$t = \int h \Delta n \, ds.$$  \hspace{1cm} (22)

Thus for a field covered by streamlines spaced at constant $\Delta \psi$, the transit time in an individual stream tube is proportional to the volume of the tube. Since we have shown that the alveolar sheet remains quite uniform in thickness over a wide range of pressure, it is expected that the variation in thickness will not affect the frequency distribution function significantly. The mean transit time given in Eq. 20 has already accounted for the variation in thickness.

### Transit-Time Distribution in the Whole Lung

Cumming et al. (21) have computed the transit-time distribution from morphological data of a human lung. Their result for a
The dependence of the mean transit time through a pulmonary alveolar sheet on the arteriole and venule pressures. Curves give $T_\text{m}$. The mean transit time, $t$, is given by $t = \frac{n}{3} \frac{aL}{fH}$, where $n$ is the coefficient of viscosity of blood, $f$ is a friction factor depending on post geometry (computed and measured in refs. 3–5), $a$ is the slope of the thickness-pressure curve of the sheet, and $L$ is the mean path length of blood in the sheet.

FIGURE 10
Convolution of transit times, $t_1$, $t_2$, and $t_3$, of blood in the pulmonary arteries, capillaries, and veins, respectively. Upper left: Arterial, from Cumming et al. (21). Middle left: Capillary. Lower left: Venous. Right: Result of convolution.

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particle to pass from the pulmonary valve down to terminal branches of the order of 50 $\mu$m with a pulmonary blood flow of 80 ml/sec is sketched in the upper left corner of Figure 10. Adding to this the transit time in the alveolar sheet and the veins, we can obtain the transit time through the entire lung. Since it is well known that the distribution function of the sum of several random variables is the convolution of the distribution functions of the individual variables, we see that if the transit times, $t_1$, $t_2$, and $t_3$, in the arteries, alveoli, and veins are distributed as shown in Figure 10, the transit time in the whole lung from the pulmonary valve to the left atrium will be distributed as shown on the right of the figure.

Although the real problem is best handled by computers, it will be interesting to illustrate the mathematical procedure by a simple example. Consider the following case. Let the frequency functions for $t_1$, $t_2$, and $t_3$ be

$$f_1(t) = \frac{2}{\alpha} (t - a)^2 e^{-a(t-a)} H(t-a)$$

$$f_2(t) = \varepsilon b(t-b) + (1-\varepsilon) \beta e^{a(t-b)} H(t-b)$$

$$f_3(t) = \frac{2}{\alpha} (t - c)^2 e^{-a(t-c)} H(t-c)$$

where $H(t-a)$ is the unit-step function which equals 0 when $t < a$ and 1 when $t \geq a$. The characteristic function of $f_1(t)$ is

$$\int_{-\infty}^{\infty} e^{i\omega t} f_1(t) dt = \frac{\alpha e^{\epsilon\omega a}}{(\alpha - i\omega)^3}$$

Similarly the characteristic function of $f_2$ and $f_3$ are, respectively,

$$\varepsilon e^{\epsilon\omega b} + (1-\varepsilon) \frac{\beta e^{b\omega}}{(\beta - i\omega)}$$

Since the frequency function of $t_1 + t_2 + t_3$ is the convolution $f_1*f_2*f_3$, the characteristic function of $t_1 + t_2 + t_3$ is the product of the three characteristic functions:

$$\frac{\alpha^2 \varepsilon^2 e^{\epsilon\omega a+b+c}}{(\alpha - i\omega)^3 (\gamma - i\omega)^3} \left[ \epsilon + (1-\epsilon) \frac{\beta}{(\beta - i\omega)} \right].$$

(26)
The frequency function of $t_1 + t_2 + t_3$ is the inverse Fourier transformation of the above. The calculation becomes very simple in the case $\alpha = \beta = \gamma$; then the frequency function of $t_1 + t_2 + t_3$ is

$$f(t) = \frac{\epsilon \alpha}{6l} \tau^2 e^{-\tau} + (1 - \epsilon) \frac{\alpha^2}{6l} \tau_0 e^{-\tau} \quad (27)$$

for $t \geq a + b + c$, while it is 0 for $t < a + b + c$, where

$$\tau = t - (a + b + c). \quad (28)$$

The frequency function (Eq. 27) is more peaky than those given in Eq. 23, a feature which is illustrated in Figure 10. The general case in which $\alpha \neq \beta \neq \gamma$ can be resolved by using partial fractions.

The frequency function of transit times through the lung can be measured by indicator-dilution method. In a recent abstract, Tancredi and Zierler (23) reported that at a given $p_{alv}$ and $p_{LA}$ a family of the density function of transit times, $h(t)$, with different mean transit times, $\bar{t}$, can be transformed to a nearly coincident function, $\bar{h}(t/\bar{t})$. This is exactly the function, $f(t/\bar{t})$, described in our Eqs. 15 and 17. Figure 11 shows a frequency function of transit times through the whole pulmonary circulation from pulmonary artery to left atrium, obtained by Maseri et al. (24) for the dog. Its general form is in agreement with the theoretical curve, except for the leading edge which is very sharp in the experimental curve. We suspect that this is due to the neglect of smaller quantities. Maseri et al. showed that the frequency function is not affected by the heart rate or by the presence or absence of respiratory movements.

**Discussion**

The features of sheet flow derived above have been analyzed earlier by other authors and were attributed to Starling's mechanism and recruitment. In basic assumptions, our analysis differs from that of Permutt et al. (20) only in two small but important points: (1) For an inflated lung, the alveolar sheet is readily distensible in the thickness direction. We used experimental thickness-pressure relationships in working out our examples. (2) At the small Reynolds number of the alveolar blood flow, quasi-static conditions prevail. There will be no flutter, and the elastic deformation of the sheet can be analyzed statically. Because of these, the venous exit pressure in the capillary sheet in zone 2 cannot be smaller than the alveolar pressure, and the distinction between zone 2 and zone 3 disappears. On the other hand, there exists in zone 2 a certain level, $z = z_m$, above which the flow is maximal for a given arteriole pressure and below which the maximal condition is not met. In the latter case, flow can be increased by lowering left atrial pressure.

The basic explanation of alveolar flow in terms of Starling resistors was proposed by Bannister and Torrance (14) and Permutt et al. (13). The pressure-flow relationships of a Starling resistor have been described in simplified terms by Permutt et al. (13), Permutt and Riley (25), and earlier but implicitly, by Duomarco and Rimini (26). Dynamics of Starling resistors of finite size are indeed quite complicated, and details were not given in any of these references. Under
the second simplification listed in the preceding paragraph, an exact solution can be given. Our result presented in Eq. 2 is an exact solution for a two-dimensional Starling resistor (Appendix C of ref. 6), whereas in three dimensions it is an approximate solution for the alveolar sheet. One sees in Eq. 2 that the two pressure terms are raised to the fourth power. If the second term, \( h_v \), is significantly smaller than the first term, \( h_a \), the fourth power of the second term, \( h_v^4 \), will be much smaller than the fourth power of the first term, \( h_a^4 \). This is why the pulmonary blood flow is relatively insensitive to variations in venule pressure as compared with its response to variations in arteriole pressure. In fact, for the same variation in the arteriole and venule pressure, \( d(p_{ven}) = d(p_{art}) \), the ratio of the changes in flow can be derived from Eq. 2:

\[
\frac{\partial Q}{\partial p_{ven}} = \left( \frac{h_a + \alpha \Delta p_{ven}}{h_n + \alpha \Delta p_{art}} \right)^3 = \left( \frac{h_v}{h_a} \right)^3 \tag{29}
\]

In this formula \( \Delta p_{ven} = p_{ven} - p_{art} \), and \( \Delta p_{art} = p_{art} - p_{art} \). If \( \Delta p_{ven} \ll \Delta p_{art} \) and \( \alpha \Delta p_{art} \) is comparable with \( h_n \), then the right side of Eq. 29 may be much smaller than 1. In this special case, one may say that a change in venous pressure has little effect on the flow. This situation is aptly described as sluicing or waterfall.

Therefore, the analyses presented here and in references 2 and 6 may be regarded as a static but more exact version of the sluicing or waterfall theory. Because of the simplification due to small Reynolds number, we are able to fill in a great deal of details which would be difficult to derive if we have to consider Starling resisters of finite size at Reynolds numbers greater than 1. As Permutt’s theory has been very successful since it was proposed 10 years ago, and since our theory leads to about the same results quantitatively, it is not surprising that our theory is in general agreement with experimental results. The quantitative aspects also relieve the old theory from some of the difficulties. The most important ones are: (1) the uncertainties of the site of collapse of the Starling resisters; (2) the heavy reliance on the critical closing pressure as part of the theory. In addition, the merging of zone 2 and zone 3 is welcome, because it renders possible a uniform treatment of pulmonary mechanics.

The purpose of this article is to present the theoretical consequences of the sheet structure of the pulmonary alveolar septa. The results are expressed in simple formulas containing the relevant physical and physiological parameters. The values of most of these parameters are unknown at this time. Undoubtedly a continued effort to measure them is required. In the meantime, with more accurate knowledge about the morphology of the alveolar sheet, improvement of the accuracy of theoretical predictions beyond the formulas presented in this paper can be pursued along the lines indicated in reference 2 or by a more sophisticated theory. Thus the existence of room for improvement is evident, even within the framework of sheet flow. Beyond the alveolar sheet, other factors enter into the problem of circulation and ventilation in the lung. However, it is thought worthwhile to offer the present analysis in the hope that it will help to simplify our thinking about the lung and indicate the interaction of the many parameters that together govern a very complex phenomenon.

### Appendix A

**BASIC EQUATIONS GOVERNING THE MOTION OF A CAPILLARY BLOOD VESSEL AND THE QUESTION OF FLUTTER**

The basic equations derived in references 2 and 6 are limited to static conditions. When the possibility of flutter is considered, we must consider dynamic conditions. Flutter is studied extensively in aeronautical engineering (27, 28). In pulmonary capillary models Permutt et al. (13), Permutt and Riley (25), Rodbard and Saiki (29) and Conrad (30) have reported flutter in experiments at large Reynolds numbers (at least in excess of 100). Now the Reynolds number is defined as \( R_x = \frac{VL}{\rho \mu} \), where \( V \) and \( L \) are the characteristic velocity and length, \( \rho \) is the density, and \( \mu \) is the viscosity of the fluid. In a capillary, let us consider a mean velocity of 1 mm/sec, a diameter of 10 \( \mu \)m, a density of 1, and an apparent viscosity of 4 cP, then \( R_x = 0.0025 \), which is much smaller than 1. At \( R_x = 1 \), the inertia force and the viscous force are of equal importance in a flow. When \( R_x \) is greater than 1, the inertia force is more important. When \( R_x \) is...
less than 1, the viscous force is more important (31, p 227). In a capillary blood flow, $R_N$ is much less than 1, and the flow is dominated by the viscous forces; hence we are concerned with a different kind of flow than those reported in references 13, 25, 29, and 30.

Let $\rho$ and $\mu$ be the fluid density and viscosity, $v$ and $p$ be the local fluid velocity and pressure, $t$ be the time, and $\nabla$ be the vector nabla operator. Let $V$, $L$, and $\tau$ be, respectively, a representative velocity, length, and time, and introduce the dimensionless variables

$$U = \frac{v}{V}, \quad P = \frac{pL}{\mu V}, \quad T = \frac{t}{\tau},$$

where $r$ is the position vector, then the Navier-Stokes and continuity equations may be written in dimensionless forms

$$R_N \left( \frac{L}{\tau V} \frac{\partial U}{\partial t} + U \cdot \nabla U \right) = -\nabla P + (\nabla')^2 U.$$

$$\nabla' \cdot U = 0.$$ 

Eq. A2 can be simplified into the Stokes’s equation

$$\nabla^2 v = \frac{1}{\mu} \nabla P$$

either when $R_N \to 0$ or when $R_N (L/\tau V)$ and $U \cdot \nabla' U$ are negligible. The parameter $R_N (L/\tau V)$ is the square of a parameter $\alpha = L/\sqrt{\nu/\mu}$, (where $\nu = \mu/\rho$ and $\omega = 1/\tau$ is a frequency) introduced by Stokes originally and by Womersley (32, 33) later. Whereas $\alpha >> 1$ for the pulsatile flow in large arteries, it is << 1 in the capillary blood vessels.

Consider an axisymmetric flow in a long tube with a wavelength that is long compared with the tube radius, then the radial velocity, $v_r$, is significantly less than the axial velocity, $u$, and $\partial u/\partial r << \partial u/\partial t$, so that Eq. A4 becomes

$$\frac{\partial p}{\partial r} << \frac{\partial p}{\partial t}, \quad \frac{\partial p}{\partial x} = \frac{1}{r} \frac{\partial}{\partial r} \left( r \frac{\partial u}{\partial r} \right).$$

Hence, if the inner wall of the tube is located at $r = a(x, t)$, then

$$u = -\frac{1}{4\mu} \left( a^2 - r^2 \right) \frac{\partial p}{\partial x}.$$ 

Substituting Eq. A6 in Eq. A3, reducing, and integrating, we obtain

$$v_a = \frac{1}{16\mu} \frac{1}{a} \frac{\partial}{\partial x} \left( a^2 \frac{\partial p}{\partial x} \right).$$

where $v_a$ is the radial velocity of the fluid at the wall; $v_a$ could be due to fluid permeation across the capillary blood vessel or to wall motion. For the latter, if we assume linear elasticity so that the tube radius is proportional to the transmural pressure (in analogue with the alveolar sheet),

$$a = a_0 + \alpha \rho,$$

where $\alpha$ is the compliance coefficient; then $v_a = \partial a/\partial t = \alpha \partial p/\partial t$. Hence we obtain

$$\frac{\partial p}{\partial t} = \frac{1}{16\mu} \frac{1}{a} \frac{\partial}{\partial x} \left( a^2 \frac{\partial p}{\partial x} \right)$$

and finally, the basic equation

$$\frac{\partial a^2}{\partial t} = \frac{1}{40\mu \alpha} \frac{\partial^2 a}{\partial x^2}.$$ 

This basic nonlinear differential equation is new; a search in the mathematical literature does not reveal any previous treatment.

A corresponding development of the two-dimensional case of flow through a channel with collapsible walls located at $y = \pm h/2$, and with the notations of reference 6, Appendix C, leads to the following equation governing the thickness distribution

$$\frac{\partial h}{\partial t} = \frac{1}{6\mu} \frac{\partial}{\partial x} \left( h^3 \frac{\partial p}{\partial x} \right) = \frac{1}{24\mu \alpha} \frac{\partial^2 h^4}{\partial x^2}.$$ 

It is beyond the scope of the present paper to discuss the full solution of the nonlinear Eqs. A10 and A11. For the purpose of studying stability, let us consider small perturbations about the equilibrium positions, assuming constant end conditions and constant external pressure. Let $d(x)$ and $h(x)$ be the static solutions of Eqs. A10 and A11, respectively:

$$\frac{\partial^2 h^5}{\partial x^2} = 0, \quad \frac{\partial^2 h^4}{\partial x^2} = 0,$$

and consider all possible small perturbations

$$a(x, t) = a(x) + \epsilon a^*(x, t) \quad (A13)$$

$$h(x, t) = h(x) + \epsilon h^*(x, t), \quad (A14)$$

where $\epsilon$ is a small constant. Then on substituting Eqs. A13 and A14 into Eqs. A10 and A11, respectively, and neglecting higher powers of $\epsilon$, we obtain the linearized equations

$$\frac{\partial^2}{\partial x^2} \left[ \frac{\partial a^*}{\partial x} a^*(x, t) \right] = 16\mu a \frac{\partial}{\partial t} a^*(x, t).$$
These are linear diffusion equations with variable coefficients. The boundary conditions pertinent to equations are the same as those governing the equilibrium configurations and $A_16$ are identically zero. Without much ado the solution is identically zero. Therefore, the stable with respect to tube at all times. Our experience tells us that diffusion of gases in a tube with no gas in the corresponds to the mathematical statement that there will be no gas in the tube, which happens when the Reynolds number is large tube at the beginning and no gas entering the tube at all times. Our experience tells us that there will be no gas in the tube, which corresponds to the mathematical statement that the solution is identically zero. Therefore, the equilibrium configurations $\hat{a}(x)$ and $\hat{h}(x)$ are stable with respect to all small perturbations.

Let us complete the analysis by showing what happens when the Reynolds number is large while the nonlinear term $v \cdot \nabla v$ is negligible. Then the steady-state solutions $\hat{a}(x)$ and $\hat{h}(x)$ are identical with what was deduced above. The perturbation velocity $v^* = V_0'$ and pressure $p^* = p_0' \rho V^2$, however, now satisfy the equation (31, p. 225)

$$\frac{\partial v^*}{\partial t} = -\nabla p^* + \frac{1}{R_s} \nabla^2 v^*.$$  \hspace{1cm} (A17)

When $R_s$ large, the last term may be neglected, then for a long wave we have

$$\frac{\partial a^*}{\partial z^2} - 2 \rho \frac{\partial}{\partial t} \left( \frac{1}{\rho} \frac{\partial a^*}{\partial t} \right) = 0 \hspace{1cm} (A18)$$

which is a wave equation. In this case we know a nontrivial solution exists. To see this we merely remark that Eq. A18 is identical with that describing the vibrations of musical strings, in which nontrivial vibrations are of course possible.

Therefore we conclude that the static solutions are stable at small Reynolds numbers, but are subjected to oscillations at large Reynolds numbers. Since pulmonary micrcirculation corresponds to small Reynolds numbers, its stability may be assumed. The full nonlinear equation might contain a limit cycle which has not yet revealed itself, but should be investigated in the future.

**Appendix B**

**INFLUENCE OF GRAVITATION ON VARIOUS FACTORS AFFECTING PULMONARY ALVEOLAR BLOOD FLOW**

The alveolar blood flow is given by Eq. 2. The principal effect of gravity on the flow, $Q$, is undoubtedly its influence on the gradient of arterial and venous pressures. This is shown in Figure 12, in which $Q(z) = [h_0 + \alpha (p_{art} - p_{alv})]^4 - [h_0 + \alpha (p_{ven} - p_{alv})]^4$ is plotted against the level of $z$ for $h_0 = 2.5\mu$, $\alpha = 0.125$, $p_{art} = 0$, $p_{ven} = 1$, and $p_{alv} = p_{alv}(0) - \rho g z$. The venule pressure is set at $p_{ven}(0) = \rho g z$ if it is positive and at 0 if the latter is negative, where the flow becomes maximal as we have discussed before. The flow per sheet, $Q$, is equal to $Q'(z)/C(z)$, where

$$C(z) = 4 \mu L \alpha/(S A).$$

(Eq. 25 of reference 6). The symbols are: $\mu =$ coefficient of viscosity of the blood, $f =$ friction factor, $\alpha =$ compliance coefficient $= \text{slope of the thickness-pressure curve}$, $L =$ mean path length of blood in each sheet, $S =$ vascular space-tissue ratio, $A =$ mean area per sheet. Since all factors, except $S$ and $f$, vary with the hydrostatic pressure head, $z$, the factor $C(z)$ will depend on $z$.

West and his associates (16) have done a great deal to clarify the regional differences in blood flow and ventilation of the lung. Following their work and others, we can sketch the variations of the various parameters with $z$ as shown in Figure 13. In all these figures the vertical axis is the height of the level $z$ in an upright lung, with the apex at the upper end.

The alveolar volume, $V$, and the sheet area, $A$ are sketched in Figure 13a. Relative volume of alveoli depends on the degree of inflation and on the elastic modulus of the lung tissue. The more highly the lung is inflated, the more uniform is the volume of the units.

From $V$ we can deduce $A$, the mean sheet area. The mean path length, $L$, should be proportional to the average linear dimension of the sheet; but Staub and Schultz (34) have shown that each sheet may consist of several alveolar septa and span over several alveoli. They gave the average distance between arterioles (less than 60$\mu$ diameter) and venules (less than 60$\mu$ diameter) as 600–800$\mu$ in dog and cat and 550–650$\mu$ in rabbit; each spans over 5–7 different alveoli. In Figure 13a, $L$ is sketched as proportional to $A^{1/2}$. The ratio $L/A$, which directly enters $C(z)$, thus varies like $A^{-1/2}$.

The alveolar sheet compliance coefficient, $\alpha$, depends primarily on the tension in the sheet, which in turn varies with lung inflation, elastic modulus, position of animal, gravity, acceleration, etc. From tension, $T$, we can compute $1/T$ and $\alpha$ in a manner shown in Eq. 21 of reference 6. This is sketched in Figure 13b.

It is well known that blood viscosity in large vessels or in an ordinary viscometer increases with increasing hematocrit, but in capillaries, the red
blood cells are so large compared with vessel diameter that it is no longer permissible to speak about viscosity of the blood as a homogeneous fluid. Therefore it is of interest to learn that in pulmonary blood flow the average resistance increases with increasing hematocrit (35). This was corroborated by testing results in our own laboratory on alveolar sheet models. Now it is also clear on the general principle that in a multichannel flow field the red cells tend to move into the faster channels so that the hematocrit is higher in the vessels where the flow is faster and lower in those vessels where the flow is slower, the distribution of hematocrit in the lung would be nonuniform. The hematocrit will be lower at the apex than at the base. Glazier et al. (9) have shown some evidence to this effect. The expected variations of the hematocrit and the apparent viscosity with \( z \) are sketched in Figure 13c.

On the other hand, the vascular space tissue ratio, \( S \), and the friction factor, \( f \), are essentially independent of the alveolar strain (4-6) and therefore independent of \( z \). In contrast, the number of sheets per unit volume, \( N(z) \), is inversely proportional to \( V \) and therefore varies strongly with \( z \). These are sketched in Figure 13d.

The final result is a \( C(z) \) that is curved (Fig. 13e). Dividing \( Q'(z) \) by \( C(z) \), we obtain a plot of the regional flow per sheet, \( Q \). Multiplying \( Q \) by the number of sheets per unit volume, \( N(z) \), we obtain the flow per unit volume, as sketched in Figure 13f. It is the last figure that should be compared with the experimental curves of West (16).

The comparison cannot yet be satisfactorily quantified because so many details about the variation of the individual parameters are unknown. But the point is that such an analysis is feasible and it surely will be improved in the future.

Appendix C

AN ESTIMATION OF THE COMPLIANCE COEFFICIENT OF THE DOG'S LUNG IN EXPERIMENTS REPORTED BY PERMUTT ET AL.

We can estimate the value of \( \alpha \), the compliance coefficient, corresponding to the preparation of Permutt et al. (20) as follows. In Figure 14 their experimental data on the slope \( \Delta p_{PA}/\Delta p_{LA} \) when the left atrial pressure was varied while the flow was kept constant and the expiration pressure was maintained at 5 cm H\( _2 \)O are reproduced. This curve can be computed theoretically. If the pressure at the venules is greater than the alveolar pressure, then the flow per sheet is given by Eq. 2.
Writing

\[ C\eta /\alpha^3 = K, \quad (h_n/\alpha) - p_{atv} = A, \quad p_{ven} = x, \quad p_{art} = y, \]

from which we obtain

\[ dy/dx = (A + x)^3 \left[ K + (A + x)^4 \right]^{-3/4}. \]  

If we know an experimental value of \( dy/dx \) for a specific value of \( x \), we can compute \( K \) from Eq. C3 and then plot \( dy/dx \) vs. \( x \) with \( A \) as a parameter. By varying \( A \), we can choose one \( A \) which makes a good fit between the theoretical curve and the experimental results. Figure 14 illustrates such a fit to data of Permutt et al. (20) if we take, roughly, \( p_{atv} = 5 \) cm H\(_2\)O, \( p_{ven} = 10 \) mm Hg, \( p_{art} = 5 \) cm H\(_2\)O, \( h_0 = 2.5 \) \( \mu \)m, then \( \alpha = 0.172 \) \( \mu \)m/cm H\(_2\)O. If \( h_0 = 2.0 \) \( \mu \)m, then \( \alpha = 0.138 \) \( \mu \)m/cm H\(_2\)O.

If the left atrial pressure is equal to or lower than the alveolar pressure, then \( h_v \rightarrow 0 \) as discussed previously following Eq. 4. In that case the flow is maximal and is independent of \( p_{LA} \) thus \( dy/dx = 0 \). Hence in Figure 14 the theoretical curve is horizontal between \( p_{LA} = 0 \) and 3.68 mm Hg. The jump at \( p_{LA} = 3.68 \) mm Hg (corresponding to \( p_{atv} = 5 \) cm H\(_2\)O) is caused by our simplifying hypothesis that the alveolar sheet thickness vanishes when the transmural pressure is zero. If actual data as shown in Figure 1 were used the change would be smooth. If a detailed account of the pulmonary venous resistance is made the point of jump would be shifted somewhat to the left.

The ability of the theoretical curve to fit the entire set of data by knowing only one point can be taken as another evidence that the theory is basically correct.

**Appendix D**

**MODEL EXPERIMENT ON THE STABILITY OF A COLLAPSED STARLING RESISTOR IN FLOW AT LOW REYNOLDS NUMBER**

By Y. C. Fung, R. T. Yen, and E. Mead

To examine the stability of Starling resistors, an experiment was carried out. Thin-walled rubber tubes were tested in a tank described in Lee and Fung (36), modified for the present purpose as shown in Figure 15. Dow Corning 200 series fluid with a viscosity of 300 poise was used to perfuse the tubes. With a tube diameter of 2.00 cm (relaxed) and flow velocity in the range of 0.03-3 cm/sec, the Reynolds number based on tube diameter lies in the range 0.0002-0.02, which is comparable to that in the pulmonary alveoli. The tube was immersed in water. The pressure at the inlet \( (p_{art}) \) could be controlled and varied from 20 to 30 cm H\(_2\)O above the external pressure \( (p_{atv}) \); the pressure at the reservoir far downstream (in the suction tank) could also be controlled and varied from +20 to -30 cm H\(_2\)O relative to \( p_{atv} \). A typical case is shown in Figures 15 and 16. For this special tube, the radius was 1.111 cm, the wall thickness was...
An experimental set up for the study of the stability of a collapsed Starling resistor with flow at very low Reynolds numbers. The pressure in the suction tank and the levels of silicone fluid and water can be varied. The dimensions given in this figure refer to the tube shown in Figure 16.

The buckled tube was photographed every 2.5 minutes for a period of 2 hours; no detectable change in shape was found. Flow was from right to left. Transmural pressure at entry section was positive; that at the exit section was negative.

0.0346 cm, the Young’s modulus of the material in the natural state was $2.7 \times 10^7$ dyne/cm$^2$. With the pressure heads maintained constant as shown in Figure 15, the inlet end of the tube was distended, while the exit end was collapsed. A photograph was taken every 2.5 minutes for a period of 2 hours. No detectable change in shape was found. The tube did not flutter. The elastic deformation of the tube appeared to be about the same as those published in references 13, 29, and 30. Since the static solution is uninfluenced by Reynolds number, this agreement is expected. The absence of flutter is, however, surely the effect of flow at low Reynolds number.

To apply the modeling results to pulmonary blood flow, we must consider the difference in time constants between the model and the lung. Eqs. A16 and A17 show that the similarity parameter is $Lr/(\mu\alpha)$, where $L$ is a characteristic length and $\tau$ is a characteristic time. (This can be...
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seen by nondimensionalizing these equations.) Hence the time scale for the model is
\[
\tau_{\text{model}} = \tau_{\text{lung}} \left( \frac{\mu\alpha}{L} \right)_{\text{model}} \left( \frac{\mu\alpha}{L} \right)_{\text{lung}}.
\]

(D1)

An estimate can be made as follows. For the lung, the viscosity, \( \mu \), is about 0.07 cP, \( \alpha \) is 0.122 \( \mu\text{m/cm H}_2\text{O} \) or 0.122 \( \times 10^{-7} \text{ cm dyne}^{-1} \text{ cm}^2 \), \( L \) (typical thickness) is about 8 \( \mu\text{m} \). For the model, \( \mu \) is 300 poise, \( L \) is 1.11 cm, \( \alpha \) for a cylinder under internal pressure is equal to \( R^2/(hE) \) where \( R \) is the tube radius, \( h \) is the wall thickness, and \( E \) is the Young's modulus. On substituting the given parameters into Eq. D1, we find that \( \tau_{\text{model}} \approx 430 \tau_{\text{lung}} \). Since in our model test, there was no flutter in at least 2 hours, we may interpret the result to mean that there is no flutter in the pulmonary alveolar sheet in a period shorter than at least 17 seconds. This is already quite long compared with the period of breathing or heart beat. Therefore we may say that the model experiment suggests that there is no flutter in the pulmonary alveolar sheet with a frequency either comparable to or faster than the heart rate.

Footnotes

1For example, Starling (15) used a rubber fingerstall as a resistor in his heart-lung preparation. The Reynolds number of his flow probably was in the range of 200 to 3000.

2We believe that the zonal classification based on the thickness of the alveolar sheet at the arteriole end and venule end is simpler and more basic than that based on the pressures in the pulmonary artery, left atrium, and trachea.

3The sheet may be kept open at the entry or exit ends in spite of the condition \( p < 0 \) because of patent arteriole and venule. The linear relation \( h = h_0 + a_p \) is not expected to hold at these ends. Hence there may be a small flow.

5Such a situation seems to prevail in frog's lung. See photograph of a living frog lung in reference 19.

9See, for example, Cramer (22, p 235). The \( f_1, f_2 \) and \( f_3 \) are the famous \( x^2 \) distributions of degrees of freedom 6, 2, and 6 respectively. The resultant of convolution given in Eq. 27 is a sum of two \( x^2 \) distributions of degrees of freedom 12 and 14. These functions are tabulated.

References


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