Computational pulmonary edema: A microvascular model of alveolar capillary and interstitial flow

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ABSTRACT
We present a microvascular model of fluid transport in the alveolar septa related to pulmonary edema. It consists of a two-dimensional capillary sheet coursing by several alveoli. The alveolar epithelial membrane runs parallel to the capillary endothelial membrane with an interstitial layer in between, making one long septal tract. A coupled system of equations is derived using lubrication theory for the capillary blood, Darcy flow for the porous media of the interstitium, a passive alveolus, and the Starling equation at both membranes. Case examples include normal physiology, cardiogenic pulmonary edema, noncardiogenic edema, Acute Respiratory Distress Syndrome (ARDS) and hypoalbuminemia, and the effects of positive end expiratory pressure. COVID-19 has dramatically increased ARDS in the world population, raising the urgency for such a model to create an analytical framework. Under normal conditions, the fluid exits the alveolus, crosses the interstitium, and enters the capillary. For edema, this crossflow is reversed with the fluid leaving the capillary and entering the alveolus. Because both the interstitial and capillary pressures decrease downstream, the reversal can occur within a single septal tract, with edema upstream and clearance downstream. Overall, the interstitial pressures are found to be significantly more positive than values used in the traditional physiological literature that creates steep gradients near the upstream and downstream end outlets, driving significant flows toward the distant lymphatics. This new physiological flow may provide a possible explanation to the puzzle, noted since 1896, of how pulmonary lymphatics can function so far from the alveoli: the interstitium can be self-clearing.

INTRODUCTION
Lungs provide the interface between inhaled air and circulating blood for the exchange of oxygen and carbon dioxide. Figure 1(a) shows the gross lung anatomy in the chest including the left and right lung and parts of the airway tree (trachea, large airways), while Fig. 1(b) is a small scale view including bronchioles, neuroendocrine cells, alveoli, capillary network, alveolar liquid with a surfactant, and interstitial space. The bronchioles deliver air into and out of the alveolar sacs with ventilation. The capillary network runs adjacent to the alveoli, within the interalveolar septa where the interstitium also resides. Gas exchange occurs across the septa, between the blood and air compartments, and, overall, deoxygenated (blue) blood in the pulmonary arteries is returned as oxygenated (red) blood in the pulmonary veins. Figure 1(c) is a sketch of the pulmonary lobular anatomy in the cross section. The lobule is fed by a terminal bronchiole that branches into respiratory bronchioles. The alveoli (white) are on the order of 100 $\mu$m in diameter, and the interalveolar septa (gray) are 12 $\pm$ 3 $\mu$m thick. The capillary network runs within the septa and passes by several alveoli, see Fig. 1. From a review, the capillary path length ranges from 250 to 850 $\mu$m in several mammalian species. We call this capillary path with the adjacent septal structures the "septal tract," see Fig. 2. The lymphatics (green) in Fig. 1(c) are generally hundreds of micrometers away from the furthest alveolar septa, significantly farther than what is found in systemic tissues where the blood capillaries and the lymphatic capillaries are within tens of micrometers from one another. Systemic interstitial fluid velocities have been measured in the...
systemic circulation in the range 0.1–0.5 μm/s for intradermal mouse tumors and 0–2 μm/s with an average of 0.6 ± 0.2 μm/s in a rabbit ear preparation. The shear stress induced by the systemic filtration flow can be in the range of 0.005–0.015 dyn/cm².

Plasma fluid that exits from the capillaries into the interstitium is generally cleared by the lymphatic system. How that actually happens has been a puzzle since 1896, because of the long distances. The present model addresses this fundamental issue of lung physiology. When clearance is overwhelmed, the fluid can enter the alveolar air space causing pulmonary edema, resulting in difficulty breathing which can be fatal. In today’s global pandemic environment, COVID-19 is a devastating source of this failure. In this study, we present a microvascular, fluid mechanical model for this flow and explore normal and pathological situations. As part of the mathematical process, we calculate the interstitial fluid pressure, $p_i$, which has never been directly measured or previously calculated. We find it is quite different from traditional values that are commonly used by physiologists and physicians. An additional feature is the discovery of comparatively large interstitial fluid velocities exiting the ends of the septal tract, a newly identified flow mechanism for enhancing clearance.

The interstitium, as a component of the barrier, is also found throughout the body where it separates capillaries from tissue epithelium. Known alternatively as the extracellular matrix (ECM), it can be treated fluid mechanically as a porous media as well as a poroelastic media with viscoelastic properties. The solid component of the interstitium consists of tangled fibrils primarily of collagen, but also

FIG. 1. Lung anatomy: (a) shows the location of the lungs and airways in the body; (b) is a detailed view of the lung structures such as the bronchioles, neuroendocrine cells, alveoli, capillary network, alveolar liquid with a surfactant, and interstitial space. See https://commons.wikimedia.org/wiki/File:Lung_structure_normal.jpg for “Wikimedia Commons. File: Lung structure normal.jpg.” (last accessed October 19, 2022). (c) Pulmonary lobular anatomy showing the alveoli, interalveolar septa, arteries, veins, bronchi, interlobular septa, lymphatics, and pleura. The distribution of lymphatic vessels (green) in the pulmonary lobule. Most vessels are located in the pleura, in the interlobular septa, and associated with bronchovascular bundles. Lymphatic vessels are also present in interalveolar septa in association with arterioles and only occasionally independent of blood vessels. Arrows indicate lymphatic vessels independent of blood vessels in interalveolar septa. Reprinted with permission from Weber et al., Ann. Anat.-Anat. Anz. 218, 110–117 (2018). Copyright 2018 Elsevier.

FIG. 2. A two-dimensional model of a septal tract with capillary, interstitium, and alveolar compartments.
elastin and glycosaminoglycans, which are cross-linked to form a supportive structure. Overproduction of collagen in the lung setting can lead to Idiopathic Pulmonary Fibrosis (IPF).17–20 As the name suggests, the origin of IPF, an insidious fatal disease with no cure, is not known. However, flow over fibroblasts can affect their function,21,22 which has not been examined in the lung. The fluid component of the interstitium is similar to plasma.

Throughout the body, blood capillaries are normally permeable. They allow plasma to exit or re-enter depending on the balance of hydrostatic and osmotic (oncotic) pressures relative to the surrounding interstitium. For systemic blood circulation, typically plasma leaks into the interstitium upstream, where hydrostatic pressures are higher, and either re-enters the capillary downstream, where hydrostatic pressures are lower, or are absorbed by lymphatic capillaries. This is called filtration flow. It assists in the transport of gases, nutrients, and metabolic waste products between the blood and tissues. Excess outflow, not returned directly to the capillary, is collected by the lymphatic capillaries, which directly overlay the blood capillary bed in the systemic system. It is pumped through a series of lymph vessels with contractile elements and one-way valves, then through nodes and ducts, finally returning to blood circulation.23 The diameters of the blood capillaries are ∼5–10 μm while those of the lymph capillaries are ∼50 μm. Because of the close proximity, the travel distance for the interstitial fluid from the blood to the lymph is of a similar order, i.e., tens of micrometers. The pumping action creates a cyclical pressure variation at the entrance to the lymphatic capillary. Part of the cyclical pressure is negative compared to the surrounding fluid so there is flow into the lymphatics during the phase but no outflow due to one-way valves.

The circuit from capillary to the interstitial fluid to lymph and back to capillary has an overall flow rate estimated to be 8 l per day for the entire body. A typical blood volume for an adult, which includes red blood cells and plasma, is ∼5 l. For a normal hematocrit of 40% red blood cells, the intravascular plasma is ∼3 l, so all of it is recycled once every ∼9 h.24–25 Typical values of lung lymphatic flow are 5–10 ml/h in sheep and estimated to be 10–20 ml/h in humans.26 This flow balances the net filtration out of the capillaries, say 100 ml/h out 5–10 ml/h in = 20 ml/h net. These lymph flow rates can increase several folds in response to increased net filtration.27,28

Non-cardiogenic causes of pulmonary edema are relevant to the current COVID-19 pandemic. One of the major pulmonary targets of COVID-19 is the alveolar type II cells,29 which, along with alveolar type I cells, form the alveolar membrane separating gas from blood, see Fig. 3(a). Because alveolar type II cells produce surfactant, patients can experience a primary surfactant deficiency and collapsed lung regions from the higher surface tensions.30 We will see that surfactant deficiency also plays a role in pulmonary edema formation. Surfactant replacement therapy by tracheal or bronchoscopic instillation of exogenous surfactants into the lung is a potential means of treating this deficiency.31–33

In addition to damaging alveolar type II cells in their role as a barrier, the general inflammatory process disrupts capillary membranes, increasing their permeability. Thus, both boundaries, capillary endothelium, and alveolar epithelium are disrupted. The overall picture leads to Acute Lung Injury (ALI), ALI, and Acute Respiratory Distress Syndrome (ARDS), in general, are associated with sepsis, pneumonia, aspiration of gastric contents, and major trauma of the lung or non-lung structures. The resulting pulmonary edema is a protein-rich fluid that creates severe hypoxemia and bilateral infiltrates seen in chest x-rays.34–36 Prior to the COVID-19 pandemic, the incidence of ALI/ARDS in the U.S. has been estimated as 200 000 cases/year and the mortality rate varies in the range of 40%, so ∼80 000 deaths/year.37–39 However, cases and mortality around the world have skyrocketed into millions since the pandemic was initiated in early 2020.

The basic flow in the alveolar interstitium, having permeable capillary endothelial and alveolar epithelial boundaries, with a background lymphatic drainage, is a complicated fluid mechanical environment. There are compartmental models of pulmonary interstitial and lymphatic flows utilizing resistance and compliance components,40–46 including effects of ventilatory motion. However, in the face of a worldwide pandemic, there is a compelling motivation to establish and investigate a detailed fluid mechanical model.

RESULTS

To explore the model, it is important to choose parameter values that are representative of common respiratory conditions, both healthy and diseased. Normal physiology, case (A), shown in Figs. 4 and 5, uses the values calculated in Methods section and listed in Tables I and II. This is the base set. A sketch of the normal alveolus is shown in Fig. 3(a).26 Note the thin liquid lining the inside of the alveolus which has a surfactant layer, the type I and type II epithelial cells forming the alveolar wall, and the capillary with red blood cells and its endothelial wall, and the interstitium in between. The remaining figures are for pathological conditions.

Case (B) in Fig. 6 is cardiogenic pulmonary edema where capillary pressures p c, p v are elevated while the other parameter values are held at base levels. A sketch of cardiogenic pulmonary edema is in Fig. 3(b), which shows flow driven into the alveolus by increased hydrostatic pressures. The capillary diameter is larger due to the pressure increase, but not included in Fig. 6. Typically, this scenario is part of congestive heart failure. Noncardiogenic pulmonary edema of ARDS, is studied in case (C), Fig. 7. A sketch of ARDS is in Fig. 3(c), which shows elements of inflammation involving macrophages and neutrophils. For COVID-19, lymphocytes are also prevalent.31 There are increased leaks (hydraulic conductivities) in both the capillary endothelium, k c, and alveolar membrane, k A. The alveolar edema fluid is rich in proteins that cross through the reduced barrier and remain from inflammatory cellular breakdown. An essential contribution to the Starling equation is the capillary osmotic pressure, π, which is largely attributable to plasma proteins like albumen. Low levels, hypoalbuminemia, occur from reduced production by the liver, increased loss through the gastrointestinal tract or kidneys, and malnutrition. Case (D), Fig. 8, reduces π from the base value, leading to edema. An immediate therapeutic modality for pulmonary edema is to increase the alveolar gas pressure, P A, using Positive End Expiratory Pressure (PEEP), for example. This increases the alveolar liquid pressure, p AL, and can reverse the situation from edema to clearance as shown in case (E), Fig. 9, for cardiogenic edema.

Figure 4(a) shows normal cardiopulmonary physiology, case (A), using our base state parameter values from Tables I and II. The capillary dimensional pressure p(X) in Fig. 4(a) starts with the arterial value p A = 9 mm Hg at X = 0 and drops to the venous value p v = 6 mm Hg at X = 1. It is not a straight line, as would be expected for Poiseuille flow with insulated capillary walls. Instead, it has
negative curvature. Figure 4(b) shows the dimensionless capillary velocity field, \((U, V)\), and streamlines indicating that fluid enters the capillary from the interstitium through the capillary membrane at \(Y = 1\). The negative curvature for \(P(X)\) is consistent with the negative \(Y\)-velocity at \(Y = 1\) from Eq. (3), where \(V(1) = (1/3) \frac{d^2 P}{dX^2} < 0\). This crossflow displaces the upstream streamlines toward the capillary centerline at \(Y = 0\).

Figure 4(c) consists of the interstitial dimensionless velocity vector field \((U_i, V_i)\), streamlines, and dimensional pressure distribution.
The septal tract end-flow velocities, also seen as the end vectors at \( X \), steep changes at the ends to match drops with \( X \) due to the capillary pressure drop, and there are very steep changes at the ends to match \( p_i \). We call these transduced as \( n \).

Liquid, through the alveolar membrane at \( \eta = 1 \), and into the interstitium. From there, nearly all of the fluid crosses the interstitium in the \( \eta \)-direction into the capillary. We call this the septal crossflow. The rest exits in the \( X \)-direction through the ends at \( X = 0 \) as we will see below. Figure 4(d) shows more detail for the interstitial pressure distribution at three values of \( \eta = -1, 0, 1, p_i (0 \leq X \leq 1, \eta = -1, 0, 1) \). It drops with \( X \) due to the capillary pressure drop, and there are very steep changes at the ends to match \( p_i \).

Figure 5 shows additional results for case (A), including Fig. 5(a), which plots the interstitial crossflow velocities at the alveolar membrane, \( u_i (X, \eta = 1) \), and the capillary membrane, \( u_i (X, \eta = -1) \). They are essentially equal away from the end boundaries \( X = 0,1 \), so whatever crosses one of the membranes crosses the other. Both are in the velocity range \(-4 \) to \(-5 \) \( \mu \)m/s and have negative slopes with increasing \( X \) reflecting the capillary pressure drop. Figure 5(b) is \( u_i (X, \eta = 0) \) for \( X = 0 \), where \(-10 < u_i (X = 0) < -25 \) \( \mu \)m/s with an average of \(-13.7 \) \( \mu \)m/s and \( 5 < u_i (X = 1) < 15 \) \( \mu \)m/s with an average of \( 8 \) \( \mu \)m/s. We call these the septal tract end-flow velocities, also seen as the end vectors at \( X = 0 \) in Fig. 4(c). The interior velocities are plotted in Fig. 5(c) for \( X = 0.01, 0.2, 0.4, 0.6, 0.8, 0.99 \) in the range \( 10^{-3} \) to \( 10^{-2} \) \( \mu \)m/s. Since the capillary pressure drop over \( L \) is \( p_a - p_i = 3 \) mm Hg, the interstitial pressure drop, for the interior region \( 0.01 < X < 0.99 \) is similar, \( \Delta p_i \approx 3 \) mm Hg. An average \( X \)-velocity in this interior, using Darcy law, is \( u_i = K \Delta p_i / \mu L = 6.15 \times 10^{-3} \) \( \mu \)m/s in the positive \( X \) direction, which falls in the range of Fig. 5(c).

Fig. 6(b) plots streamlines and velocity vectors for fluid that exits the capillary and enters the interstitium, opposite to case (A) in Fig. 4(b). Both membranes cross the other. Both are in the velocity range \(-4 \) to \(-5 \) \( \mu \)m/s and have negative slopes with increasing \( X \) reflecting the capillary pressure drop. Figure 5(d) and 5(e) show the velocities and pressures near the ends. There are rapid changes of both \( p_i (\eta = 0) \), as we saw in Fig. 4(d), and \( u_i (X, \eta = 0) \) in the regions \( 0 \leq X \leq 0.01 \) and \( 0.99 \leq X \leq 1 \). These values fall in the range used in fluid mechanics, these two regions are called boundary layers, where there are rapid changes in the variables to match a boundary condition. Overall, it is immediately obvious that \( p_i = p_{ab} = -7.35 \) mm Hg only at the ends, \( X = 0,1 \), where it is imposed. Otherwise, \( p_i \) is significantly more positive, contrary to traditional physiological assumptions that \( p_i \) is in the range of \(-7 \) to \(-10 \) mm Hg everywhere in the interstitium.

An example of cardiogenic edema is shown in Fig. 6, case (B), by using our base parameter set, but with elevated capillary pressures \( p_a = 28 \) mm Hg, \( p_v = 25 \) mm Hg. These values fall in the range used in isolated, perfused dog lungs to study pulmonary hypertension and edema formation.

The positive value of \( V(Y = 1) \) corresponds to a positive curvature for \( p(X) \) through Eq. (3). The interstitial fluid pressure, Fig. 6(c), is in the range \( p_i = 13-16 \) mm Hg for the interior \( X \)-range, while satisfying the...
end pressures $p_{AL} = -7.35$ mm Hg at $X = 0, 1$. The crossflows at the capillary and alveolar membranes in Fig. 6(d) are essentially equal, as in case (A), in the interior. Both are positive in the range $3–4\mu m/s$ capillaries, so fluid overall leaves the capillary, crosses the interstitium, and enters the alveolar liquid. The septal end-flow velocities are $-30 < u_i(X = 0) < -130\mu m/s$ with an average of $-49.8\mu m/s$ and $30 < u_i(X = 1) < 120\mu m/s$ with an average of $44\mu m/s$, see Fig. 6(e). These are much larger values compared to case (A), reflecting the much larger pressure jump at the ends.

Case (C) is representative of edema from ARDS, see Fig. 7. Our base parameter set is modified to increase both $k_c$, $k_A$ by a factor of 10 for greater permeability of the capillary and alveolar membranes; decrease $p_{AL}$ to be more negative, reflecting the inactivation of surfactant with higher surface tension; and increase $\pi_{AL}$ for increased proteinaceous material in the alveolar liquid. Accordingly, the new parameter values are $k_c = 1 \times 10^{-5} \text{cm s}^{-1} \text{mm Hg}^{-1}$, $k_A = 5 \times 10^{-7} \text{cm s}^{-1} \text{mm Hg}^{-1}$, and $p_{AL} = -7$ mm Hg, $\pi_{AL} = 10$ mm Hg. Like case (B), fluid crosses from the capillaries, through the interstitium, and into the alveolar liquid, see Figs. 7(b) and 7(d). The septal crossflow velocity ranges from 1.5 to 4.3 $\mu m/s$. The interstitial pressure, $p_i$, varies spatially in a range $-3$ to $-6.5$ mm Hg away from the end boundaries in Fig. 7(c). The septal end-flow velocities of Fig. 7(e) are $-3 < u_i(X = 0) < -35\mu m/s$ with an average of $-9.7\mu m/s$ and $3 < u_i(X = 1) < 12\mu m/s$ with an average of $3.6\mu m/s$. 

**Fig. 5.** Continuing with case (A), normal physiology, the additional results are (a) alveolar membrane crossflow velocity, $v_i(\eta = 1)$, and capillary membrane crossflow velocity, $v_i(\eta = -1)$ in $\mu m/s$ (b) X-velocity $u_i(X, \eta)$ for $X = 0, 1$ (c) X-velocity $u_i(X, \eta)$ for $X = 0.01, 0.2, 0.4, 0.6, 0.8, 0.99$, (d) $u_i(X, \eta = 0)$, $p_i(X, \eta = 0)$ for $0 \leq X \leq 0.03$, and (e) $u_i(X, \eta = 0)$, $p_i(X, \eta = 0)$ for $0.97 \leq X \leq 1$. 

**FIG. 5.**
Case (D) consists of low blood osmotic pressure shown in Fig. 8. This situation can occur clinically with hypoalbuminemia, which has been investigated by others. Different from the previous cases, the value of $\pi = 11$ mm Hg is specifically chosen to make the septal capillaries experience pulmonary edema. The septal tract experiences pulmonary edema. The septal end-venous pressure, $p_{AV}$, drops downstream from 8 to 6 mm Hg; however, within the interstitial layer, it starts with $p_{i}(\eta = -1) > p_{i}(\eta = 1)$, forcing fluid from the capillary into the alveolus, and then switches to $p_{i}(\eta = -1) < p_{i}(\eta = 1)$, forcing fluid from the alveolus to the capillary. Likewise, the curvature of $p$ switches from positive to negative in Fig. 8(a) at the same crossover point, $X \sim 0.55$.

The model can also be used to explore and understand therapy. Figure 9, case (E), is another example of cardiogenic edema, less severe than case (B). The vascular pressures are $p_{a} = 22$ and $p_{a} = 19$ mm Hg. Figure 9(a) shows the alveolar membrane crossflow velocity, $v_{i}(\eta = 1)$, and capillary membrane crossflow velocity, $v_{i}(\eta = -1)$ in $\mu$m/s for the base alveolar liquid pressure $p_{AL} = -1.47$ mm Hg. The result is pulmonary edema. However, in Fig. 9(b), the alveolar gas pressure is increased so that $p_{AL} = 3$ mm Hg. This may be done using PEEP with a ventilator, BiPAP (Bilevel positive airway pressure), or CPAP (continuous positive airway pressure) and now the crossflow is reversed, stopping the edema and promoting clearance. Raising $p_{AL}$ through $p_{AG}$ is an example of potentially patient-specific therapies, since the effect of PEEP will also depend on the other parameters in the model, all of which can vary from patient to patient. The model provides a framework to sort out which therapies are available and adjustable by exploring which parameters are the most influential and can also be measured.
DISCUSSION

Our microvascular model of lung interstitial fluid transport solves the pressure and velocity fields of the coupled system for capillary (lubrication theory), interstitial (Darcy flow), and alveolar (passive) compartments. In addition to mass and momentum conservation within each compartment, boundary conditions of fixed pressures at the ends ($X = 0, 1$) and the Starling equation at both the capillary–interstitium boundary and alveolar–interstitium boundary are imposed. The system is solved using the Fourier series, so is available for potential users. The calculations are only for the initial fluid mechanical response. They do not include tissue compliance, active fluid, and solute transport, lymphatics, constraints on alveolar liquid supply, the dependence of parameters on one another (e.g., pressure dependent $K, d, b$), adaptations over time, three dimensional effects, or respiratory motions.

Case (A) shows fluid exiting the alveolus and entering the capillary over the interior of the septal tract, $0.01 \leq X \leq 0.99$, while the flow is in the opposite direction for pulmonary edema in cases (B) and (C).
(C) and bidirectional for case (D). The use of PEEP to reverse edema is shown in case (E). For all of the figures, the decreasing capillary pressure, $p$, downstream, causes a downstream drop in the interstitial pressure, $p_i$. Thus, the bidirectional flow could occur in any of the edema cases, not just case (D), with convection into the alveolus upstream and out of the alveolus downstream. Such situations may be a source of different levels of clinical and radiographic findings. For example, inspiratory crackles are lung sounds used to monitor pulmonary edema and have been implicated in causing injury to small airways. The crossflow velocities at the alveolar and capillary membranes are essentially equal in the interior.

As part of the analysis, the interstitial pressure, $p_i(x, y')$, is calculated and found to be very different from traditional values used in lung physiology. To our knowledge, this is the first calculation of $p_i$ from a detailed fluid mechanics model. Because of the absence of direct measurements, the model’s computations can help to establish a foundation for understanding and interpreting basic lung physiology and pathophysiology. Micropipette pressure measurements in nearby
interstitial tissue\textsuperscript{4,65} were imposed as the end pressures \( p_{\text{al}} = -7.35 \text{ mm Hg} \). This value is similar to indirect estimates of a constant \( p_{\text{al}} \approx -9 \text{ mm Hg} \) and \(-8 \text{ to } -7 \text{ mm Hg}\).\textsuperscript{37} Others have proposed more positive values of \(-5 \text{ to } 0 \text{ cm H}_2\text{O}\).\textsuperscript{38} However, the only way for \( p_{\text{al}} = p_{B} \) everywhere in the model is to make both the alveolar and capillary membranes impermeable by setting \( k_i = k_t = 0 \). These values force \( a_u = b_u = f_u = 0 \), so only the constant \( p_{B} \), term survives in Eq. (9). Consequently, because of the Darcy flow model, there is no interstitial fluid velocity, \( (u_i, v_i) = -(K/\mu)(\partial p_i/\partial x, \partial p_i/\partial y) = (0, 0) \) under these conditions.

What we see, instead, is that \( p_{\text{al}} \) is much more positive than \( p_{B} \), which leads to septal tract end-flows in the boundary layer regions. This is a new physiological flow phenomenon. Under traditional views \( p_{\text{al}} = p_{B} \) everywhere, so such a flow would not be possible. The septal end-flow velocities can be relatively large, tens of micrometers per second and higher, and include contributions from the capillary and
alveolar liquid. Because the membrane permeabilities terminate sharply at $X = 0.1$, the end-flow velocities are exaggerated in magnitude in the boundary layer regions because of the very steep pressure gradient, $\partial p_i / \partial x$, there. Physiologically we would expect a gentler spatial attenuation of the permeabilities with smaller septal end-flow velocities distributed over larger end boundary layer segments. However, these flows are a form of self-clearance for the alveolar interstitium, since they expel fluid toward the lymphatics and are much larger velocities than a lymphatic-driven flow.

We can estimate lymphatic-driven flow velocity, $u_t$, by applying the Darcy model. The pressure drop over the distance $L$ is $\Delta p_t = \mu u_t L / K$. Using our values, the result is $\Delta p_t = 4.87 \times 10^6 \times u_t \text{ mm Hg}$. For $u_t = 1 \text{ mm/s} = 10^{-4} \text{ cm/s}$, the pressure drop would have to be $487 \text{ mm Hg}$, which is not physiologic. More reasonable values would be on the order of $1\%$ of these, $0.01 \text{ mm/s}$ and $4.87 \text{ mm Hg}$. This speed is similar to $u_t$ calculated for case (A) in the interior. Thus, the background interstitial velocity in the interior is already on par with a potential lymphatic component. By comparison, the septal end-flows are significant.

The puzzle of how the lymphatics can function so far away from the alveoli has captivated lung physiologists and anatomists dating back to 1896. The early quest was to find lymphatics much closer, next to the alveolar walls, but they were not there. As pointed out by Staub, Tobin’s comment captures the frustration: “this concept (no alveolar wall lymphatics) has made it difficult to understand by what means foreign material or fluid in the alveoli may be transported to the nearest lymphatics.” As Staub says, “the problem posed by Tobin remains and demands a rational answer.” One possible explanation is the septal tract end-flow in our model, i.e., interstitial pressure created by the coupled compartments, drives its own clearance. This is a new physiological flow.

**METHODS**

Figure 2 is a two-dimensional model of a septal tract with three compartments: capillary, interstitium, and alveolus. The assumption of two dimensions is well justified since the alveolar capillary system geometry is often considered as flow between parallel alveolar sheets. There is normally a thin liquid layer coating the inside surface of an alveolus. The surface tension, $\sigma$, between it and the alveolar gas is reduced by surfactants produced by alveolar epithelial type II cells.

Four alveoli are represented with alveolar gas pressure $p_{AG}$, liquid pressure $p_{AL}$, surface tension, $\sigma$, at the gas–liquid interface, and osmotic pressure, $\pi_{AL}$, the inset shows the radius, $R$, of the alveolus. The upper half of the capillary is bounded by $0 \leq x \leq L, \ 0 \leq y \leq b$, while the top interstitium strip occupies $0 \leq x \leq L, -d \leq y' \leq d$. Note that the capillary-interstitial boundary occurs at $y' = -d$, which is the same as $y = b$. The lower half of the capillary and the lower interstitium strip, not shown, will be the mirror image of the upper halves, so there is symmetry of the entire system with respect to the capillary centerline, $y = 0$.

The capillary flow is driven by pressure differences between the upstream arterial, $p_a$, and downstream venous, $p_v$, ends. That motion is governed by the Navier–Stokes equations, which we simplify for thin layers using lubrication theory. Flow in the interstitium obeys Darcy’s equations, appropriate for a porous media, and the alveolar liquid is passive.

The capillary membrane at $y = b$, $y' = -d$, is semipermeable, allowing fluid crossflows, in either direction, between the capillary blood and the interstitial fluid. Likewise, the semipermeable alveolar membrane at $y' = d$ allows crossflows between the interstitium and the alveolar liquid.

Pulmonary edema occurs when fluid crosses into the alveolus at a rate faster than it can be cleared. The mathematical analysis involves solving for the conservation of mass and momentum for the capillary blood flow where the pressure is $p$, the $x$-velocity is $u$, and the $y'$-velocity is $v$. In addition, mass and momentum are conserved for the interstitium where the pressure is $p_i$. The $x$-velocity is $u_i$ and the $y'$-velocity is $v_i$. The Starling equation is applied at both the capillary membrane and the alveolar membrane, and the tract ends have an applied pressure, $p_o$.

**Capillary blood flow**

Using the parameter and variable definitions in Tables I–III, the dimensionless $x$-velocity, $U$, and pressure, $P$, satisfy the dimensionless Navier–Stokes equation simplified for lubrication theory,
Dimensionless variables

| Symbol | Description |
|--------|-------------|
| P      | Capillary blood pressure |
| p₀     | Interstitial fluid pressure |
| U      | Capillary blood x-velocity |
| u₁     | Interstitial fluid x-velocity |
| V      | Capillary blood y-velocity |
| v₁     | Interstitial fluid y-velocity |
| x      | Capillary horizontal coordinate |
| y      | Interstitial horizontal coordinate |
| y'     | Interstitial vertical coordinate |

Dimensional variables

| Symbol | Description |
|--------|-------------|
| P      | Interstitial fluid pressure |
| P₁     | Capillary blood pressure |
| U      | Capillary blood x-velocity |
| u₁     | Interstitial fluid x-velocity |
| V      | Capillary blood y-velocity |
| v₁     | Interstitial fluid y-velocity |
| X      | Capillary horizontal coordinate |
| ζ      | Interstitial horizontal coordinate |
| η      | Interstitial vertical coordinate |

From the Y-component of Eq. (1), we learn that P is independent of Y, so P = P(X). Integrating the X-component of Eq. (1) leads to the solution form of U,

\[
U = \frac{1}{2} \frac{dP}{dX} (1 - Y^2),
\]

where U(Y = ±1) satisfies no-slip at the capillary membranes and we see that U is locally parabolic.

Conservation of mass is given by \(\partial U/\partial X + \partial V/\partial Y = 0\), which allows us to solve for the y-velocity, V. Enforcing no crossflow at the centerline, V(Y = 0) = 0, due to symmetry V is

\[
V = -\int_0^Y \frac{\partial U}{\partial X} dY = \frac{1}{2} \frac{dP}{dX} \left( Y - \frac{Y^3}{3} \right).
\]

**Interstitium**

Modeled as a porous media, the interstitium has permeability, K, also known as the specific hydraulic conductivity, and fluid viscosity, \(\mu_i\). The ratio \(K/\mu_i\) is termed hydraulic conductivity, and its inverse is hydraulic resistance. Conservation of momentum is given by the dimensionless form of the Darcy equations,

\[
U_i = -\frac{\partial P_i}{\partial \xi}, \quad V_i = -\frac{\partial P_i}{\partial \eta},
\]

where \(U_i, V_i\) are the dimensionless velocities in the \(\xi, \eta\) directions, respectively, and \(P_i\) is the dimensionless pressure. The coordinate value ranges are \(0 \leq \xi \leq \lambda, -1 \leq \eta \leq 1\). The conservation of mass equation is \(\partial U_i/\partial \xi + \partial V_i/\partial \eta = 0\) which, after inserting Eq. (4), yields Laplace’s equation for \(P_i\),

\[
\frac{\partial^2 P_i}{\partial \xi^2} + \frac{\partial^2 P_i}{\partial \eta^2} = 0.
\]

The crossflow at the permeable capillary membrane is given by the Starling equation \(^\star\) in a dimensional form \(v(y = b) = k_c(p - p(y' = -d) - \sigma_i(p_i - p_i))\), where \(k_c\) is the hydraulic conductivity, often denoted by \(L_p\) in the physiological literature. The osmotic pressures operate in the opposite direction as the hydraulic pressures. The larger osmotic pressure side draws fluid away from the lower osmotic pressure side, hence the negative sign in front of the reflection coefficient, \(\sigma_i\). The value of \(0 \leq \sigma_i \leq 1\), gauges the ability of osmotically active molecules, like albumin or other plasma proteins, to cross the membrane. For \(\sigma_i = 1\), those molecules do not cross, while a value of \(\sigma_i = 0\) indicates a freely permeable membrane with no effective osmotic pressure difference. The Starling model has further revisions to account for specific issues \(^\star\) which we do not address. Using the dimensionless variables, substituting for \(V(Y = 1) = (1/3)(d^2P/dX^2)\) from Eq. (3), Starling’s equation becomes a differential equation for \(P_i\) coupled to \(P_i\) in the \(\xi\) variable,

\[
\frac{d^2P_i}{d\xi^2} - k_c^2 P_i = k_c^2(P_i(\eta = 1) - S_i).
\]

We also need to match the crossflow velocities at the endothelial boundary, \(v(y' = -d) = v(y = b)\). In the dimensionless form, this condition is

\[
V_i(\eta = 1) = \beta V(Y = 1).
\]

The permeable alveolar membrane boundary condition is also modeled using Starling’s equation \(v(y' = d) = k_c(p(p(y' = d) - p_{AL}) - \sigma_i(p_i - p_{AL}))\), where \(k_c\) is the hydraulic conductivity while \(p_{AL}\) and \(p_{AL}\) are the alveolar liquid and osmotic pressures, respectively. This membrane also has active transport processes for water and salt, \(^\star\) which can help to resolve pulmonary edema over time. We will not model active transport features in the current model. In the dimensionless form, the flux across the alveolar membrane is

\[
V_i(\eta = 1) = -\frac{\partial P_i}{\partial \eta}
\]

\|_{\eta=1} = k_c^2((P_i(\eta = 1) - P_{AL}) - S_i).
\]

**Solution**

We solve the above system of equations and boundary conditions using Fourier analysis. For interstitial end boundary pressures, \(P_i = P_{ib}\) at \(\xi = 0, \lambda\), let the leading order pressure field be given by the Fourier sine series,

\[
P_i = P_{ib} + \sum_{n=1}^{N} f_n(\eta) \sin(k_n \xi),
\]

where \(f_n\) is the Fourier sine coefficient, \(k_n\) is the wave number, and \(N\) is the order of the Fourier series. Solution of this equation for the crossflow velocities, \(V_i\), yields

\[
V_i(\eta = 1) = -\frac{\partial P_i}{\partial \eta}
\]

\|_{\eta=1} = k_c^2((P_i(\eta = 1) - P_{AL}) - S_i).
\]
where \( k_a = n\pi/\lambda \), where \( N = 2000 \) in our computations. Inserting Eq. (9) into Eq. (5) yields a differential equation for \( f_a(\eta) \), \( f_a''(\eta) - k_a^2 f_a = 0 \), whose general solution is \( f_a = a_n e^{k_a \eta} + b_n e^{-k_a \eta} \). Using Eq. (6) and substituting for \( P_l(\eta - 1) \) from Eq. (9) yields

\[
\frac{d^2 P}{d\xi^2} - k_c^2 P = -k_c^2 \left( P_{ib} + \sum_{n=1}^{\infty} (a_n e^{-k_n \xi} + b_n e^{k_n \xi}) \sin(k_n \xi) \right) - k_c^2 S_c,
\]

switching to the \( \xi \) variable for both sides where \( \xi = \lambda \xi \). The solution to Eq. (10), now in terms of \( \xi \), is given by

\[
P = (c_0 e^{\xi} + d_0 e^{-\xi}) + S_c + P_{ib} + \sum_{n=1}^{\infty} c_n \sin(n\pi X),
\]

where the first bracketed term is the homogeneous solution, involving the coefficients \( c_0 \), \( d_0 \), and the rest is the particular solution. By inserting Eq. (11) into Eq. (10) and equating coefficients of \( \sin(n\pi X) \), the values of \( c_n \) are found to be \( c_n = \frac{k_c^2 (a_n e^{-k_n \xi} + b_n e^{k_n \xi})}{(k_n^2 + k_c^2)} \).

Imposing the upstream and downstream blood pressure conditions on Eq. (11), \( P(X = 0) = P_d \), \( P(X = 1) = P_s \), determine \( c_0 = (P_{ib} + S_c - P_d) \), \( c_1 = (P_s - P_d) \), \( c_2 = (P_{ib} + S_c - P_d) \), \( c_3 = (P_s - P_d) \), and \( d_0 = (P_{ib} + S_c - P_d) \). The solutions for \( U, V \) come from substituting for \( P \), from Eq. (11) into Eqs. (2) and (3).

\[
U = -\frac{1}{2} (1 - Y^2) \left( k_c \xi_0 c_0 e^{\xi_0} - k_c d_0 e^{-\xi_0} \right)
+ \sum_{n=1}^{\infty} \frac{n\pi c_n \sin(n\pi X)}{(n\pi)^2}
\]

\[
V = \frac{1}{2} \left( Y - \frac{3}{4} \right) \left( k_c \xi_0 c_0 e^{\xi_0} + (k_c \xi_0)^2 d_0 e^{-\xi_0} \right)
+ \sum_{n=1}^{\infty} \frac{n^2 \pi c_n \sin(n\pi X)}{(n\pi)^4}.
\]

Substituting Eqs. (4) and (9) into the left-hand side of Eqs. (7) and (12) into the right-hand side of Eq. (7) yields an equation involving the coefficients \( a_n \) and \( b_n \). Further manipulation is needed to express the exponentials in their own sine series: \( e^{\pm k_n \xi} = \sum_{m=1}^{\infty} g_m \sin(k_m \xi) \), where \( g_m = 2m(1 - e^{-k_m \xi}(-1)^m)/(\pi^2 n^2 + k_m^2 \xi^2) \) and \( e^{\pm k_m \xi} = \sum_{m=1}^{\infty} h_m \sin(k_m \xi) \), where \( h_m = 2m(1 - (-1)^m e^{-k_m \xi})/(\pi^2 n^2 + k_m^2 \xi^2) \).

Collecting the coefficients of \( \sin(k_m \xi) \) yields

\[
-(k_n a_n e^{-k_n \xi} - k_n b_n e^{k_n \xi}) = \frac{\beta}{4} \left( k_c \xi_0 \right)^2 c_0 \sin(k_n \xi) + (k_c \xi_0)^2 d_0 \sin(n^2 \pi^2 c_n \sin(n\pi X)).
\]

Substituting for \( P_l \) from Eq. (9) into Eq. (8) gives us a second equation for \( a_n \) and \( b_n \), and again, we need to express all terms in the form of sine series. Let \( k_a^2 (P_{ib} - P_{ib} - S_c) = \sum_{n=1}^{\infty} d_n \sin(k_n \xi) \), where \( d_n = -2(k_n^2 (P_{ib} - P_{ib} - S_c) ((-1)^n - 1))/(n\pi) \). Now, all of the terms multiply \( \sin(k_n \xi) \) and we can equate the coefficients:

\[
-k_a (a_n e^{-k_n \xi} - b_n e^{k_n \xi}) - k_c^2 (a_n e^{k_n \xi} + b_n e^{-k_n \xi}) = d_n.
\]

The two equations, Eqs. (13) and (14), are solved for the remaining two unknown coefficients, \( a_n \), \( b_n \).

Parameter values

The Navier–Stokes equations are simplified by lubrication theory assuming the capillary channel height is much smaller than its length, \( 2b/L \ll 1 \). A typical capillary diameter, \( b \), has a range of 6.3–8.3 \( \mu \)m (Refs. 77 and 78) while its length, \( L \), continues past several alveoli. The path length through the alveolar capillary network ranges from 250 to 850 \( \mu \)m in several mammalian species.2–8 For our base state, we choose \( L = 500 \mu \)m, \( b = 3 \mu \)m, so that \( \varepsilon = 0.0066 \). The total interstitial thickness, 4\( d \), across the alveolar septum has been measured over a range, 1.63 ± 0.16,2 1.24 ± 0.15,4 and 1.72 \( \mu \)m.40 Typically, there is a thinner side and a thicker side, but we will use a symmetric model where both sides are equal. We choose \( d = 0.4 \mu \)m, which makes \( D_0 = d/b = 0.133 \) and, consequently, \( \lambda = L/d = 1/eD_0 = 1250 \).

We treat the capillary blood as a uniform Newtonian fluid of apparent viscosity, \( \mu \), which takes into account the presence of red blood cells. This viscosity was modeled in macroscopic flows using elastic pellets for RBCs, apparently at room temperature, 22 °C. Using reasonable values of the hematocrit (0.45), the ratio of red blood cell diameter to channel depth (0.79), and the plasma viscosity of 0.013 poise, their resulting curve-fit equation yields \( \mu = 0.025 \) poise. To account for the reduction of viscosity with increasing temperature, we settle on \( \mu = 0.02 \) poise. Interstitial fluid viscosity of rabbits was found to be \( \mu_i = 0.013 \) poise at 37 °C,10 not surprisingly similar to the viscosity of the lymphatic fluid \( \mu_{lymph} = 0.012 \) poise in dogs.9 Consequently, the dimensionless viscosity ratio parameter is \( \gamma = \mu_i / \mu = 0.65 \).

Physiologists use the Starling equation at the capillary membrane, \( v = k_i (p - p_i - \sigma_i (\pi - \pi_i)) \), to interpret and predict pulmonary fluid balance including edema. To do so, they assume \( p \) and \( p_i \) are constants. While a constant (average) pulmonary capillary blood pressure can be reasonably estimated from pulmonary wedge pressures, measuring \( p_i \) is a technical challenge due to the small dimensions of the alveolar interstitium. Micropipettes of 2–3 \( \mu \)m diameter tips have been inserted into the interstitium surrounding >30 \( \mu \)m diameter blood vessels, a region known as the perivascular space with a representative value of ~7.35 mm Hg.15,16 Since our model has spatially varying \( p_i \), this value is assigned to the end boundary pressures, \( p(x = 0) = p(x = L) = p_a = 7.35 \) mm Hg. For capillary pressures, an average value of 6.6 mm Hg has been measured.44 Within this range, we choose \( p_a = 9 \), \( p_b = 6 \) mm Hg, which makes \( P_a = p_a/(p_a - p_b) = 3 \), \( P_b = p_b/(p_a - p_b) = 2 \), and \( P_{ib} = p_{ib}/(p_a - p_b) = -2.45 \). For our channel flow, the average velocity is calculated as \( u_{avg} = (p_a - p_b)b^2/(3 \mu l) = 0.12 \) cm/s, which is similar to measurements \( u_{avg} = 0.075 \) cm/s for surface alveolar capillaries of rabbit lungs.10

Capillary hydraulic conductivity has been measured as \( k_c = 1 \times 10^{-7} \) cm/m/mm Hg in frog muscle,2 2–20 \( \times 10^{-7} \) cm/m/mm Hg in frog mesentery,11 1.7 \( \times 10^{-7} \) cm/m/mm Hg in rat mesentery,13 and 0.36 \( \times 10^{-7} \) cm/m/mm Hg in rat hindquarter.14 The last value was derived19 from the original data.20 From this range, we select a base value of \( k_c = 1 \times 10^{-6} \) cm/m/mm Hg and note that 1 mm Hg = 1333 dyn/cm² for adjusting the units.

Measurements of alveolar epithelial hydraulic conductivity in bullfrog lungs include \( k_{A} = 2.85 \pm 0.04 \times 10^{-7} \) cm/m/mm Hg).18 and 3.51 \( \pm 0.44 \times 10^{-8} \) cm/m/mm Hg (Ref. 92). The bullfrog lungs are hollow saccs with no airway tree or alveolar structure, making the epithelial transport surface area much simpler. From this
range, we choose a base value of \( k_A = 5 \times 10^{-8} \text{cm}^2/(\text{mm Hg} \cdot \text{s}) \). These choices yield \( \kappa_A = (3k_A \mu_D^2/b)^{1/2} = 1.89 \times 10^{-3} \).

Alveolar septal interstitial permeability, \( K \), is not reported directly in the literature. In general, \( K \) varies across different tissues over 3 to 4 orders of magnitude and depends on a number of factors, including the state of hydration, pressure, stretch, and presence of disease. In rat abdominal muscle, \( K/\mu = 15 - 78 \times 10^{-8} \text{cm}^2/(\text{mm Hg s}) \), which computes to \( K = 1.46 - 7.6 \times 10^{-12} \text{cm}^2 \). For rabbit aorta and intima, the results are \( K = 2.53 \times 10^{-14} \text{cm}^2 \). Rat subcutaneous tissue has \( K = 4.35 \times 10^{-13} \text{cm}^2 \), while dog subcutaneous interstitium has \( K = 2.3 \times 10^{-11} \text{cm}^2 \) (Ref. 96) as interpreted.1 From this range, we choose \( K = 1 \times 10^{-13} \text{cm}^2 \), which makes the Darcy number \( Da = K/d^2 = 6.25 \times 10^{-5} \). Now, we can compute the values \( \nu_A = (k_A \mu_d/K)^{1/2} = 0.51 \) and \( \beta = c^2/\nu_A D = 2.81 \).

There are consistent data measuring \( p_{AL} \) while varying transpulmonary pressure, \( TPP = p_{AG} - p_{PL} \), by inflation where \( p_{PL} \) is the pleural surface pressure. This was done in isolated lungs of adult rabbits, mature and immature fetal rabbits, and dogs. For isolated lungs, the pleural surface is surrounded by atmospheric air, so \( p_{PL} = 0 \). In other studies, five values of \( TPP = 5, 10, 15, 20, 25, \text{ and } 30 \text{ cm H}_2\text{O} \) yielded \( p_{AL} = 1.8, 6.2, 9.5, 13.3, 16.8 \text{ cm H}_2\text{O} \), respectively, in the 31-day mature fetal rabbits. We can consider \( TPP = 5 \text{ cm H}_2\text{O} \) as corresponding to an intact normal lung at end expiration. However, in that case, \( p_{PL} = -5 \text{ cm H}_2\text{O} \) and \( p_{AG} = 0 \). Therefore, \( p_{AL} = 1.8, -6.2, -9.5, -13.3, 16.8 \text{ cm H}_2\text{O} \), noting that the \( p_{AL} < 0 \) and increasingly negative for larger lung volumes. The jump in pressure across the air-interface is due to the surface tension, \( \sigma \), roughly as Laplace’s law \( \sigma = \pi \rho g h \), where \( \pi \) is the alveolar radius to the interface, see Fig. 2. In surfactant deficiency, as occurs in premature birth or COVID-19, the surface tension \( \sigma \) increases. In acute respiratory distress syndrome (ARDS), the present surfactant can be made ineffective due to inflammation. Additionally, \( \sigma \) varies with lung volume125 as the interfacial surfactant concentration reduces with the increasing surface area. That results in higher \( \sigma \) as the lung inflates. A normal value at FRC is found in Ref. 101 to be \( \sigma = 4 \text{ dyn/cm} \) for cat, dog, rabbit, and rat, by contrast \( 98 \text{ mature and immature fetal rabbits, 99 and dogs. 100 For isolated } \)

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### AUTHOR DECLARATIONS

**Conflict of Interest**

The authors have no conflicts to disclose.

### Ethics Approval

Ethics approval is not required.

### Author Contributions

**James B Grotberg:** Conceptualization (equal); Data curation (equal); Formal analysis (equal); Funding acquisition (equal); Investigation (equal); Methodology (equal); Project administration (equal); Resources (equal); Software (equal); Supervision (equal); Validation (equal); Visualization (equal); Writing – original draft (equal); Writing – review & editing (equal). **Francesco Romano:** Conceptualization (equal); Data curation (equal); Formal analysis (equal); Funding acquisition (equal); Investigation (equal); Methodology (equal); Project administration (equal); Resources (equal); Software (equal); Supervision (equal); Validation (equal); Visualization (equal); Writing – original draft (equal); Writing – review & editing (equal).

### DATA AVAILABILITY

The data that supports the findings of this study are available within the article.

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