Commentaries on Viewpoint: Unresolved mysteries

CHANGE THE PERSPECTIVE!

TO THE EDITOR: Mysteries remain unresolved if the approach is misconceived. In this Viewpoint (3) alveoli are considered as structures sui generis—but they are not. Alveoli are rather air pockets within the ingenious architecture of a fiber continuum designed to expose capillary networks over a large surface to air refreshed from alveolar ducts (4). This fiber continuum spans from the peripheral fiber net in the pleura through the alveolar septa, where the fine fibers are interwoven with the capillary network, to the axial fiber network of alveolar entrance rings that forms the "wall" of the alveolar ducts (5). Alveoli pop open at the entrance rings when the fiber continuum is increasingly tensed upon inflation, a process governed by surface forces active at the air-tissue interface and modulated by surfactant (5). In—here disregarded—studies Bachofen et al. (1) have shown that the alveolar surface area increases steeply when deflated lungs are gradually inflated to TLC, thus confirming the observation of Hajari et al. (2). But that is not the end of the story: when these inflated lungs are deflated-inflated between 80% and 40% TLC (the breathing range in exercise) the surface area changes by a mere 20% for a factor 2 change of air volume (1). This is the result of surfactant-modulated surface forces that are effective as we breathe along the deflation limb of the pressure-volume curve (1, 5). The "mysteries" are resolved if we consider not alveoli but the micromechanics of the interaction between fiber tension and surface forces in "making alveoli."

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PREVENTING ARDS BY NORMALIZING ALVEOLAR MECHANICS

TO THE EDITOR: Understanding alveolar mechanics (i.e., the dynamic change in alveolar size and shape during ventilation) is critical to understanding the mechanisms of ventilator-induced lung injury (VILI), which plays a key role in the pathophysiology of the acute respiratory distress syndrome (ARDS). However, we still do not understand how the lung changes volume at the alveolar level in normal lungs, much less the alveolar mechanics of a lung with ARDS. The recent publication entitled "Unresolved mysteries" highlights our ignorance of dynamic alveolar physiology (4). In "Unresolved mysteries" multiple hypotheses of normal alveolar mechanics are discussed, without a clear consensus. Our work supports alveolar recruitment/derecruitment (R/D) (1) and changes in size of the alveolar duct (2) as mechanisms of normal lung volume change. In ARDS the alveolar mechanics shift to a pathologic form of R/D, probably due to a loss of surfactant function. This dramatic transformation in alveolar mechanics is a principal mechanism of VILI (5). In theory, if alveolar mechanics could be normalized with appropriate mechanical ventilation, the lung injury associated with ARDS would be prevented. Because alveolar volume change in the ARDS lung becomes pathologic R/D it might be possible to "stent" these alveoli open with a ventilator strategy featuring an extended time at peak inspiratory pressure. In a recent study we used our time-driven ventilation protocol, applied before lung injury, and prevented ARDS (3). This study highlights the importance of understanding the dynamic physiology of lung inflation at the alveolar level, because this knowledge can lead to improved patient care.

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VIEWPOINT RESPONSE TO UNRESOLVED MYSTERIES

TO THE EDITOR: Inconsistences between the studies of Hajari and Smaldone (3) result from differences in the interpretation of findings based on particle deposition and MRI measurements. The aerosol deposition analysis depends on the settling velocity of an even distribution of particles in the periphery of the lungs during a 6-s breath-hold to estimate Lm. Although this technique is unique, questions remain: *1*) K/Lm increased from ~0.25, during lung inflation, to ~0.6 then stayed constant during lung deflation before rising sharply to ~0.9 at low lung volumes. If the lung were reinflated, K/Lm would presumably decrease abruptly, while total lung volume remained nearly unchanged. One explanation is that the airways contribute significantly to particle deposition in the lung during lung inflation. *2*) In another study, when Lm of the air spaces in the lung's periphery was determined using a laser light scattering technique (1), Lm increased as lung volume increased and was larger during lung inflation than deflation. *3*) Gas trapping, resulting from liquid film formation, occurs normally in excised lungs (2). The films impede particle diffusion much more than respiratory gases (4). Methods

to reduce gas trapping were reported (4), but it is doubtful that film formation was completely eliminated. Another interpretation of the aerosol results is that alterations in deposition resulting from the formation and movement of liquid barriers in airways could account for the increase in K/Lm during lung inflation. As a result, aerosol deposition may not exclusively reflect changes in the geometry of peripheral lung structures.

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ACINAR BREATHING MOVEMENTS APPEAR TO BE IRREGULAR AND MAY INCLUDE A REDISTRIBUTION OF SURFACTANT

TO THE EDITOR: Breathing-induced structural changes of the lung parenchyma surely represent a scientifically and clinically important unsolved question (4).

Using 3-dimensional high-resolution datasets of the rat lung parenchyma we simulated breathing movements at subacinar level. We were able to show that the stretch of the alveolar septa appears to be irregular and included hot spots of high stretch (1). Unpublished data of our and other groups suggests that the structural changes are also irregular at the acinar level. Due to these irregularities, 3-dimensional high-resolution imaging methods are required to resolve the "unresolved mystery." Fortunately, first results based on these methods are gradually emerging and will contribute to answer the raised questions.

During lung development and growth, new alveoli form by the septation of existing air spaces. The newly formed septa start off as low ridges forming very shallow alveoli that are located in a former larger airspace [see figure 4 in (3)]. Most of them, but not all of them, will grow to full size septa/alveoli (2, 3). How may the postulated inflation induced recruitment of alveoli work? Most likely not following the above mentioned process. But the above described low ridges (alveolar septa) may be hidden by surfactant at a low inflation rate and exposed at a higher inflation rate of the lung because in the latter case the surfactant film has to covers a larger surface. On the basis of this speculation, alveolar recruitment would represent a redistribution of surfactant and not a sudden emerging of new alveolar septa.

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RESOLVING UNRESOLVED MYSTERIES: MORE AGREEMENT THAN DISAGREEMENT

TO THE EDITOR: In their Viewpoint article, Smaldone and Mitzner (4) hold that Hajari et al.'s results (3) are not in full agreement with their 1983 article, implying mean linear intercept goes down during inflation to TLC. It is challenging to compare these two results on equal footing, because the techniques, experiments, and assumptions are quite different: aerosol deposition measurements in ex vivo canine lungs in (4) vs. in vivo ^{3}He lung morphometry (5) measurements in humans (3). However, we are struck more by the amount of agreement between the results than the differences—in both works the largest contribution to lung volume expansion is recruitment of previously closed alveoli, which is also in agreement with Ref. 1. The major implication is that alveolar volume changes much less with lung inflation than expected from uniform microscopic expansion. Smaldone and Mitzner (4) take issue with specific aspects of the manuscript that we can address directly: the acinar airway model for the ^{3}He lung morphometry measurements is based on the highly regarded geometrical model of alveolar ducts from Weibel (2). The ^{3}He lung morphometry method (5) is rather straightforward, relying on two parameters only—average acinar airway radii and alveolar sleeve depth. It accounts for variability in acinar airways sizes reported in Ref. 2. Furthermore, this technique results have been well validated by morphometry (5). To study subtle details of lung microstructure, the ^{3}He lung morphometry method might need further tuning but it already offers a unique opportunity to study human and animal lungs in vivo, helping in resolving "unresolved mysteries."

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