On the Role of Surface Tension in the Pathophysiology of Emphysema

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Pulmonary emphysema is a disease that is characterized, if not defined, by the destruction of lung parenchyma (1). This destruction is believed to result principally from the damaging effects of proteolytic enzymes and free radicals generated within the alveolar compartment in response to noxious stimuli. Other factors, including epithelial and endothelial cell apoptosis, incomplete lung remodeling in response to tissue injury, and mechanical forces, may also contribute (2, 3). Over many years, parenchymal destruction and incomplete healing result in loss of tissue collagen and elastin, enlargement of alveolar airspaces, and, ultimately, the classic physiologic characteristics of advanced emphysema: hyperinflation, loss of elastic recoil at a given lung volume, loss of surface area for gas exchange, and severe flow limitation.

Because the major histologic difference between the normal lung and the emphysema lung is loss of lung parenchyma, it is logical to conclude that the physiology of emphysema is mechanically determined by loss of the tissue component of recoil. However, in the normal lung, recoil pressure decreases by 50 to 60% in the fluid-filled state, indicating that surface tension contributes substantially to lung recoil at any given pressure (4, 5). An obvious question is whether the same is true in the emphysema lung. Although emphysema is not primarily a disorder of surfactant, reflection on the critical role of surface tension in the normal lung indicates that an alteration in the *physiologic effects* of surface tension and the surfactant monolayer on overall lung recoil must occur in the emphysema lung. Otherwise one might naively expect that recoil pressure in emphysema could never decrease below one half to two thirds of normal.

Why ask this question? Emphysema is irreversible destruction of lung tissue. Does it really matter whether surface tension contributes 30, 50, or 70% of recoil, or whether this percentage changes as disease progresses? For reasons outlined later, we believe the answer is a resounding "yes." If surface tension does contribute significantly, surface-active agents designed to safely and favorably modulate surface tension might be used to increase recoil in emphysema.

This perspective examines the relative importance of isovolume tissue and surface-tension recoil in the normal and emphysema lung using continuum mechanics and micromechanics modeling. A systematic review of the literature has demonstrated that little experimental data are available to answer this important question. Thus, the arguments and conclusions presented here are based largely on models, which are supported by experimental data and consistent with physiologic observations. They suggest that surface tension does play an important role in determining recoil in emphysema. Moreover, they suggest that treatments that alter surface tension in very specific ways could be designed to safely increase recoil, reduce hyperinflation, and improve lung function in advanced emphysema.

MACROMECHANICS OF LUNG RECOIL

Lung compliance relationships have classically been described by the following empiric exponential equation:

$$V(P) = V_{max} - (V_{max} - V_{min})e^{-kP} \quad (1)$$

where V_{max} is the asymptotic lung volume at infinite distending pressure, V_{min} is lung volume at zero distending pressure, and k is a coefficient that describes the shape of the pressure–volume relationship (6). Studies involving healthy individuals, smokers without obstructive lung disease, and patients with varying degrees of emphysema have reported characteristic differences in V_{max}, V_{min}, and k (7, 8). As emphysema worsens and tissue destruction progresses, V_{max}, V_{min}, and k all tend to increase, implying loss of recoil pressure and reduced maximal expiratory flows (9). However, Equation 1 is strictly phenomenological; it provides no insight into which factors contribute to the loss of recoil. Specifically, this relationship cannot be used to distinguish loss of tissue recoil from loss of surface-tension recoil, both of which are important in the normal lung. Nevertheless, the relationships between pressure and volume described by Equation 1 apply regardless of how recoil is determined at the micromechanical level.

MICROMECHANICS OF LUNG RECOIL

The current understanding of the microstructural basis of lung macromechanics derives largely from the seminal works of Bachofen and Bachofen (10), Wilson (11, 12), Hoppin and Hildebrandt (13), and Weibel and Gil (14). These studies have provided morphometric information used to develop continuum mechanics models of lung recoil. These models allow partitioning of recoil pressure into tissue and surface-tension components during quasi-static lung inflation. Using data measured in air-filled and fluid-filled rabbit lungs, Wilson (11) showed that over a wide range of volumes (20–80% of total lung capacity [TLC]), macrophysiology could be accurately accounted for by microstructural continuum mechanics in the healthy lung.

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A modification of the original Wilson model, developed by Stamenovic (15), was adopted in this analysis to describe and compare the micromechanics of the normal and emphysema lung. Both the Stamenovic model and Wilson's original model are derived from energetic considerations, but the former contains mathematic expressions that are directly associated with specific microstructural components of the parenchyma and can therefore be modified to simulate the effects of specific changes in tissue structure or surface film properties. By assuming that alveolar duct geometry can be modeled as a circular ring (e.g., rather than as a hexagon), the explicit form of the Stamenovic continuum mechanics model becomes

$$P_{tp} = (N\ F(L)\ L)/3V + 2/3\ \gamma(S)\ S/V + (n\ F(l)\ l)/3V \quad (2)$$

where N is the number of structural fibers in the peripheral tissue network (including their extensions into the parenchyma) that contribute to recoil, F(L) is the force–length relationship for these fibers, L is fiber length, V is volume, an implicit function of fiber length, $\gamma(S)$ is surface tension expressed as a function of alveolar surface area S, n is the number of fibers in the alveolar duct network, F(l) is the force–length relationship for the alveolar duct, and l is the circumferential length of the alveolar duct. Explicit expressions for F(L) and F(l) consistent with those reported for lung parenchyma were used in this analysis and are similar to those originally described by Wilson (11). Parameters for N, n, L, l, and $\gamma(S)$ representing the normal lung were selected from published morphometry and biomechanics data or determined from internal equilibrium considerations. Additional details concerning parameter selection, its relationship to physiologic data, and the method of calculation of recoil pressures are described in the online supplement. The model was validated for the "normal healthy state" by matching simulated pressure–volume (P–V) curves to those described for normal control lungs, and to P–V curves generated using Wilson's (11) original modeling approach. Results are summarized in Figure 1. Recoil pressures as a function of lung volume for both models are nearly identical, demonstrating that the parameters selected for the Stamenovic model are nearly equal to those of Wilson's empiric model (Figure 1, *left*). V_{max}, V_{min}, and k values of compliance curves generated from micromechanics modeling were comparable to those reported in the literature for normal, healthy subjects. Figure 1 (*right*) shows the partitioning of recoil pressure into tissue (P_{tissue} = N F(L)L/3V), parenchymal surface tension ($P_\gamma = 2/3\gamma(S)S/V$), and alveolar duct effects (P_{ducts} = n F(l)l/3V) in this setting. Recoil forces generated by the tissue network account for 50% of total recoil. The remainder is contributed by surface tension acting at the level of the alveolus and alveolar duct. Partitioning of P_{tp} into tissue recoil and surface-tension recoil using this model is consistent with results measured in air-filled and fluid-filled healthy lungs (10, 11).

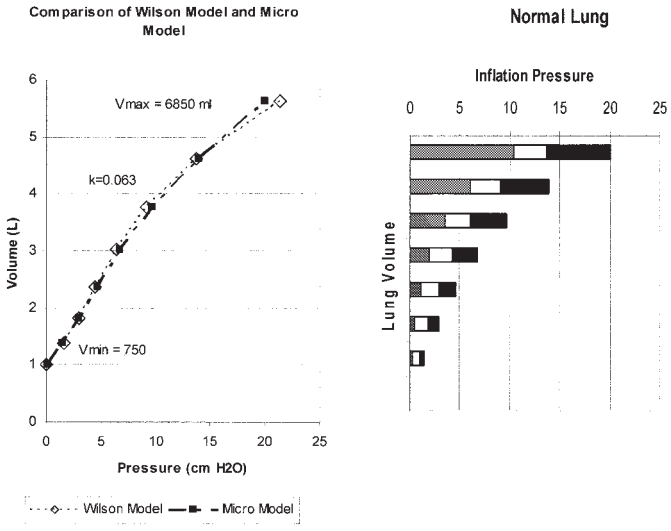


Figure 1. Comparison of simulated P–V results for the normal lung obtained using Wilson's original model and the model described by Equation 2. *Left panel*: Simulations validate the utility of this model and parameter selection in the normal condition. *Right panel*: Partitioning of recoil pressure into tissue (P_{tissue} = *gray bar*), alveolar surfactant layer (P_{alv} = *open bar*), and alveolar duct effects (P_{ducts} = *black bar*).

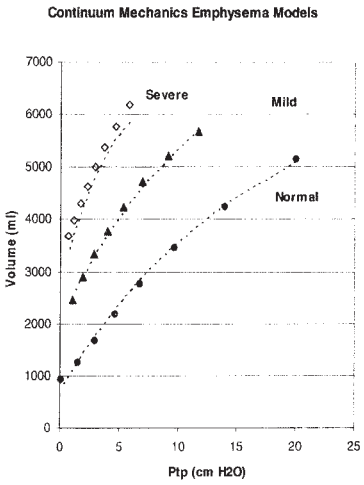
SIMULATING THE EFFECTS OF EMPHYSEMA ON TISSUE AND SURFACTANT RECOIL

To simulate emphysema, changes consistent with destruction of parenchyma were applied to the model. Specifically, a decrease in the number of fibers in the peripheral network (N), a decrease in the number of alveolar ducts (n), an increase in fiber length (L, and its corresponding unstressed length, L_o), and an increase in alveolar duct size (l, and its corresponding unstressed length, l_o) were incorporated. Changes were applied such that simulated lung volumes and surface area–to-volume (S/V) ratios representing the emphysema state matched corresponding values reported in the literature from computed tomography imaging and lung volume measurements in patients with mild and severe emphysema (16). Mild emphysema was represented by a 50% reduction in alveolar wall number and alveolar duct number. Severe emphysema was represented by a sixfold (83%) reduction in alveolar wall number and alveolar duct number. $\gamma(S)$ in emphysema was assumed to be the same as in the normal lung. The mechanical properties of the individual alveolar walls and alveolar ducts, as embodied in the constitutive expressions F(L) and F(l), were also assumed to be the same as in the normal lung. Changes in lung volume, S/V ratio, and recoil pressures were dictated solely by destruction of alveolar walls and loss of surface area. The predicted effects of these microstructural changes on lung recoil are summarized in Figure 2, which shows deflation quasi-static P–V curves from TLC to residual volume (RV). Simulated P–V results are consistent with those reported for patients with emphysema (6–9). The k, V_{max}, V_{min}, and V_{max}/V_{min} ratio increase and alveolar dimensions increase as tissue content is reduced, consistent with worsening emphysema.

Simulations indicate that as emphysema progresses, and alveolar dimensions and surface area-to-volume ratio change, tissue recoil and surface-tension recoil both change. This process is depicted in Figure 3 and in additional figures presented in the online supplement. Although these simulations suggest that most of the loss of recoil in mild emphysema is caused by a decrease in tissue elasticity, substantial decreases in surface-tension recoil also occur. In more severe disease, once sufficient tissue destruction has occurred to reduce S/V ratio below 50% of normal, decrements in surface-tension recoil begin to dominate quasi-static physiology. The assumptions on which these predictions are based, and the limitations of these assumptions, are described in detail in the online supplement.

CONCLUSIONS FROM CONTINUUM MECHANICS

Calculations performed using this continuum mechanics model demonstrate that lung tissue and surface tension contribute about equally to recoil in the normal lung, as indicated by experimental data. As emphysema develops, simulations suggest that tissue recoil decreases rapidly, such that, in mild emphysema,



Data fits to equation [1] are as follows:

	V_{max} (ml)	V_{min}(ml)	k	S/V $(ml)^{-1}$
Normal	6850	750	0.063	249
Mild	6900	1900	0.121	164
Severe	7050	3000	0.255	105

Figure 2. Simulated quasi-static P–V deflation curves for normal, mild, and severe emphysema showing recoil at a given lung volume over the volume range from total lung capacity to residual volume. Recoil pressures were determined using Equation 2. Values for model parameters were based on computed tomography image and physiology data taken from the literature (16). Details of the method used to solve Equation 2 for each experimental condition are summarized in the online supplement.

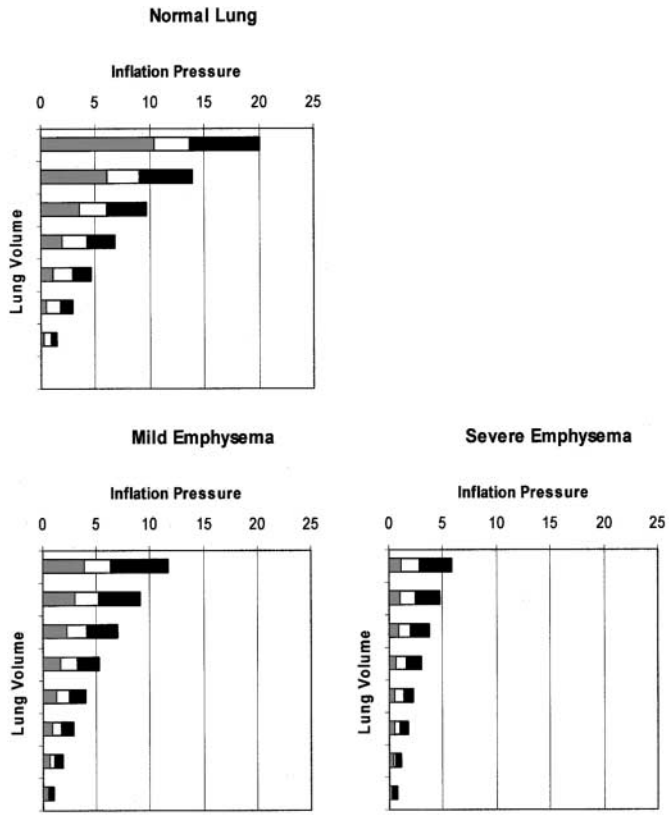


Figure 3. Tissue, alveolar surface tension, and alveolar duct components of recoil at baseline (*top left*), in mild emphysema (*bottom left*), and in severe emphysema (*right*). Simulated profiles represent quasi-static P–V deflation curves showing recoil at a given lung volume over the volume range from total lung capacity to residual volume. Values for model parameters were based on computed tomography image and physiology data taken from the literature. Details are summarized in the online supplement. (P_{tissue} = *gray bar*; P_{alv} = *open bar*; P_{ducts} = *black bar*.)

surface tension contributes substantially to recoil. In severe emphysema, modeling predicts that surface tension continues to play an essential role in determining overall recoil.

SURFACE TENSION, HETEROGENEITY, AND PARENCHYMAL INTERDEPENDENCE

The arguments presented previously are based entirely on calculations applying the principles of continuum mechanics, and the solutions are entirely deterministic. These calculations assume that the lung functions as a uniform mechanical structure and that alterations in lung structure and function that occur as emphysema develops are distributed homogeneously throughout the lung. However, this is not the case in advanced emphysema, where physiology can be dictated to a large extent by structural and functional heterogeneity.

To more accurately consider the effects of surface tension on structural heterogeneity, a network model of the lung was developed that incorporates both surface tension and tissue elasticity (3). A "chest wall" anchors the boundaries of the parenchymal network, and is assumed to be much stiffer than the tissues. Simulations of parenchymal microstructure were determined at steady state (i.e., equilibrium) by minimizing the total energy of the network, which includes an elastic energy contribution from the stretched tissues and a surface energy contribution from surface tension at the air–liquid interface. The individual cells of the network are hexagonal, and the geometry is considered in two rather than in three dimensions, similar to the network model originally proposed by Mead and coworkers (17). This network model does not consider alveolar duct mechanics or parenchymal interdependence in three dimensions but does provide useful insights into how alterations in surface tension could affect parenchymal microstructure in heterogeneous emphysema through parenchymal interdependence. The network model was specifically used to consider how both regional and global changes in surface tension influence structural heterogeneity and local force distributions throughout a heterogeneous region of lung parenchyma.

Simulations were performed in which alveolar size was varied in one half of the network to represent the airspace enlargement of emphysema but was maintained uniform in the other half to simulate a region of intact parenchyma. In the absence of surface tension (Figure 4A), an equilibrium is reached in which the damaged area appears markedly overexpanded, extending into the normal region. Raising surface tension uniformly throughout the network by a small amount (Figure 4B) simulates the effects of surface tension in the presence of native lung surfactant. Although the two networks do not appear substantially different, the mean force within the network (equivalent to P_{tp}) increased by 9%, and the variability in hexagonal cell size decreased by 27%. A further uniform increase in mean surface tension (Figure 4C) throughout the network produced a more dramatic effect, "volume reducing" the damaged area and causing a further reduction in the variability of hexagonal cell size. In going

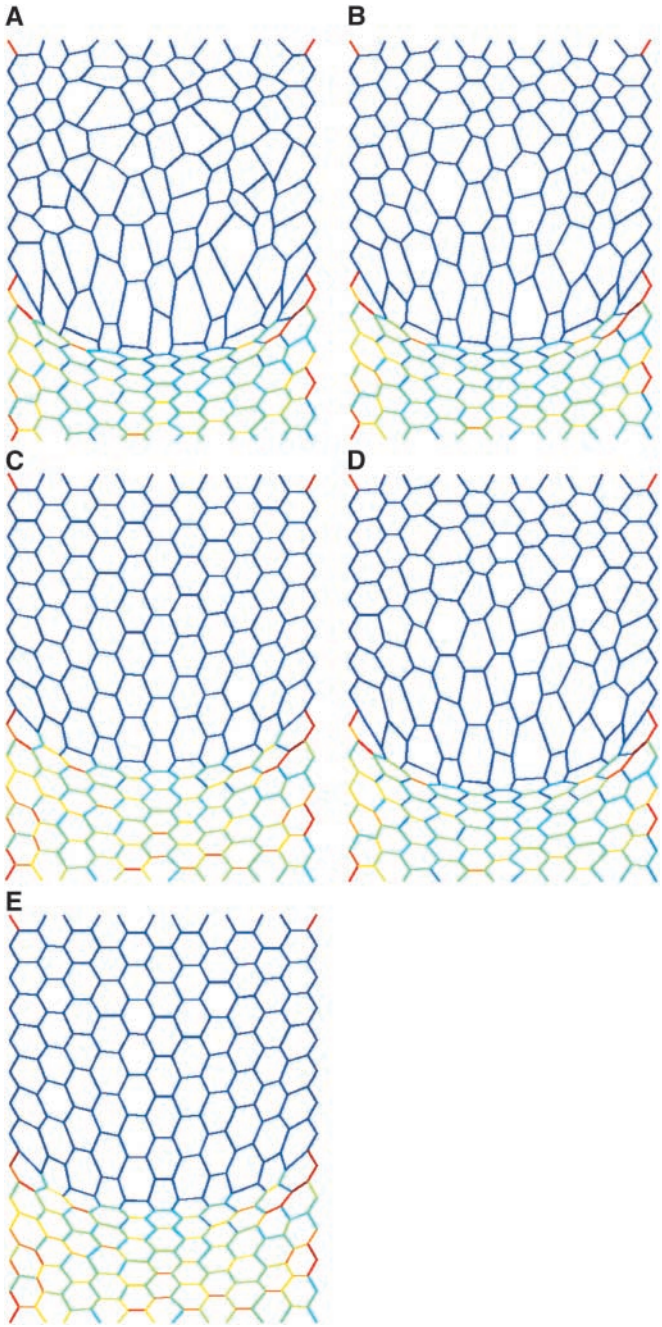


Figure 4. Network simulations showing the effects of surface tension in a heterogeneous network simulating a region of emphysema adjacent to a more normal region of lung parenchyma. (*A*) In the absence of surface tension, alveolar dimensions and alveolar wall tensions are determined solely by the elastic recoil properties of the alveolar wall tissue components. The damaged region (*upper region in blue*), intended to represent a region of emphysema, is overstretched as if hyperinflated, and impinges into the more normal regions of the network, which possess higher fiber elasticity. (*B*) The effect of increasing surface tension by a small amount uniformly throughout the network. Subtle changes in the shape of the individual cells of the damaged "emphysema" area are noted. Addition of surface tension is associated with a reduction in variability in hexagonal cell size and an increase in mean force, but a reduction in the distribution of tissue fiber forces within the network. (*C*) An even larger incremental, uniform increase in surface tension. Mean network force increases, and variability in hexagonal cell size decreases further. (*D*) The effect of increasing surface tension only in the lower normal area. A slight reduction in the size of this region and a corresponding small increase in the size of the upper emphysema region compared with zero surface tension are noted. (*E*) The effects of adding surface tension only to the upper emphysema region. Results are similar to those in *C*, where surface tension has been applied uniformly throughout the network.

from the Figure 4A to 4C simulation, mean force on the network elements increased 25%, but the maximum force experienced by any fiber within the network decreased by 40%, indicating that the addition of surface tension increased the mean value but decreased the variance of the distribution of forces within the network.

To assess the mechanical effects of nonuniform surface-tension distribution in a region of heterogeneous lung tissue, additional simulations were performed in which the effect of surface tension was added to either the normal region alone (Figure 4D) or the emphysema region alone (Figure 4E). Increasing surface tension only within the normal region of parenchyma increased recoil and reduced simulated volumes in this area only a small amount relative to conditions of zero surface tension. Increasing surface tension only in the damaged area produced a slightly greater reduction in the simulated volume of this region compared with that achieved with a uniform increase in surface tension throughout the network.

POTENTIAL IMPLICATIONS FOR FUTURE THERAPY

Results obtained from both continuum mechanics analysis and network modeling suggest that surface tension plays an important role in determining lung recoil in emphysema. Network modeling further suggests that addition of surface tension in an incremental fashion reduces heterogeneity in regions of simulated damage and increases overall recoil without increasing maximum fiber force. It is therefore theoretically possible that treatments that alter surface tension might be therapeutically beneficial for patients with advanced emphysema. During lung inflation, a surfactant monolayer that generates surface tensions more than natural lung surfactant would theoretically be desirable because it would increase recoil at the alveolar parenchymal and duct levels, directly reducing alveolar size at a given inflation pressure, producing volume reduction. On deflation, these films might tend to reduce gas trapping by decreasing the dynamic component of RV, RV′ (where $RV' = P_{tm'} \times C_L$, $P_{tm'}$ is the critical transmural closing pressure of the airways, and C_L is lung compliance) through a reduction in lung compliance (*see* online supplement). Increased surface tension may also increase the dimensions of the alveolar duct, reducing narrowing and increasing the effective stiffness of these small airways. Alveolar size heterogeneity should also decrease, resulting in an improvement in diffusing capacity by decreasing the mean diffusion distance for O_2 and CO_2 in damaged, oversized alveoli.

On the other hand, a haphazard increase in surface tension or selection of a surface-active material with undesirable biological effects could have dangerous consequences. To be safe and of potential therapeutic benefit in emphysema, treatments that alter surface tension must do so in a very specific manner, and surface-active material must distribute to the most damaged regions of lung. Surface tensions at low inflation pressures must approximate those of normal surfactant, and surface film compliance ($d\gamma/dS$) throughout the respiratory cycle must be positive, or alveolar

instability and collapse could occur (14). Pharmacokinetics would have to be such that a therapeutic level of agent could be achieved using a realistic dosing schedule. Lipid components selected would have to be noninflammatory and not promote development of lipoid pneumonia. Whether it is possible to accomplish these objectives using biocompatible, biodegradable, surface-active formulations remains to be determined.

MODEL LIMITATIONS

The arguments presented here suggest that surface tension may play an important role in dictating the physiology of emphysema, and that a better understanding of surface-tension effects could lead to new treatment strategies. However, because of the unavailability of experimental data, these arguments are based largely on modeling, and are far from conclusive. The continuum mechanics model fails to incorporate the effects of regional tissue heterogeneity or alveolar instability that could lead to collapse and adversely affect gas exchange. The network model, which does incorporate heterogeneity, does not consider nonlinear viscoelastic effects, tissue yield stress, alveolar collapse, or the details of chest wall–parenchymal interactions. In addition, little is known about surfactant properties in emphysema, and the assumption that lung surfactant in emphysema functions normally may not be entirely correct. To assess the importance of these different processes, additional modeling and experimental validation are needed.

CONCLUSIONS

This perspective suggests that, although altered tissue mechanics are central to the pathophysiology of emphysema, surface-tension effects, which are frequently overlooked in emphysema, are also quite important. Modeling results suggest that it may be possible to develop new treatments for emphysema that alter surface tension, increase recoil, and promote medical volume reduction, resulting in improved respiratory function. Although the results and discussion presented here are largely based on quasi-static theoretic models and can, at best, be interpreted qualitatively, the analysis is founded on established physiologic principles, and findings are consistent with available clinical data and previous experimental results. Future research characterizing the micromechanics of the emphysema lung with respect to both tissue and surface tension properties is therefore warranted. Insight gained from such studies could more clearly define whether designing new therapies that modulate lung surface tension can be useful in the treatment of emphysema.

Conflict of Interest Statement: E.P.I. is a scientist for Aeris Therapeutics of Woburn, MA, a biotechnology company that is evaluating new therapies for emphysema, and this company has filed a patent describing the use of novel surfactants for the treatment of emphysema; L.W.T. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript; A.M. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript; B.S. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript.

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