Morphometric Study of Emphysema: An Hypothesis on the Evolution of the Anatomic Damage of the Disease

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ABSTRACT

Mathematical analysis of morphometric studies on the destruction of pulmonary tissue in cases of centrilobular emphysema has been used to identify degrees and localization of structural damage. From the data, an hypothesis of sequential, cumulative, individual destructive events has been developed to explain the distributive and progressive parenchymal changes in the lungs.

Centrilobular emphysema has been studied extensively, and the early development of destruction of the pulmonary alveolar parenchyma in relation to the terminal branches of the bronchiolar tree has been implicated as the earliest of the events which lead to extensive debilitating pulmonary disease. Despite recognition of many of the morphologic changes which characterize the progressive disease, correlation of the structural damage and the physiological decrement associated with the process have not been particularly successful. Patients who have been carefully followed with pulmonary function studies seem to have only the most grossly correlated morphologic pulmonary changes.3,4,11,12,14,15

During a study of patients dying with emphysema, and in an effort to define anatomic parameters which are better related to the functional deficits defined during the development of their disease, a postmortem morphometric study and mathematical analysis of lung tissue loss has yielded data which has permitted us to offer a hypothesis. Progressive emphysematous damage can be explained by a series of individual damaging events, the results of which are cumulative in areas of maximum tissue loss. In addition, by evaluating all areas of the emphysematous lung, evidence can be adduced which indicates that the individual destructive events can be identified in areas of minor damage in the presence of major lung pathology elsewhere. This suggests that the distribution of the agent(s) of the destruction is not uniform in the lung, nor do sequential episodes of damage occur in the same distributive pattern each time.

Materials and Methods

Whole lung sections of inflated, infused lungs were prepared under standardized conditions by the method of Weiss and
Sections were made in the coronal plane at the level of the vascular hilum, thereby providing a sample of the entire lung from apex to base. Lung sections from 20 cases of centrilobular emphysema were studied by intercept analysis. A grid divided into one millimeter intervals was placed over the slide of the whole lung preparation and the number of alveolar wall intercepts per centimeter were counted in each slide. The data were recorded both for the whole lung sections and as it reflected areas of the lung. The areas were selected by dividing the lung arbitrarily into upper, middle and lower thirds. All bronchial and vascular intercepts were ignored in this analysis.

Reference data were obtained by (1) employing the same intercept analysis in lungs which were morphologically normal by inspection and (2) analyzing those areas in abnormal lungs which were normal to inspection to provide an internal reference standard. Although such “eyeball” evaluation is subject to observer bias, comparisons of the results of analysis of areas selected as “normal” in diseased lungs were surprisingly uniform, and compared well with studies of normal lungs.

All lungs studied were from patients over the age of 16. Lungs containing areas of pneumonia, malignancy or the effects of left-sided cardiac failure were eliminated from this study.

Each study was repeated by two independent observers. Although there was a minor degree of variance in interobserver data collection, analysis of the independent studies showed the maximum variation in any one case to be less than 5 percent. The data presented are single observer results, rather than averages of the two independent studies.

Five of the cases studied are presented as typical and representative of the entire group studied.

**Results**

Examples of the frequency distributions of intercepts per centimeter are presented for a normal lung (figure 1), a normal but hyperinflated lung (figure 2), three emphysematous lungs in which the data for an entire lung section is represented as a single plot (figures 3, 4 and 5) and one emphysematous lung in which the data is recorded both for the entire section and by region (figure 6). On each plot, the area of the lung visually identified as normal is noted by that portion of the horizontal axis labeled “n”. For each plot, the total number of centimeters studied (n), the mean of intercepts per centimeter (x), standard deviation and coefficient of variation are presented.

**Normal and Normal Hyperinflated Lungs**

The plots of both normal and normal hyperinflated lung sections show a Gaussian distribution of the frequency of intercepts. The normal lung is presented with a foreshortened x-axis to emphasize the very close relationship between what was visually identified as normal lung and the very narrow range of measurements which fell outside the normal curve. Furthermore, the high, peaked, narrow curve expresses the uniformity of pulmonary alveolar structure under normal conditions.

The hyperinflated lung had almost no tissue which could be considered to be normal. The increase in lung inflation resulted in a shift of the intercept frequency toward the lower end of the scale, indicating the greater expanse of space between alveolar walls. That the shift was not uniform can be seen by the widening of the frequency curve, indicating that expansion was greater in some areas than in others. Nevertheless, simple pressure-induced pulmonary hyperexpansion does not cause rupturing of the alveolar walls under the conditions of preparation;
hence, the frequency curve remains in an approximately Gaussian plot which is slightly skewed to the right. The skewness of the plot represents the presence of less efficiently expanded portions of the lung.

**EMPHYSEMATOUS LUNGS, SINGLE PLOT**

Intercept frequency plots of whole lung sections from three cases of centrilobular emphysema are presented in figures 3, 4 and 5. All of the plots show an irregular distribution of intercept frequencies representing the varying degrees of tissue destruction in the lungs. Each lung also contains an area which could visually be described as normal, the plot of which can be compared with the remainder of the lung plot. An analysis of these plots was undertaken to attempt to describe them in terms of a uniform mathematical or statistical statement by testing the data with a large number of theoretical formulations. The only model which produced a successful fit with the observed curves assumes that the areas under the curves are a series of normal Gaussian curves which overlap and are superimposed upon one another.

Biologically, such a model can be explained by a sequence of discrete destructive events of varying magnitude which (1) are not uniformly distributed in the lung and (2) have cumulative destructive effects on the alveolar walls when a series of individual insults occur in the same site. Furthermore, the model can accommodate both an irregular distribution of each discrete event and varying distributions of any series of events.

**EMPHYSEMATOUS LUNG (MIXED CENTRILOBULAR AND PANLOBULAR); MULTIPLE PLOTS BY REGION**

The emphysematous lung analysis presented in figure 6 contains four intercept frequency curves. Curve A is similar
to the curves presented in the preceding figures and is an overall representation of the entire lung structure. Curves B1, B2 and B3 are curves of the data obtained from the upper, middle and lower lung fields, respectively. Since the n number for each of the lung fields is the same as the n number for the whole lung, the three regions are much more representative of the differences among them than can be seen in the overall curve.

The interpretation of the findings is that the upper lung field is relatively nonemphysematous since the frequency below the normal range is very low, but the presence of a significant intercept frequency above the normal range establishes the presence of atelectasis. The curves for the middle and lower lung fields are characteristic of the emphysematous process, being shifted to the left with multiple discrete peaks. By examining such separate lung areas, the multiple Gaussian types of distribution of alveolar wall damages become more obvious, whereas there is a strong tendency for the superimposed curves to become submerged in the total lung analysis. The reasons for this include superimposition of data and a smaller number of observations made on the overall sample than on the total of the separate parts. The plot of this case emphasizes the need for enough measurements of appropriately selected samples of pulmonary tissue in order to establish an adequate basis for interpretation.

Discussion

Morphometric studies of human lungs with centrilobular emphysema have repeatedly produced reasonably refined data concerning the extent and severity of the destruction of pulmonary alveolar tissue. The failure of an accurate fit of morphologic and physiologic data in such cases is due to the complex relationship of ventilation (V) and vascular perfusion (Q) and the homeostatic mechanisms which are designed to keep them at equality even under abnormal circumstances. In emphysema, the loss of the alveolar diffusing membrane reduces perfusion by destruction of the alveolar capillaries as part of the membrane loss.

Compensation for the reduction in vascular perfusion is produced by reduction in local ventilation. This rebalancing system is maintained until the capacity of the compensatory system is exceeded by the degree of damage. As long as some degree of compensation is effective, the measurable amount of destruction will exceed the degree of functional embarrassment as measured by the blood gases. As compensation fails, the local physiological parameters of functional decrement will reflect the morphologic loss more closely. However, measurements of the function of the entire diseased lung, either by ventilatory measurements or by blood-gas analyses, reflect varying degrees of compensation and compensation failure in many pulmonary lobules and segments simultaneously. Under these conditions, physiologic and morphologic evaluations can be expected to be different.
The morphometric studies reported are subject to the same interpretive problems. By using a finer grid (1 mm) than usual, more accurate data have been accumulated regarding the degree of pulmonary wall damage; however, the overall problem of physiological correlation is unchanged.

Analyses of the intercept frequencies of the lungs under study do serve to clarify a few functional relationships. All portions of the plotted complex data curves which appear below the normal range, representing wider spaces between alveolar walls, are semi-quantitative expressions of alveolar wall destruction, including loss of alveolar vasculature. In areas of maximal damage (lowest intercept frequencies), perfusion can be considered to be nil. Ventilation characteristics are undetermined in this analysis, so it is not known if we are dealing with totally unventilated dead space or segments of partially ventilated, nonperfused lung. Only the latter would contribute to a gas exchange deficiency.

On the other hand, all portions of the curves which appear above the normal range, representing areas of the lung in which alveolar walls are closely apposed to one another, are expressions of degrees of atelectasis. In the more severe atelectatic areas, ventilation can be assumed to be negligible, while perfusion continues at a low rate. In this type of area, it can be assumed that there exists a V/Q inequality contributing to the total gas exchange embarrassment.

In addition, any significant reduction in the height of the Gaussian curve segment representative of normal lung tissue is a reflection of disturbed lung structure which is directly related to abnormal function, both compensated and uncompensated.

With respect to other conclusions which can be adduced from the data, the interpretation of the complex curves produced from the cases of emphysema as a series of normal distribution curves, superimposed at random upon one another, provided the basis for a biological interpretation. A single tissue destructive event of any magnitude will reduce the curve representing the normal tissue and produce a graphic representation of the destruction at a lower intercept frequency. If the tissue destruction were uniform in magnitude, producing a tissue population of equally separated alveolar walls, the new tissue morphology would be described by a single narrow peak. Any variance from uniform tissue damage would produce either a wider curve or a discontinuous curve. The curve analyses in the cases studied by the present authors are all interpretable as representing curves of normal distribution, each of varying width. Under usual statistical circumstances, such curves could be defined by their individual standard deviations; however, under the circumstances of complex superimposition of curves and the relative crudity of the data, such definition would be deceptive.

Accepting our interpretation that the plotted data have produced a series of normal curves, the biological interpretation follows that a series of independent destructive events of varying magnitude caused the alveolar tissue destruction. Since the curves are randomly superimposed on one another, it also follows that the distribution of the individual destructive episodes in the lungs were not the same each time. It can be concluded that the morphometric analysis provides a preliminary insight into the kind of disorder under study, a destructive disorder with a definable magnitude of each destructive event and with a random distribution in the organ. The data do not support the concept that previous destruction in one lung area predicts for continued damage in that same area.
Agents which may damage lung tissue in the manner assumed from the morphology include irritant gases and dusts, infectious agents, both bacterial and viral, particulate material in an irritant form and the proteolytic enzymes of inflammatory cells.

In the environment in which cases of centrilobular emphysema are found and flourish, it is highly unlikely that any one of the proposed agents is exclusively responsible for the multiple events leading to respiratory distress. The evidence for multiple events, discontinuous in time and variable in both magnitude and distribution, and the evidence cited in the literature for multiple agencies of lung damage are mutually supportive concepts which can form a testable hypothesis for the evolution of centrilobular emphysema.

References