Commentaries on Viewpoint: Use of mean airspace chord length to assess emphysema

MEAN AIRSPACE CHORD LENGTH IS USEFUL IN ASSESSING EMPHYSEMA

TO THE EDITOR: Although mean airspace chord length ($L_m$) lacks the elegance of some stereology methods and requires careful attention to technique (4), Mitzner (3) argues that $L_m$ has utility in studying experimental emphysema.

Clearly, $L_m$ reflects the dimensions of alveoli but is not a direct estimate of alveolar diameter or mean alveolar size. The functional significance of $L_m$ lies, however, in its inverse relationship to the surface-to-volume (S/V) ratio of pulmonary airspaces. The S/V ratio determines the density of elastic recoil forces resulting from surface tension, as well as the surface available for gas exchange per unit volume of ventilated lung (1, 2). These are important correlates of $L_m$ that are particularly relevant to understanding how emphysema affects lung function.

High correlation ($r^2 > 0.80$) has been found between $L_m$ and indexes of lung elasticity in excised non-diseased lungs of humans (1) and several animal species (2) and emphysematous human lungs (1). Fitting an exponential function, $V = A - Be^{K_P}$ (where $A$, $B$, and $K$ are constants), to static pressure-volume (P-V) curves over the upper half of lung volume allows estimation of the exponential constant $K$, which is inversely related to the bulk elastic modulus of the lungs (2). Thus $L_m$ is also inversely related to the bulk elastic modulus.

Whether $L_m$ is the optimal measure of the S/V ratio is debatable. The simplicity of its measurement using automated methods and its physiological correlates suggest that $L_m$ is useful in studying experimental emphysema, provided careful attention is given to preparation of specimens for counting.

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TO BE OR NOT TO BE—ACCURATE

TO THE EDITOR: The ATS and ERS have commissioned a Joint Task Force to define the “Standards for Quantitative Assessment of Lung Structure”; the author of this Viewpoint article (2) is a member of the Task Force. The Joint Task Force report, currently under review at ATS and ERS, contains a subchapter on the estimation of mean linear intercept length ($L_m$) discussing the methods of estimation and the pitfalls of this parameter. There are important pitfalls in using $L_m$ and the meaning of $L_m$ is often, if not mostly, misinterpreted. The most frequent misinterpretation is that $L_m$ measures “alveolar size,” which it does not: the intercepts extend from one intersection with the alveolar surface to the next, and often they traverse alveolar ducts between the two alveoli. So the best characterization of $L_m$ is that it estimates, under a defined inflation state, the mean free path within acinar air spaces, alveoli, and ducts taken together. The information value of $L_m$ as a parameter of structure is limited because $L_m$ is strongly affected by the inflation state at which the lung is fixed: in perfusion-fixed rabbit lungs $L_m$ is nearly twice as large at 80% TLC than at 40% TLC; the difference is larger than one would expect on the basis of the volume difference because lung expansion does not occur isometrically in all parts, with alveolar ducts varying more than alveoli (1). Therefore, to be meaningful, the relationship of $L_m$ to TLC should be defined for a given experimental model, which is often not done.

The author asks: “If $L_m$ is indeed so bad that it should be discarded, then what can researchers use to quantify the pathology?” The answer is that better alternatives are available. The sine qua non of emphysema is destruction of alveolar walls with loss of alveolar tissue and surface area, which impairs alveolar gas exchange and distal airway function. Airspace enlargement and increased lung compliance occur secondary to the loss of alveolar tissue, but are not in themselves primary determinants of functional impairment.

The most direct structural measurement under light microscopy that targets the primary defect in emphysema is total alveolar surface area (SA). In the first morphometric studies of normal and emphysematous lungs (5–7), $L_m$ was used as a tool to derive the internal lung surface area and not as a primary structural characteristic. But the estimate of SA no longer needs to take this detour, because more robust techniques have evolved that obviate the need for estimating SA via $L_m$. The correlate to $L_m$, the surface area-to-lung volume ratio (SA/VL), can be easily and accurately quantified by standard intersection counting, and used to estimate absolute SA when VL is known, a very efficient and unbiased technique based on sound stereological principles (4, 8). A decline in absolute SA indicates functional parenchyma loss regardless of airspace size or shape or lung compliance. If targeting the alveoli, the unbiased parameters are total alveolar number (obtained by counting the number of alveolar openings using the disector technique) together with estimates of mean alveolar size and their variation (obtained by point counting and point-sampled intercepts, respectively; Ref. 4).

Two statements on sampling strategies need discussion. 1) “Without using proper uniform sampling procedures, selecting as few as 100 alveolar chords for measurement…may introduce substantial bias into the $L_m$ measurement…a safer approach would be to sample every alveolus in each of the sections, with a total number of chords per lung in the range of 10–15,000 (11).” 2) “If one effectively samples all the alveoli in a particular section, any possible selection bias in that section is thereby eliminated.”

These statements confuse precision (reproducibility) with accuracy (unbiasedness). Bias refers to systematic errors that cause the data to be inaccurate; inaccurate data cannot be saved by more measurements. Even in mouse lung, a few selected
microscopic sections represent such a minuscule fraction of total lung structure that variability among lung regions and among experimental animals overwhelms the variability within any section, or between test lines along which intercepts are measured. Indeed, Fig. 4 of Ref. 3, which was used by the author to support his statements, proves that it is senseless to measure intercepts on a high-density set of test lines because the variation in $L_m$ among sections is $\sim 50$ times greater than the variation among a few lines and all possible lines generated by digitizing the image.

The author finally recommends to “use low-power, high-resolution images to obtain relatively large numbers of chords,” an oxymoron that can easily be avoided by using sound stereologic principles and sampling strategies that allow measurements to be obtained at adequate resolution on a manageable number of sections.

In summary, using brute force to exhaustively measure a limited and flawed parameter ($L_m$) makes little sense, especially when more rigorous alternatives are readily available.

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PURISTS VERSUS PRAGMATISTS

TO THE EDITOR: Mitzner (2) provides us with a pragmatic counterpoint to the morphometric purists who worry that bias may render $L_m$ useless as a measure of the alveolar volume-to-surface area ratio (3). If, indeed, one’s goal is to determine accurate measures of lung geometric structure then the purists may well have cause to worry. However, Mitzner’s Viewpoint has merit because the utility of $L_m$ for many studies stems simply from its ability to detect whether lung structure is abnormal. Here what really matters is that $L_m$ can reliably separate normal parenchymal architecture from that which has been altered by disease, and so bias is irrelevant so long as $L_m$ is robust, sensitive, and reproducible. Of course, experimental conditions must be precisely controlled to achieve this, and actually I would favor registering lungs to transpulmonary pressure rather than volume as Mitzner insists. At a given inflation pressure, the airspaces in an emphysematous lung are more dilated than normal because there are fewer alveolar walls in parallel to bear transpulmonary stress. This further increases $L_m$ over that due to alveolar sparcity alone, so $L_m$ should be more sensitive to tissue damage when determined at a fixed pressure than at a fixed volume. I would also add that while Mitzner correctly asserts that distributions of $L_m$ are weighted by area rather than linear airspace dimension, it is a simple matter to obtain a distribution that is weighted by chord length by multiplying chord length frequency by chord length itself (1).

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ASSSESSMENT OF EMPHYSEMA BENEFITS FROM QUANTIFICATION OF HETEROGENEITY

TO THE EDITOR: We enjoyed Mitzner’s Viewpoint (2) on the use of mean airspace chord length ($L_m$) and agree that—provided the appropriate conditions are carefully met—$L_m$ gives an important proxy of the paramount functional impairment in emphysema: the reduction in parenchymal surface area. In addition, this measure benefits from the consideration of its distribution characteristics (variance, skewness, etc; 1, 4). This largely overcomes the concern that the cutting of a large alveolus near its periphery would give rise to a low chord length (5), as such events would be approximately random. In emphysema, where heterogeneity is a prominent feature, an increase in $L_m$ variance is, we believe, a sensitive and meaningful measurement (4).

Weibel et al.’s (5) recent reminder that extreme care in tissue preparation should be a precondition for the study of lung morphometry is well made. In this regard in vivo imaging may allow quantification of the spatially heterogeneous remodeling observed throughout an emphysematous lung. At the present time magnetic resonance (MR) imaging does not have a resolution adequate to estimate $L_m$ in small animals. However, quantitative 3D renderings to an isotropic resolution of <80 μm are currently possible (3), and technological developments promise further advances. Such measures are sensitive to lung tissue-volume changes, in even the smallest of murine lungs, and can be repeated in the same animal over the progression of age, disease, or treatment. MR, therefore, has the potential to provide knowledge (2) of heterogeneity and anisotropy in normal and pathologic lungs.

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Letter To The Editor

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PATTERN OF PARENCHYMAL DESTRUCTION DETERMINES LUNG FUNCTION DECLINE

TO THE EDITOR: In his letter, Prof. Mitzner (3) points out that using proper sampling procedures and knowledge of the reference volume, mean linear intercept (Lm) measurements can be used to estimate the loss of surface area of the lung, although questions about its sensitivity to quantify early changes in emphysema remain. Hsia et al. suggest more rigorous alternatives to quantify surface area. In this response, we would like to raise some issues not related to the technical aspects of how precisely the surface area can be measured. Instead, we will focus on what can and what cannot be learned from the knowledge of the total surface area, assuming it can be reasonably estimated. Specifically, we argue that knowledge of total surface area is only part of the link between structure and function during the progression of emphysema.

When an alveolar wall is enzymatically weakened, mechanical forces can break the alveolar wall (5). If such breaks occur at random locations within the parenchyma independently of each other, the process is called random destruction. However, the parenchyma is under a tensile prestress. Consequently, when an alveolar wall fails, the stress it carried before failure is distributed among the neighboring walls which will then experience an increased prestress and a higher probability to fail. In this case, failure of a wall can trigger further local failure of neighboring walls, a process called spatially correlated breakdown.

In a recent publication, Bates et al. (1) showed that spatially correlated breakdown has a significant impact on lung function decline. Spatially correlated destruction leads to a much faster decrease in tissue elasticity than a random destruction pattern. Thus, for the same decrease in total surface area, the loss of elastic recoil can be drastically different depending on whether the process of tissue breakdown is spatially correlated or not. Since the breaking process cannot be easily observed in vivo, how can the history of tissue breakdown be taken into account?

Due to mechanical interdependence in the alveolar structure (2), a correlated pattern of destruction would result in a few abnormally enlarged holes among many small ones whereas a random pattern would result in a comparatively less heterogeneous structure. Therefore, the size distribution of airspaces observed locally in emphysematous tissue contains information regarding the pattern of destruction that led to its present structure. The distribution of airspace sizes can be conveniently measured from 2D histological sections using a method we introduced recently (4). An even better characterization of the destruction process would require the direct measurement of the 3D size distribution of airspaces.

In conclusion, the loss of surface area and the resulting distribution of airspace sizes quantify two different aspects of structural changes in emphysema: how much tissue was destroyed and what was the pattern of destruction. While quantifying loss of surface area provides a rough estimate of the total destruction in emphysema, characterizing the spatial correlations in the destruction pattern is certainly key to unraveling the underlying mechanisms behind the progressive nature of this disease. By studying the problem from both angles, it may be possible to better understand the relationship among the mechanism of destruction, changes in structure, and loss of function in emphysema.

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WHAT DOES Lm TELL US ABOUT LUNG PATHOLOGY?

TO THE EDITOR: The Viewpoint article on the use of mean airspace chord length to assess emphysema (3) tries to purport the notion that “Lm is not that bad” as considered by others (5). Other than methodological issues discussed earlier in this journal, the major point is: what does Lm tell us about lung pathology?

As correctly emphasized by the author, Lm cannot be equated with alveolar diameter (3). Lm is not even a measure of alveolar size but can only be considered as a measure of mean free pathway within acinar airspaces, i.e. alveoli plus alveolar ducts (5). Hence, Lm is at best a structural correlate to diffusion rates measured by functional MRI (6). Lm is linked to alveolar surface area (Sa = 4V/Lm). However, the term V is not total lung volume as stated by the author (3), but total volume of lung parenchyma (excluding major airways and blood vessels; Ref. 4), which is solely but easily obtained by stereology (2). Thus Lm (alone or in conjunction with total lung volume) does not allow drawing a reliable conclusion about loss of alveolar walls or change in alveolar size, the key criteria of emphysema.

“What can researchers use to quantify the pathology?” (3): various stereological tools are available, e.g., number- and volume-weighted mean alveolar volume to quantify alveolar size (1), point/intersection and dissector counting to determine alveolar surface area, and alveolar numbers (5). Using appropriate parameters and methods is a matter of scientific accuracy, not of pragmatism or purism.

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MEAN AIRSPACE CHORD LENGTH AND HYPERPOLARIZED GAS MAGNETIC-RESONANCE MEASUREMENTS

to the Editor: With ADC (apparent diffusion coefficient) magnetic-resonance measurements using hyperpolarized helium-3 and xenon-129 gases, one can effectively obtain microstructural information on the in vivo airspaces as a whole (2). Such measurements can be repeated in the same animal over multiple time points and without side effects. Histology measurements performed with the mean airspace chord length ($L_m$) technique (1) in normal animals and emphysema disease models showed good correlations ($r = 0.78$) with ADC (2), as mentioned by Mitzner (3). Although better results may have been achieved with stereology (4), the $L_m$ showed the ability to clearly differentiate and quantify the differences from normal to emphysema in a simple way and without adding substantial time or costs. $L_m$ may not be the perfect tool, but it is a useful technique in assessing emphysema.

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