The Distinction Between Lung Maturation and Limited Injury in Human Airways: Functional and Morphometric Studies in Postmortem Examination of Lungs*

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 Morphologic alterations occur in the maturing and aging lung. These morphologic alterations are reflected in functional changes which, in the case of the aging lung, are qualitatively similar to those observed in advanced chronic obstructive pulmonary disease (COPD). Any study which attempts to evaluate the morphologic and functional changes of COPD must differentiate that part contributed by disease from that contributed by normal maturation and aging. In this report we attempt to characterize some of the functional and morphologic alterations in the airways of human nondiseased lungs over a wide age range as a basis for understanding additional changes which may be produced by disease, particularly those in early COPD.

Studies of mechanics and morphometry were performed in postmortem examination of human lungs. Left lungs are obtained from male victims of sudden non-hospital death on whom autopsies were performed in the coroner’s office. Usual causes of death include traffic accidents, myocardial infarction and exsanguinating gunshot wounds. Stringent criteria are used in selecting the lungs. Lungs heavier than 450 gm are not accepted because they usually have microscopic evidence of edema. Similarly, lungs with hemorrhage, large pleural rents or excessive bronchial secretions are not used. Mechanics are studied immediately after obtaining the lung, and in all cases are completed within 24 hours of the person’s death.

The lung is suspended by a bronchial cannula in a glass plethysmograph. Measurements of lung mechanics include static elastic recoil pressures, total pulmonary resistance by the method of Mead and Whittenberger, dynamic compliance and flow volume plots from passive and forced deflations. Barium sulfate is then insufflated into the bronchial tree and the mean diameter of all segmented bronchi is determined from the bronchogram. This value is considered a relative measure of the size of the central airways. The lung is inflated and fixed in formalin at 25-cm water pressure. Lung slices are carefully examined, and the amount of emphysema, if present, is determined by point count. Random histologic sections are obtained from which the number and mean diameter of all membranous bronchioles of less than 2 mm in diameter are determined. Mucous plugs in the peripheral airways are evaluated by quantitatively determining the proportion of bronchiolar lumen occupied by mucus on histologic section. Approximately 50 bronchioles are evaluated in each lung. The proportion of bronchial mucous gland is quantitatively determined from sections of lobar bronchi.

The results reported are from the first 26 lungs studied. The age of the donors ranges from 10-82 years. Mild emphysema, less than 10 percent by gross point count, is present in five lungs. The population studied can be considered a reasonable cross section of an urban population, consisting of persons with normal and mildly diseased lungs.

The relationship between the flow resistive properties of the lungs and measurements of airway caliber at different levels of the bronchial tree can be summarized as follows: A statistically significant (p<0.05) but weak correlation (R = 0.39) is found between mean segment diameter and the reciprocal of pulmonary resistance, conductance. In contrast, a very close correlation (R = 0.90) is found between mean bronchial diameter and pulmonary conductance. This suggests that mean bronchiole diameter is the main determinant of variations in pulmonary conductance in normal and mildly diseased human lungs. The determination of pulmonary conductance, or resistance, is more sensitive than either maximal expiratory flow rates or dynamic compliance in detecting bronchiolar narrowing.

Bronchial mucous gland hyperplasia is one of the pathologic abnormalities described in chronic bronchitis. When mucous glands occupy 15 percent or more of the bronchial wall, they are considered hyperplastic. The percentage of mucous glands in the bronchial wall exceeded this value in 6 of the 26 lungs studied (range 18.1 to 24.1 percent). Functional parameters are not significantly different in this group as compared to the other lungs studied. Emphysema or bronchiolar narrowing is not present in these six lungs, and the amount of mucus in the lumens of the peripheral airways is not increased. No age-related changes are seen in the percentage of bronchial mucous glands in this study. The bronchial mucous gland hyperplasia is not related to any functional abnormalities in this study and is not associated with other pathologic changes commonly found with COPD.

The size of the central airways, as reflected by the mean segmental bronchial diameter does not change significantly beyond the age of 20 years (Fig 1). In contrast, highly significant age-related changes occur in the mean diameter of the membranous bronchioles (Fig 2). Maximal bronchiole diameter is not reached until well into the third decade of life, with a variable decrease thereafter. Matsuba and Thurlbeck, using nearly iden-
tical methods in a study of 20 nonemphysematous lungs, reported no age-related changes in bronchiole diameter. Possibly they studied relatively few lungs from the younger age group. When their data are evaluated with the data from this study, the results are quite compatible and our original conclusions remain the same. That is, mean bronchiole diameter increases through the third decade of life; thereafter it decreases at a variable but highly significant rate. This previously unreported finding may have important implications in concepts of the pathogenesis of COPD. To what extent bronchiolar narrowing in the older lungs is related to injury or to normal aging is not clear at this point. The lungs in this study were obtained from an urban population, and complete smoking and occupational histories are not yet available. It is possible that the observed bronchiolar narrowing is due entirely to exogenous injury. However, mean bronchiole diameter in the five lungs with mild emphysema is not significantly different from age-matched nonemphysematous lungs. The usual signs of tissue injury, such as inflammation and fibrosis, are inconsistent in the narrowed bronchioles of the older lungs. The subtle decrease in diameter can only be appreciated by measurement. Furthermore, in experimental animals it is extremely difficult to induce significant bronchiolar stenosis despite prolonged exposure to high concentrations of a toxic gas such as nitrogen dioxide. These findings in experimental animals, in addition to our observations in human lungs in which many narrowed bronchioles are present without pathologic evidence of injury and repair, suggest to us that the decrease in diameter is in part related to variation in development or aging.

Bronchiolar narrowing and a consequent increase in pulmonary resistance may be caused by at least three different mechanisms. First, the lumen of the membranous bronchiole may be partially occluded by pathologic processes including inflammation, fibrosis, or mucous plugging. Secondly, bronchiole diameter is dependent on radial traction supplied by surrounding lung parenchyma. Therefore, diminished lung elasticity which occurs in the aging and in the emphysematous lung may cause a decrease in bronchiole diameter at lung values at which breathing occurs in vivo. The present study also suggests a third mechanism. Since our bronchiolar measurements are made from sections of lung fixed at a constant 25-cm water pressure, the observed decrease in bronchiole diameter in the maturing lungs and in many of the aging lungs indicates that these airways are intrinsically less compliant. This suggests that there are continuing subtle changes in the tissues of these bronchiolar walls which contribute to the observed decrease in lumenal caliber.

REFERENCES

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DISCUSSION

Dr. Thurlbeck: At what volume did you measure airway
diameters?
Dr. Niewoehner: Measurements are made from histologic sections of formalin-inflated and fixed lungs. All measurements are corrected to the air volume of the lung at a transpulmonary pressure of 25 cm H2O pressure.
Dr. Ishikawa: How do you measure dynamic compliance in dead lungs? It must be extremely difficult.
Dr. Niewoehner: The lung is suspended in a flow displace-
ment plethysmograph. It is inflated and deflated with a sinusoidal pump attached to the airway opening while measuring transpulmonary pressure and volume changes in the plethysmograph.