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Research Article

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Peripheral Airways as a Determinant of Ventilatory Function in the Human Lung

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ABSTRACT We have investigated the morphological differences responsible for the variability in two tests of pulmonary function, maximal expiratory flow rates (MEF) and the frequency dependence of dynamic compliance (CDYN ratio). Functional measurements were obtained from 53 normal and minimally diseased postmortem human lungs. Morphological measurements performed on these same lungs included airway diameter at three levels in the bronchial tree, the amount of bronchial gland mass, and the alveolar surface to volume ratio. Multiple regression analysis suggests that the diameter of the peripheral conducting airways (membranous bronchioles) is the major morphological determinant for both MEF and the CDYN ratio in lungs at any particular age. Age-dependent changes in both functional tests were associated primarily with differences in the alveolar surface to volume ratio. Minimal emphysema and a lesion associated with cigarette smoking, respiratory bronchiolitis, have no demonstrable effect on either MEF or the CDYN ratio. These studies provide further evidence that the peripheral conducting airways are a major determinant of ventilatory function in the normal human lung.

INTRODUCTION

The measurement of airflow rates during forced expiration is the standard test of ventilatory function in most clinical pulmonary laboratories. Normal population standards for spirometry and, more recently, for the maximal expiratory flow-volume (MEFV)[1] curve have been established in numerous studies (1–8). A large coefficient of variation for maximal expiratory flow (MEF) is observed in normal adult subjects even when standardized for individual differences in sex, age, and height. Efforts to relate this variability to other anthropometrical and physiological factors have been largely unsuccessful. Structural differences within the lung which might contribute to the variability in MEF have not been identified.

A practical consequence of the variability in MEF, and for the variability in other tests of ventilatory function as well, is that it severely limits their diagnostic usefulness. This problem has become more important in recent years because of the interest in detecting and studying earlier stages of chronic airways obstruction. An understanding of the morphological basis for this normal variability would aid in the clinical interpretation of these tests and might provide insights into the pathophysiology and pathogenesis of disease states.

We have previously reported that consistent and reproducible tests of lung mechanics can be performed in carefully selected postmortem human lungs. Additionally, measurements of total pulmonary resistance and lung elasticity have been related to specific morphological measurements (9, 10). The present study investigates, in a group of normal and minimally diseased human lungs, the morphological basis for the

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[1] *Abbreviations used in this paper*: ASVR, alveolar surface to parenchymal lung volume ratio; BGM, bronchial gland mass; CAD, central airways diameter; CDYN, frequency dependence of dynamic compliance; IAD, intermediate airway diameter; MEF, maximal expiratory flow; MEF_{60}, maximal expiratory flow at 60% total lung capacity; MEFV, maximal expiratory flow volume; PAD, peripheral airways diameter; TLC, total lung capacity.

variability of MEF and, in another test of lung function, the frequency dependence of dynamic compliance (CDYN).

METHODS

Source of material

The lungs used in this study were obtained at autopsy from persons who died suddenly outside hospitals. Lungs with excessive bronchial secretions, large pleural rents, and parenchymal hemorrhage were excluded. Also, lungs weighing more than 450 g were not used because they often have histological evidence of edema. This study includes the results from 53 left lungs from men 15–85 yr of age that were obtained consecutively from the same source.

Functional studies

The tests of mechanical functions performed on the postmortem lungs have been partly described in previous reports (9, 10). Functional studies were performed within 2–3 h of the autopsy and in all cases were completed within 24 h after death. The left lung was separated at the carina and a metal cannula was securely tied into the main stem bronchus. Small pleural leaks were identified by water immersion and then ligated. After six to eight inflation-deflation cycles, the lung was suspended by the bronchial cannula in a glass plethysmograph.

CDYN. The lung was inflated twice to a transpulmonary pressure of 25 cm H_2O and then deflated to a volume midway between maximum and minimum volume. The lung was then cycled at different frequencies by a Harvard pump (Harvard Apparatus Co., Inc., Millis, Mass.) attached to the airway opening. Tidal volume was held constant at approximately 300 cm^3 at all frequencies. Flow between the plethysmograph and the atmosphere was measured by a pneumotachometer attached to a separate port. The differential pressure across the pneumotachometer was amplified to obtain the flow signal, and electronically integrated to obtain volume change. Transpulmonary pressure was measured as the difference between pressure in the plethysmograph and the intrabronchial pressure at the airway opening. Flow, volume, and pressure signals were recorded against time on light-sensitive paper. Tubing lengths had been previously adjusted to eliminate any phase shifts between the transducers over the frequency range in which measurements were made. CDYN was calculated as the ratio of volume change to pressure change at points of zero flow. The ratio of CDYN at 1.50 Hz to CDYN at 0.15 Hz is subsequently referred to simply as the CDYN ratio.

MEF. Expiratory flow-volume curves were measured during forced deflations. The lung was slowly inflated to a transpulmonary pressure of 25 cm H_2O and was then forcibly deflated by manually venting the airway opening to an average pressure of 50 cm H_2O negative to the atmosphere. Flow into the plethysmograph was measured by the pneumotachometer and volume change was obtained by integrating the flow signal. The negative pressure was generated by evacuating a steel drum with a blower at very high flow rates. This reservoir was connected to the airway opening and negative pressure within this system was adjusted to the desired level by a simple valving device. Pressure variation at the airway opening during the expiratory maneuver was never greater than 5 cm H_2O.

Comparison of results among different postmortem lungs and to results in live subjects requires reference to some standard lung volume. MEF is expressed in this study as the instantaneous flow rate at different percentages of total lung capacity (TLC). TLC refers to the estimated TLC of each postmortem lung that existed during life. The method for estimating this volume and the rational for its use have been described in detail previously (10). Lungs were not inflated beyond static pressures of 25 cm H_2O, and forced deflations were initiated at that pressure. Maximal elastic recoil pressure at 100% TLC in live subjects may be considerably greater than 25 cm H_2O, particularly in younger people (11). The TLC during life was estimated by extrapolating the static pressure-volume curve of the excised lung to the pressure predicted at TLC for a live person at that age. The estimated TLC may be as much as 10% larger than lung volume at 25 cm H_2O in younger lungs, but the differences are small in older lungs.

The use of TLC as the reference volume, as opposed to the forced vital capacity, has some theoretical advantages in live subjects (12). A more practical advantage in the case of the excised lungs is that this method requires no estimate of residual volume. Whereas the minimum volume of air measured for the postmortem lung in these studies correlates reasonably well with predicted residual volume of the intact lung, uncertainties associated with the estimate of a second reference volume are avoided by expressing MEF as a function of TLC.

Morphological studies

BRONCHOGRAPHIC MEASUREMENTS. Barium sulfate dust was insufflated into the bronchial tree after completing the functional studies. Stereoscopic roentgenograms were taken with the lung inflated to a transpulmonary pressure of 25 cm H_2O. The bronchograms from the 53 lungs studied were coded and randomized. Two sets of measurements were made for each lung and all measurements were corrected for magnification error.

(*a*) *Diameter of the segmental bronchi.* The transverse diameter of each segmental bronchus (except that the lingular bronchus was used rather than its daughter branches) was measured 0.5 cm beyond its bifurcation. The mean of these seven measurements is referred to subsequently as central airways diameter (CAD).

(*b*) *Diameter of intermediate-sized airways.* The branching patterns in the bronchial tree become progressively less predictable beyond the segmental bronchi. It is impossible, for comparative purposes, to identify the same generation in different lungs beyond the most central airways. Thus, an alternate method was used to identify comparable sites of intermediate-sized airways in different lungs. The major axial pathway of each segment was identified. A point midway between the origin of the segmental bronchus and the pleural surface was determined and the transverse diameter of the airway was measured at that point. The mean of eight such measurements is termed intermediate airway diameter (IAD). These airways were usually 2.5–4.0 mm in diameter and corresponded approximately to generations five and six of the Weibel model (13).

Both sets of measurements were repeated once on all bronchograms to assess reproducibility. The correlation coefficients between measurements are 0.96 for CAD and 0.94 for IAD.

HISTOLOGICAL MEASUREMENTS. Lungs were inflated and fixed in 20% buffered formalin for 48 h. They were cut into 1-cm parasagittal slices and the cut surface was carefully examined for pathological changes. Emphysema, if present, was quantitated by point count. Multiple, random sections were taken using a 2.0 × 2.5-mm metal template.

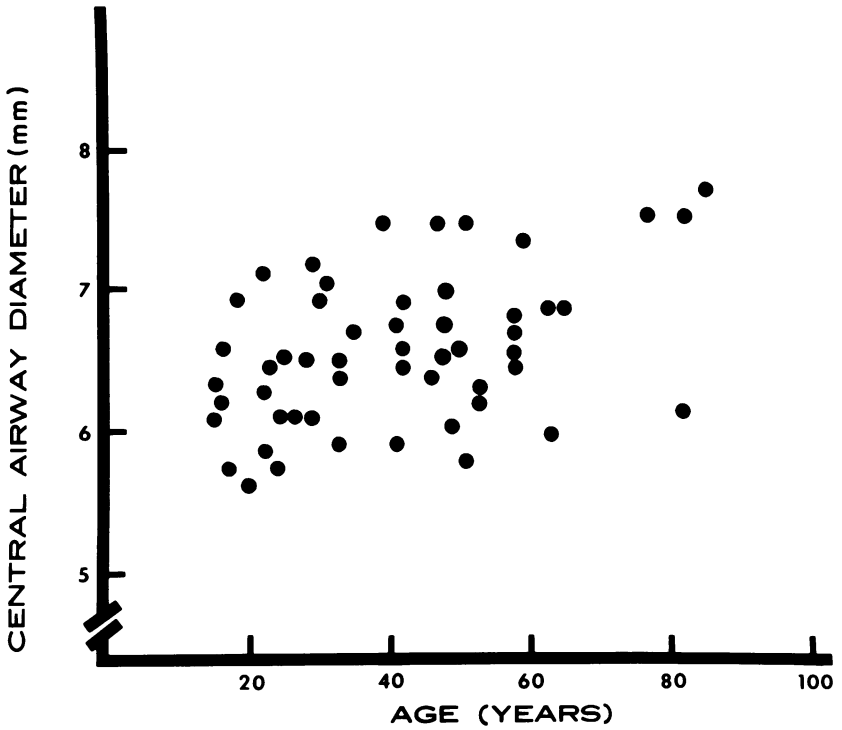

FIGURE 1 Individual values of CAD plotted against age.

Histological studies were performed on sections stained with haematoxylin and eosin.

(*a*) *Alveolar surface to parenchymal lung volume ratio (ASVR).* The mean linear intercept was determined by standard methods as the mean of 10 observations on each of 12 different sections (14). Correction was made for shrinkage and the ASVR was calculated from ASVR = 4/mean linear intercept.

(*b*) *Membranous bronchiole diameter.* The method employed for measuring the luminal diameter of membranous bronchiole has been previously described in detail (9). All membranous bronchioles less than 2 mm internal diameter were identified in 12 random histological sections. The internal diameter (the longest distance in the shorter plane of obliquely sectioned airways) was measured with a reticle in the eyepiece of the microscope. The geometric mean of luminal diameter was calculated from measurements on 50–100 membranous bronchioles in each lung and is referred to subsequently as peripheral airways diameter (PAD). The geometry mean is used because its correlation with functional measurements is slightly better than with either the arithmetic mean or the median. The geometric mean correlates closely with both the arithmetic mean ($r = 0.96$) and the median ($r = 0.92$), so that the conclusions are substantially the same with all three values.

(*c*) *Bronchial gland mass (BGM).* The proportion of gland mass relative to bronchial wall was determined by point count (14). The value reported is the mean of measurements on single sections from the upper lobe and the lower lobe bronchi.

Statistical analysis

Age is included as a factor in the analysis because most functional and morphological variables are age dependent. A polynomial regression analysis was performed to describe the relationship between age and the functional measurements, MEF and the CDYN ratio. The computer program BMD05R (15) was employed.

A multiple regression analysis was then performed using first MEF and then the CDYN ratio as the dependent variables and all morphological measurements as potential independent variables. The computer program BMD02R (15) was employed for this analysis. For each dependent variable, regression analyses were performed both with the effects of age eliminated and with age ignored. To eliminate the effects of age, the independent variable age and its higher powers, as indicated by the polynomial regression analysis, were forced into the regression function before any of the morphological measurements were considered. The analysis ignoring age simply did not include age as an independent variable.

RESULTS

The 53 lungs, including 9 lungs with minimal grades of emphysema (1–10% by point count), have been grouped together for purposes of analysis. All lungs were considered to be normal or only minimally diseased by both functional and morphological criteria. Only limited medical histories were available in most cases, but insofar as is known, none of the individuals had disabling respiratory symptoms during life. Smoking and occupational histories are not known in most cases.

The morphological measurements are presented as a function of age in Figs. 1–5. Values for CAD (Fig. 1)

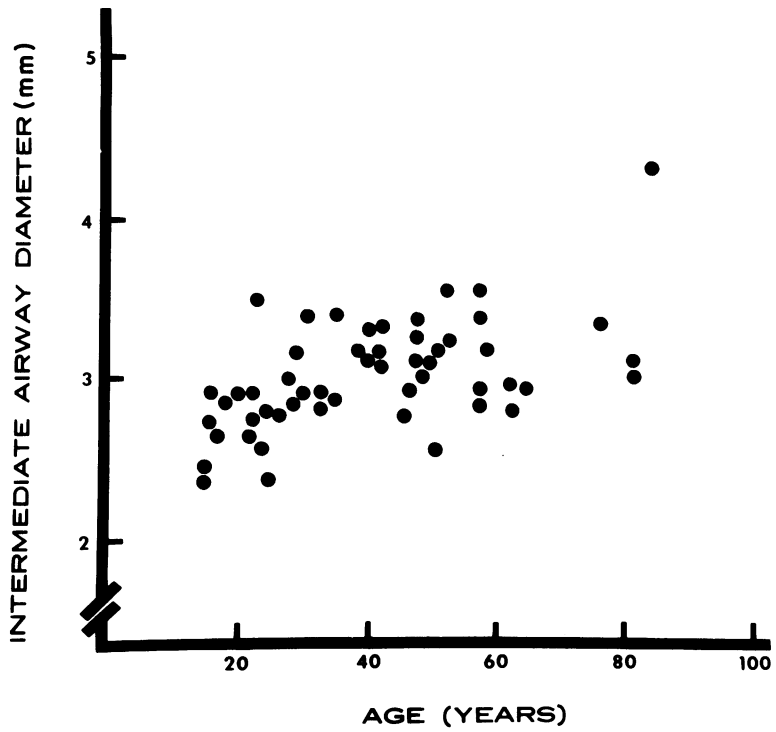

FIGURE 2 Individual values of IAD plotted against age.

ranged from 5.63 to 7.75 mm with a mean of 6.59 mm and a SD of 0.54 mm. There is a small though significant increase in CAD with advancing age ($r = 0.43$, $P < 0.01$).

Average values for IAD also increase with age ($r = 0.53$, $P < 0.001$) as shown in Fig. 2. The range of values is from 2.38 to 4.32 mm with a mean of 3.02 mm and a SD of 0.34 mm. There is a significant correlation between IAD and CAD in the same lung ($r = 0.55$, $P < 0.001$).

The mean value for PAD is 0.684 mm with a SD of 0.13 mm and a range from 0.446 to 0.991 mm (Fig. 3). There is a positive correlation between PAD and age in the 25 lungs below 40 yr of age ($r = 0.53$, $P < 0.05$). Beyond that age, average values decrease slightly and the range of values becomes somewhat larger. The largest single value is observed in an 82-yr-old man. There is no statistically significant relationship between either PAD and CAD ($r = 0.23$, $0.10 > P > 0.05$), or PAD and IAD ($r = 0.26$, $0.10 > P > 0.05$). Considering only lungs less than 40 yr of age, there is a significant correlation between PAD and IAD ($r = 0.48$, $P < 0.05$), but not between PAD and CAD ($r = 0.27$, $P > 0.05$).

Fig. 4 shows individual values of ASVR plotted against age. The range of values is 94–200/cm with a mean of 143/cm and a SD of 26/cm. There is a highly significant negative correlation between age and the ASVR ($r = 0.86$, $P < 0.0001$). The ASVR in the emphysematous lungs tends to be slightly lower than in age-matched nonemphysematous lungs.

The percentage of BGM in bronchial wall (Fig. 5) ranges from 5.0 to 24.2% with a mean value of 11.4% and a SD of 4.4%. This morphological feature is not significantly age dependent ($r = 0.14$, $P > 0.5$).

MEF data are presented only for lung volumes between 40 and 70% of TLC. MEF at these volumes is said to be effort independent (16). This means that above a critical pressure threshold, MEF is relatively independent of the pressure applied. Thus, any differences in forcing pressures between excised lungs and live subjects should have only minimal effects on MEF in this volume range. MEF at larger lung volumes in life subjects is more closely related to effort and may also be influenced to a greater extent by the geometry of the extrapulmonary airways. The other reason for restricting attention to MEF between 40 and 70% of TLC is that comparable data for live subjects exists only in this volume range (7).

As with live subjects (6), some individual differences in the shapes of the flow-volume curves are observed in postmortem lungs, although the flow-volume relationship tends to be nearly linear between 40 and 70% of TLC. It is not surprising, therefore, that MEF at volumes within this range are highly correlated. The statistical analysis is reported only for MEF at 60% TLC (MEF_{60}), but analyses of MEF at 70, 50, and 40% of TLC and the slopes of MEF as a function of percent

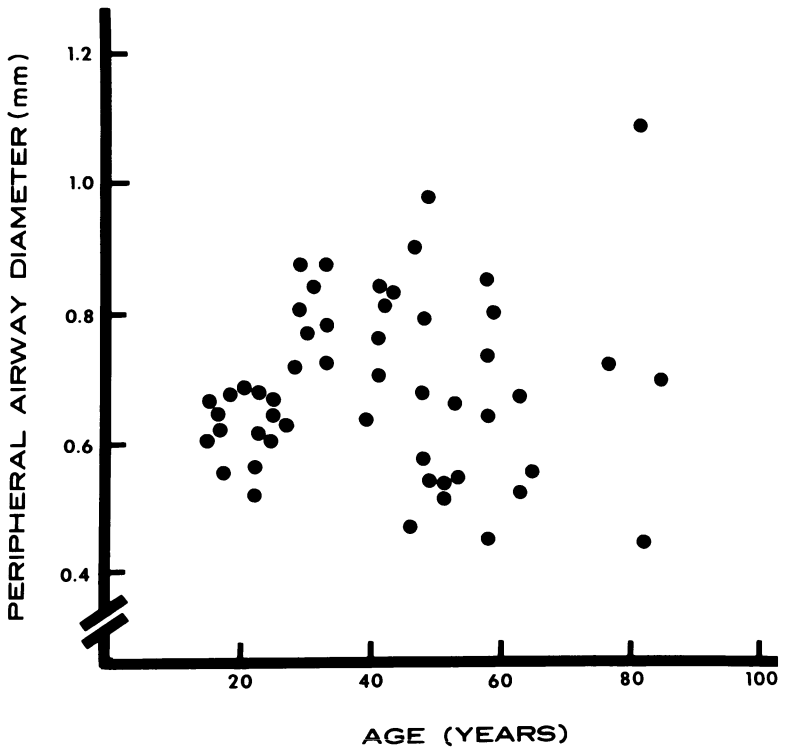

FIGURE 3 Individual values of PAD plotted against age.

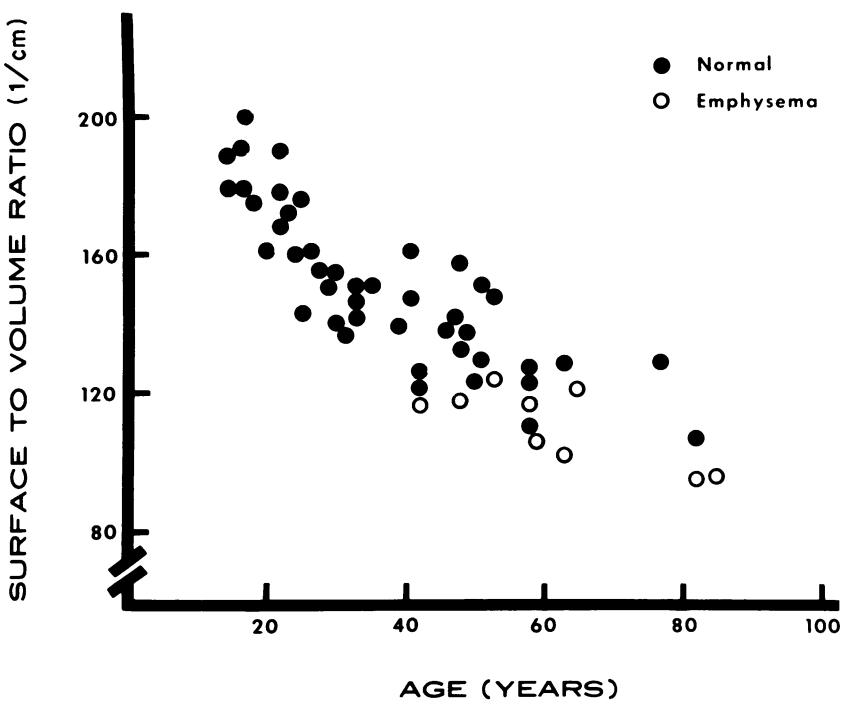

FIGURE 4 Individual values of ASVR in normal and minimally emphysematous lungs plotted against age.

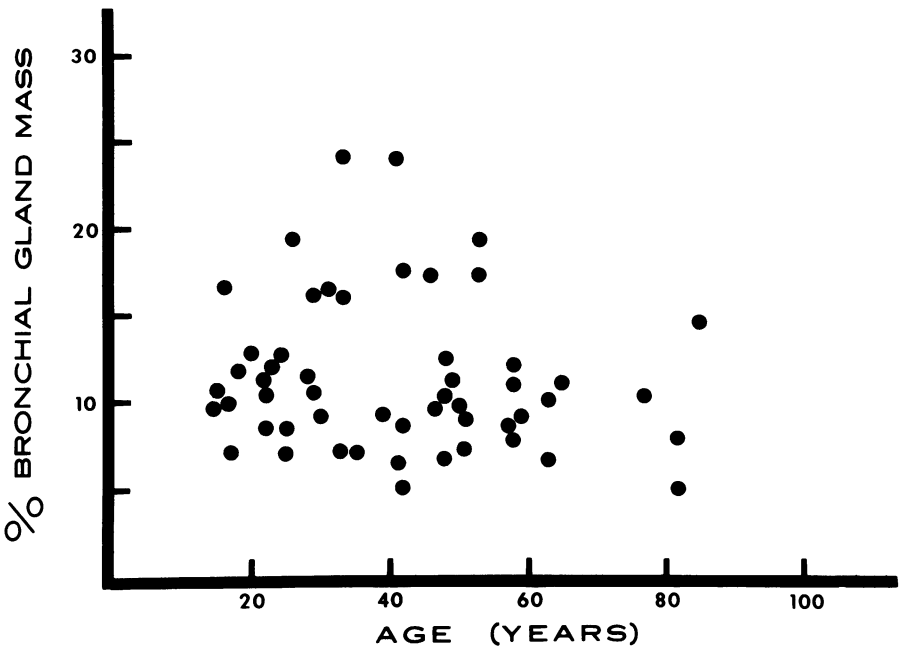

FIGURE 5 Percentage of BGM in each lung plotted against age.

TLC over this range lead to virtually the same conclusions.

Individual values of MEF_{60} are plotted against age in Fig. 6. The mean value for all lungs is 2.09 liters/s with a SD of 1.09 liters/s and a range from 0.13 to 4.55 liters/s. The relation of MEF_{60} with age is described by the curvilinear regression line. This cubic equation provides a significantly better description of the age relationship than does either a linear or a quadratic equation and is not significantly improved

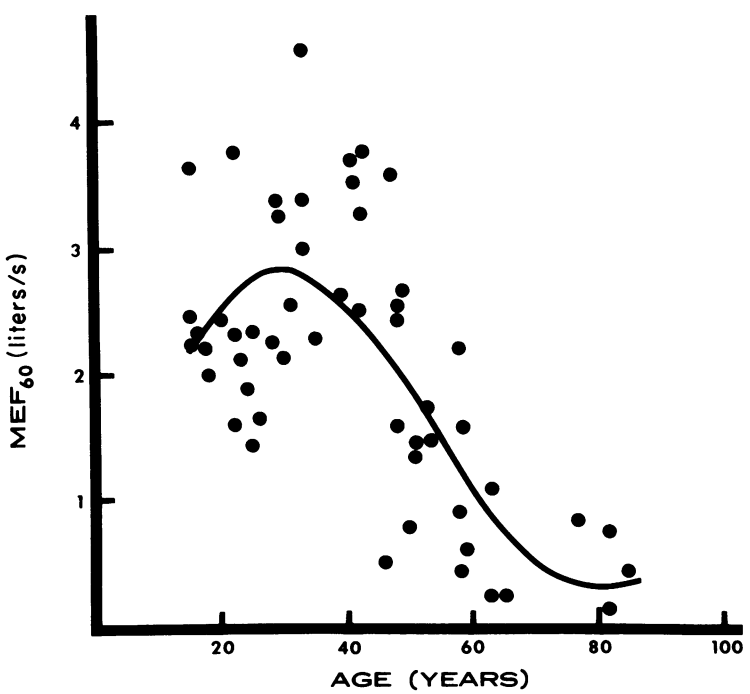

FIGURE 6 Individual values of MEF_{60} plotted against age. The regression equation (MEF_{60} = $-5.19 + 0.205$ AGE $- 0.00437$ $AGE^2 + 0.0000250$ AGE^3) is shown by the curved line.

by introducing higher order terms. The multiple correlation coefficient R of MEF_{60} with the three age terms is 0.71 (Table I). Thus, approximately 50% of the total variance in MEF_{60} is associated with aging factors.

The most important morphological feature associated with the variability in MEF_{60} at a given age is PAD, as indicated by the F value. Multiple R for age and PAD is 0.84, implying that approximately 70% of the total variance is associated with these two factors. Differences in PAD account for an additional 20% of the total variance or about 40% of the variability in MEF_{60} about the age regression. Differences in the ASVR account for a further 2.4% of the total variance but this addition to R^2 is of borderline significance. There is clearly no significant relationship between MEF_{60} and any additional morphological variable.

MEF_{60} was also analyzed by multiple regression against all morphological variables while excluding age (Table I). There are highly significant relationships between MEF_{60} and both PAD and ASVR. Multiple R for these two morphological variables is 0.77 with 27.5% of the total variance being associated with PAD and 59.1% associated with the combination of PAD and ASVR. Again, there is no significant relationship between MEF_{60} and the CAD, IAD, or BGM, given PAD and ASVR.

The CDYN ratio was analyzed in a similar fashion (Fig. 7 and Table II). The mean value for the CDYN ratio is 0.69 with a SD of 0.18 and a range from 0.21 to 0.93. An aging effect is evident in Fig. 7 and this relationship is also best described by a cubic function. Multiple R for the three age terms is 0.51, meaning that only about 26% of the total variance can be attributed to age factors.

The variability of the CDYN ratio about the age regression was analyzed with respect to the morphological features (Table II). The most important morphological variable for lungs of the same age is PAD. Multiple R for age and PAD is 0.69. An additional 22.4% of the total variance and approximately 30% of the variability at any given age is associated with differences in PAD. A further 7% of the total variance is associated with ASVR, an increase which is probably significant. No significant effect on the CDYN ratio is evident from differences in CAD, IAD, or BGM.

When age is excluded, a highly significant relationship is demonstrated between the CDYN ratio and both PAD and ASVR. Multiple R for these two morphological variables is 0.71 with 28.9% of total variance being associated with PAD and an additional 22.0% associated with the combination of PAD and ASVR. Again there is no significant improvement in R by adding CAD, IAD, or BGM to the regression.

TABLE I
Multiple Regression with MEF_{60} as the Dependent Variable

Variable	Coefficient	Multiple R	Increase in R^2	F Value*
A. Eliminating the effect of age				
(Constant)	−5.19			
Age	0.205			
Age^2	−0.00437	0.706	0.498	
Age^3	0.0000250			
PAD	4.16	0.838	0.204	36.7
ASVR	0.0142	0.852	0.024	4.1
CAD	No significant increase in R			
IAD				
BGM				
B. Ignoring age				
(Constant)	−4.67			
PAD	4.99	0.525	0.275	42.8
ASVR	0.0234	0.769	0.316	38.7
CAD	No significant increase in R			
IAD				
BGM				

* The F value is a statistic which tests whether the deletion of a particular variable from the regression equation would decrease the multiple R. A variable is retained only if its F value indicates that its removal would cause a significant decrease in R. For part B of Tables I and II, the F values have 1 and 50 degrees of freedom. An F value of approximately 4.0 indicates that the removal of that variable would cause a decrease in R significant at a level of 0.05. An F value of approximately 8.6 is significant at a level of 0.005. In part A of Tables I and II the age terms were forced into the function first and F values are given only for those variables included after age. The degrees of freedom for these F values are 1 and 47 and the critical values for significance are virtually the same as for part B.

DISCUSSION

These studies have demonstrated highly significant relationships between functional and morphological measurements in a group of normal and minimally diseased human lungs obtained at autopsy. The major conclusions from these studies are: (*a*) the variability in measurements of MEF and the CDYN ratio in lungs of the same age is related primarily to differences in the caliber of the peripheral airways, and (*b*) age-dependent variability in these functional measurements is primarily associated with differences in the ASVR and, to a lesser extent, with changes in the PAD.

It bears emphasizing that these conclusions do not depend on the particular statistical model employed. For example, if instead of a cubic age regression, a single linear age term is used, the results are not appreciably different. In this case, age accounts for 36% of the total variability in MEF_{60}, and PAD accounts for an additional 30% (The corresponding

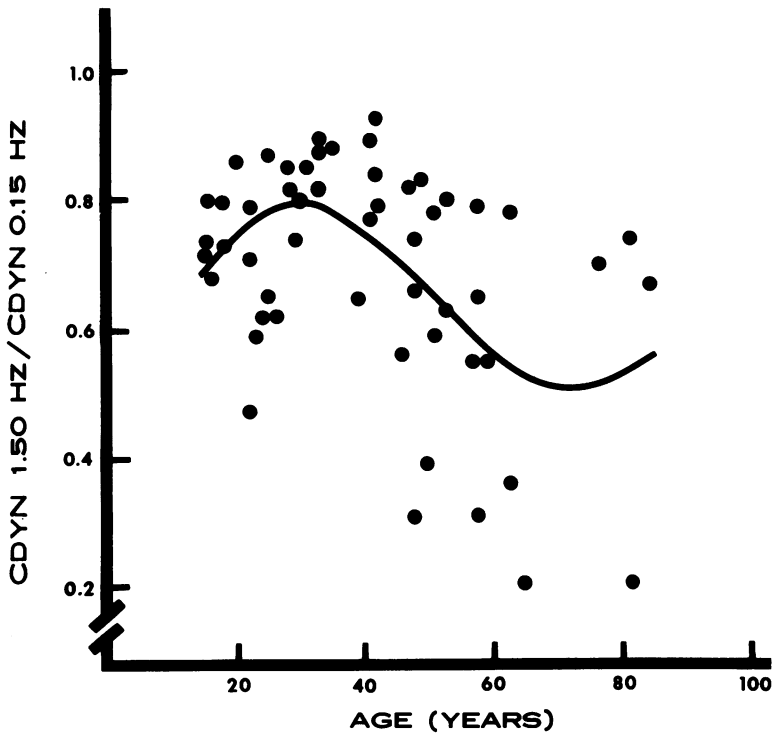

FIGURE 7 Individual values of the CDYN ratio plotted against age. The regression equation (CDYN ratio = $-0.891 + 0.0374$ AGE $- 0.00077$ AGE$^2 + 0.0000048$ AGE^3) is shown by the curved line.

values using three age terms are approximately 50% for age and 20% for PAD). The ASVR is of very marginal significance statistically and again BGM, CAD, and IAD are clearly not significant. It was also shown that when age is completely ignored (Tables I and II), PAD still emerges as a highly significant morphological variable.

TABLE II
Multiple Regression with CDYN Ratio as the Dependent Variable

Variable	Coefficient	Multiple R	Increase in R^2	F Value
A. Eliminating the effects of age				
(Constant)	−0.891			
Age	0.0374			
Age^2	−0.00077	0.508	0.258	—
Age^3	0.0000048			
PAD	0.717	0.694	0.224	25.5
ASVR	0.00396	0.744	0.072	7.5
CAD, IAD, BGM	No significant increase in R			
B. Ignoring age				
(Constant)	−0.315			
PAD	0.809	0.537	0.289	35.7
ASVR	0.00316	0.714	0.220	22.4
CAD, IAD, BGM	No significant increase in R			

ASVR is a highly significant variable when the effects of age are ignored, but is relatively unimportant when age terms are included. The reason for this is evident from Fig. 4 which shows that ASVR is itself closely correlated with age and is relatively constant at any particular age. To what extent the ASVR is causally related to the age-dependent changes in MEF_{60} and the CDYN ratio is not entirely clear. There could well be other unidentified aging changes in lung structure which are of equal or greater functional significance than the ASVR. However, it has been noted previously in human lungs and in an animal model of emphysema that the ASVR correlates closely with lung elastic recoil (10, 17). Since elastic recoil is thought to be an important physiological determinant of MEF and CDYN ratio (18, 19), it seemed logical to evaluate ASVR as a potentially important morphological variable.

The pattern of aging observed in the functional tests, particularly the MEF, although principally associated with changes in the ASVR, can also be attributed partly to the age dependence of PAD. The absolute decreases in the ASVR are greatest in the young adult.

However, average MEF remains nearly constant between 20 and 50 yr of age. This may be explained by the fact that average PAD increases during this same period. The decrease in MEF, and to a lesser extent in the CDYN ratio, coincides with that period when average PAD also begins to decrease.

All lungs in this study are either normal by conventional pathological criteria or contain minimal disease. Inflammation, fibrosis, and goblet cell metaplasia in the membranous bronchioles are very unusual histological findings in these lungs. 9 of the 53 lungs had minimal grades of emphysema, but even in the most severely diseased lung, less than 10% of the parenchyma was destroyed. In four of the nine emphysematous lungs, less than 2% of the lung was involved.

Another specific pathological feature was recognized in many of the younger lungs. Respiratory bronchiolitis is a lesion associated with cigarette smoking in young adults (20) and it consists of minimal inflammatory changes, primarily in the respiratory bronchiole. These lesions were identified in 15 of the 25 lungs from men less than 40 yr of age.

It is possible that the relationship observed between MEF_{60} and PAD, when all lungs are considered as a single group, reflects primarily those lungs with evidence of minimal disease. If this is true, when the predictive capability of our regression equation would be much better in those lungs with emphysema and respiratory bronchiolitis than in the remaining lungs in which specific pathological changes are not identified. This is not the case. The correlation coefficient between the predicted MEF_{60} and the observed MEF_{60} for all lungs is +0.85. For the 24 lungs with minimal emphysema or respiratory bronchiolitis, this value is +0.86 and for the remaining 29 lungs, it is +0.84. Formal statistical tests for the equality of the regression coefficients between the two groups also indicate no significant difference. For example, the F value for this difference in part A of Table I is 1.35 (for 6,41 degrees of freedom, an F value of less than 1.9 indicates a significance level of greater than 0.10), and in part B of Table I the F value is 1.53 (for 3,47 degrees of freedom, an F value of less than 2.2 indicates a significance level of greater than 0.10). The regression equations for the entire group apply equally to the two separate groups.

In Fig. 8, individual values of MEF_{60} have been plotted against age and those lungs with minimal emphysema or respiratory bronchiolitis have been identified. It is apparent from inspection that these specific pathological lesions have little effect on MEF_{60} when compared to lungs of the same age without those lesions.

An important question is whether conclusions from studies in postmortem lungs can be extended to live populations. The relevance of functional studies in autopsied lungs would be best demonstrated if no differences were observed in measurements shortly

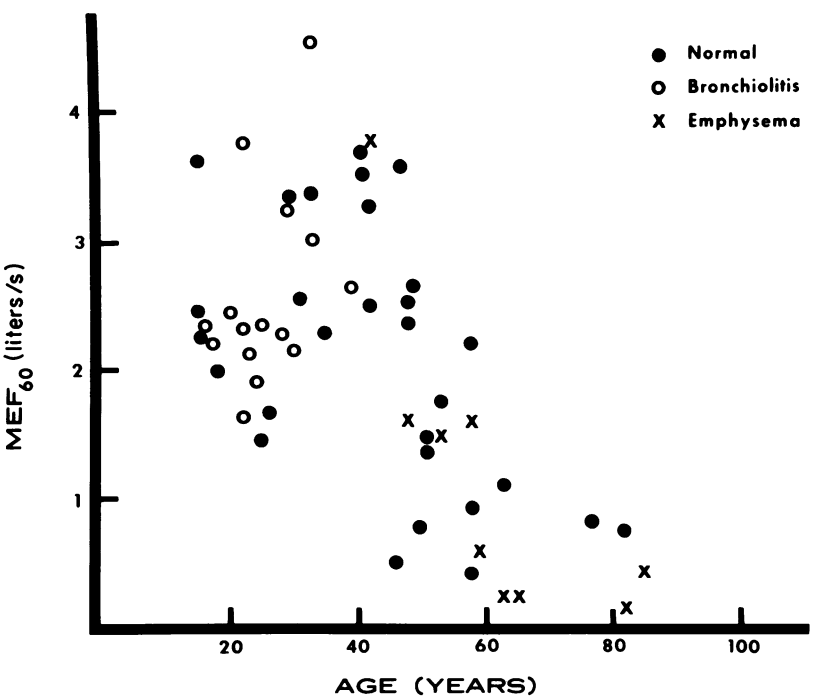

FIGURE 8 Individual values of MEF_{60} plotted against age. Lungs with respiratory bronchiolitis and with minimal emphysema are compared to lungs of similar age without these lesions.

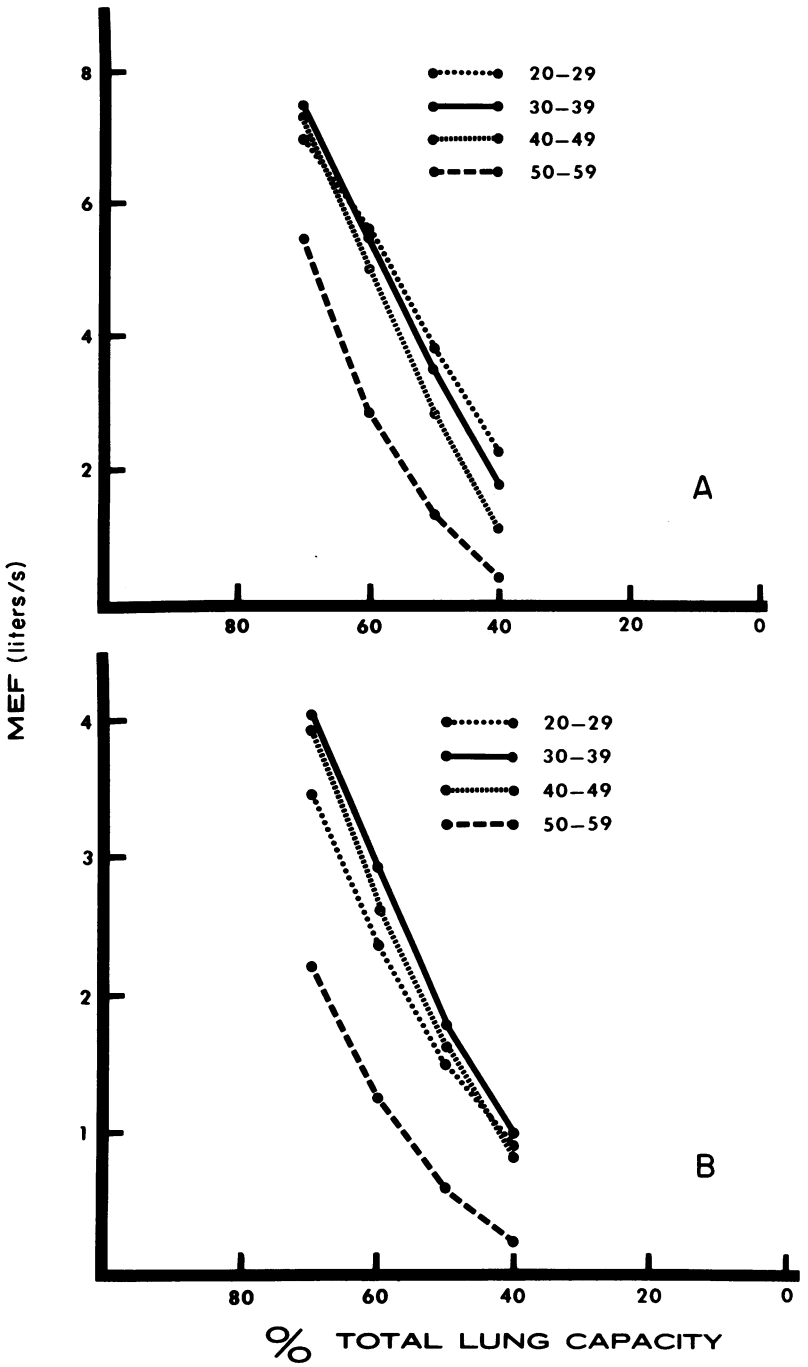

FIGURE 9 (A) Mean MEF at 40–70% TLC for each decade in live men between 20 and 59 yr of age reported by Black and associates (7). Their data for smokers and nonsmokers have been pooled. (B) Mean MEF at 40–70% of estimated TLC for each decade in postmortem lungs from men between 20 and 59 yr of age. The flow scale is expanded twofold compared to A.

before and after death. This is not practical, but functional data from postmortem lungs can be compared with similar measurements in live subjects. Normal population standards for MEF have been determined in numerous studies, but only Black and associates (7) report their results as instantaneous flows at different percentages of TLC in adults. These investigators measured flow-volume relationships in 83 men of

various ages who had no respiratory symptoms. Their data for smokers and nonsmokers, which differ only slightly, have been combined and mean MEF at 40, 50, 60, and 70% of TLC for the third through sixth decades of life is plotted in Fig. 9A. Comparable data from the postmortem lungs is shown in Fig. 9B. The flow scale for the postmortem lungs has been expanded twofold for comparative purposes because only the left lung was tested. Allowing for this difference, the closeness of mean values in the different age groups is evident. The variability of individual values about the mean is also similar in the two studies. The coefficients of variation for MEF_{60} in live subjects for the third through sixth decades are respectively 0.24, 0.30, 0.35, and 0.42 (7). Corresponding figures in the postmortem lungs are 0.31, 0.26, 0.42, and 0.42. The similarity of the results suggests that studies in excised lungs are relevant to live populations even though the conditions for the measurement are considerably different.

Normal population standards are not as well established for the CDYN ratio. This measurement is technically more difficult and the invasiveness of the procedure is a practical limit to its application in large populations. A considerable range of "normal" values is reported from different laboratories which is probably related largely to differences in methods (21). There is only one study in which the age dependence of the CDYN ratio has been systematically investigated. Begin and his associates (22) determined the ratio of CDYN at 1.00 Hz to CDYN at 0.25 Hz in adult subjects who had no respiratory symptoms. Mean values in the third through eighth decades of life for nonsmokers were respectively: 0.95, 0.95, 0.91, 0.79, 0.78, and 0.82. A similar age relationship is observed in the postmortem lungs, though average values tend to be less. Mean values for the third through sixth decades in the postmortem lungs (the number of older lungs is not sufficient to make meaningful comparisons) are respectively: 0.82, 0.82, 0.76, and 0.60. The differences in average values may be partly explained by the different frequency ranges (0.15–1.50 Hz vs. 0.25–1.00 Hz) over which CDYN was measured and may reflect a greater element of disease in the postmortem lungs as well as other differences.

The frequency dependence of CDYN is thought to be determined by regional differences in mechanical time constants of the lung (19). Each regional time constant is the multiple of the relevant resistance and compliance. Assuming that PAD reflects airflow resistance in the peripheral airways and that the ASVR provides some measure of parenchymal elastic behavior, it seems surprising that the CDYN ratio varies with average values for these measurements in each lung. The frequency dependence of CDYN also depends upon the magnitude of the time constants relative to the cycling frequencies (19). A fixed dispersion of time constants about a large mean should cause a larger fall in CDYN than would the same dispersion of time constants about a smaller mean. Some regional variation in the ASVR can be demonstrated even in normal lungs. It is reasonable to assume that luminal diameters in the same generation of peripheral airways of each lung are not identical, but it is not possible to adequately quantify this from the available data. If the distribution of airway diameters and the regional ASVR about the mean is assumed to be nearly constant in all lungs, the relationship that we have found between mean values for these measurements and the CDYN ratio would be anticipated. An additional part of the variance in the CDYN ratio might be explained if the regional variability of these morphological features within each lung were better defined.

It has generally been believed in recent years, based largely on the work of Hogg and associates (23), that airflow resistance in the peripheral airways of normal lungs is negligible. Accepting this premise, Green and his associates (6) concluded that the geometry of the peripheral airways is irrelevant to the MEFV curve in normal lungs. Modeling experiments by Pardaens and his co-workers (24) and by Van de Woestijne (25) indicate that if peripheral resistance is negligible, neither MEFV curves nor the CDYN ratio would be particularly sensitive to changes in small airway caliber, but would be sensitive to large airway diameter. Yet it is frequently stated that MEFV curves and the CDYN ratio are sensitive tests of small airway function and minimal abnormalities in these tests have in numerous clinical studies been interpreted as evidence of "small airways disease" (26–29). It is difficult to reconcile these different viewpoints. If the small airways are not important as a morphological determinant of these tests in normal lungs, it is difficult to see how they can be sensitive tests of minimal disease in that region of the lung.

The present study clearly indicates that MEFV curves and the CDYN ratio would be sensitive to minimal pathological narrowing in the membranous bronchioles because the peripheral airways are an important determinant of these physiological tests in normal lungs. Moreover, there is no evidence that in the excised lung the MEF_{60} or the CDYN ratio are any more sensitive to differences in PAD than in total pulmonary resistance measured during slow tidal ventilations. A close correlation between total pulmonary resistance and mean bronchiole diameter was reported previously (9) and those initial observations have been confirmed in subsequent studies. The correlation coefficient between total pulmonary resistance and PAD for all lungs in this study is +0.85. This compares closely with the multiple R of age and PAD

with MEF_{60} (0.84) and is slightly better than multiple R of age and PAD with the CDYN ratio (0.69). Although not all of the variance has been explained, these results strongly suggest that the geometry of the membranous bronchiole is highly relevant to all three tests. Far from being the lung's "quiet zone" (30), these airways appear to be major determinants of ventilatory function even in the normal human lung.

The luminal diameter of the membranous bronchiole has been shown to be a structural feature critically related to several tests of ventilatory functions in normal and minimally diseased lungs. Factors determining the normal variability in PAD are entirely unknown. It might be suspected that those persons who by virtue of normal variability have a small PAD might be at greater risk in developing chronic airways obstruction because morphological and physiological studies indicate that the principal site of obstruction in advanced disease is located in the peripheral airways (23, 31–34). Certainly the functional consequences of the same degree of injury would be greater in the lung with the smaller peripheral airways. Whether the normal variability in PAD is an important factor in the pathogenesis of chronic airways obstruction is not presently known and can be determined only by longitudinal physiological studies in live subjects.

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REFERENCES

1. Kory, R. C., R. Callahan, H. G. Boren, and J. C. Syner. 1961. The Veterans Administration-Army cooperative study of pulmonary function. I. Clinical spirometry in normal men. *Am. J. Med.* **30:** 243–258.
2. Birath, G., I. Kjellmer, and L. Sandqvist. 1963. Spirometric studies in normal subjects. II. Ventilatory capacity tests in adults. *Acta. Med. Scand.* **173:** 193–198.
3. Morris, J. F., A. Koski, and L. C. Johnson. 1971. Spirometric standards for healthy nonsmoking adults. *Am. Rev. Respir. Dis.* **103:** 57–67.
4. Cherniack, R. M., and M. B. Raber. 1972. Normal standards for ventilatory function using an automated wedge spirometer. *Am. Rev. Respir. Dis.* **106:** 38–46.
5. Bass, H. 1973. The flow volume loop: Normal standards and abnormalities in chronic obstructive pulmonary disease. *Chest.* **63:** 171–176.
6. Green, M., J. Mead, and J. M. Turner. 1974. Variability of maximum expiratory flow-volume curves. *J. Appl. Physiol.* **37:** 67–74.
7. Black, L. F., K. Offord, and R. E. Hyatt. 1974. Variability in the maximal expiratory flow volume curve in asymptomatic smokers and nonsmokers. *Am. Rev. Respir. Dis.* **110:** 282–292.
8. Knudson, R. J., R. C. Slatin, M. D. Lebowitz, and B. Burrows. 1976. The maximal expiratory flow-volume curve: Normal standards, variability, and effects of age. *Am. Rev. Respir. Dis.* **113:** 587–600.
9. Niewoehner, D. E., and J. Kleinerman. 1974. Morphologic basis of pulmonary resistance in the human lung and effects of aging. *J. Appl. Physiol.* **36:** 412–418.
10. Niewoehner, D. E., J. Kleinerman, and L. Liotta. 1975. Elastic behavior of postmortem human lungs: effects of aging and mild emphysema. *J. Appl. Physiol.* **39:** 943–949.
11. Turner, J. M., J. Mead, and M. E. Wohl. 1968. Elasticity of human lungs in relation to age. *J. Appl. Physiol.* **25:** 664–671.
12. Bouhuys, A., V. R. Hunt, B. M. Kim, and A. Zapletal. 1969. Maximum expiratory flow rates in induced bronchoconstriction in man. *J. Clin. Invest.* **48:** 1159–1168.
13. Weibel, E. R. 1963. Geometric and dimensional airway models of conductive, transitory, and respiratory zones of the human lung. *In* Morphometry of the Human Lung. Springer-Verlag KG., West Berlin, Germany. 139.
14. Dunnill, M. S. 1962. Quantitative methods in the study of pulmonary pathology. *Thorax.* **17:** 320–328.
15. Dixon, W. J., editor. 1973. BMD: Biomedical Computer Programs. University of California Press, Berkeley, Calif. 3rd edition. 305–330, 365–372.
16. Hyatt, R. E., D. P. Schilder, and D. L. Fry. 1958. Relationship between maximum expiratory flow and degree of lung inflation. *J. Appl. Physiol.* **13:** 331–336.
17. Niewoehner, D. E., and J. Kleinerman. 1973. Effects of experimental emphysema and bronchiolitis on lung mechanics and morphometry. *J. Appl. Physiol.* **35:** 25–31.
18. Mead, J., J. M. Turner, P. T. Macklem, and J. B. Little. 1967. Significance of the relationship between lung recoil and maximum expiratory flow. *J. Appl. Physiol.* **22:** 95–108.
19. Otis, A. B., C. B. McKerrow, R. A. Bartlett, J. Mead, M. B. McIlroy, N. J. Selverstone, and E. P. Radford, Jr. 1956. Mechanical factors in distribution of pulmonary ventilation. *J. Appl. Physiol.* **8:** 427–443.
20. Niewoehner, D. E., J. Kleinerman, and D. B. Rice. 1974. Pathologic changes in the peripheral airways of young cigarette smokers. *N. Engl. J. Med.* **291:** 755–758.
21. Guyatt, A. R., J. A. Siddorn, H. M. Brash, and D. C. Flenley. 1975. Reproducibility of dynamic compliance and flow-volume curves in normal man. *J. Appl. Physiol.* **39:** 341–348.
22. Begin, R., A. D. Renzetti, Jr., A. H. Bigler, and S. Watanabe. 1975. Flow and age dependence of airway closure and dynamic compliance. *J. Appl. Physiol.* **38:** 199–207.
23. Hogg, J. C., P. T. Macklem, and W. M. Thurlbeck. 1968. Site and nature of airway obstruction in chronic obstructive lung disease. *N. Engl. J. Med.* **278:** 1355–1360.
24. Pardaens, J., K. P. van de Woestijne, and J. Clément. 1972. A physical model of expiration. *J. Appl. Physiol.* **33:** 479–490.
25. Van de Woestijne, K. P. 1976. Spécificité des tests proposés pour le dépistage de la maladie des petites voies aériennes. *Bull. Eur. Physiopath. Resp.* **12:** 477–486.
26. McFadden, E. R., Jr., and D. A. Linden. 1972. A reduction in maximum mid-expiratory flow rate. A spirographic manifestation of small airway disease. *Am. J. Med.* **52:** 725–737.
27. McFadden, E. R., Jr., R. Kiker, B. Holmes, and W. J. deGroot. 1974. Small airway disease. An assessment of the tests of peripheral airway function. *Am. J. Med.* **57:** 171–182.
28. Gelb, A. F., and N. Zamel. 1973. Simplified diagnosis of

small-airway obstruction. *N. Engl. J. Med.* **288:** 395–398.

29. Woolcock, A. J., N. J. Vincent, and P. T. Macklem. 1969. Frequency dependence of compliance as a test for obstruction in the small airways. *J. Clin. Invest.* **48:** 1097–1106.
30. Mead, J. 1970. The lung's "quiet zone" (Editorial). *N. Engl. J. Med.* **282:** 1318–1319.
31. Bignon, J., F. Khoury, P. Even, J. Andre, and G. Brouet. 1969. Morphometric study in chronic obstructive bronchopulmonary disease. Pathologic, clinical, and physiologic correlations. *Am. Rev. Respir. Dis.* **99:** 669–695.
32. Bignon, J., J. Andre-Bougaran, and G. Brouet. 1970. Parenchymal, bronchiolar, and bronchial measurements in centrilobular emphysema. Relation to weight of right ventricle. *Thorax.* **25:** 556–567.
33. Matsuba, M., and W. M. Thurlbeck. 1973. Disease of the small airways in chronic bronchitis. *Am. Rev. Respir. Dis.* **107:** 552–558.
34. Scott, K. W. M. 1976. A pathological study of the lungs and heart in fatal and non-fatal chronic airways obstruction. *Thorax.* **31:** 70–79.