Rate of increase in pulmonary distensibility in a longitudinal study of smokers

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ABSTRACT   To examine the hypothesis that an abnormally rapid increase in pulmonary distensibility occurs in cigarette smokers, 39 adult smokers (24 men), mean age 47 (SD 8) years, who were not disabled were studied on two occasions over a mean interval of 3·5 (SD 0·5) years. Exponential analysis of static pressure-volume data obtained during deflation of the lungs gave the exponent K, an index of distensibility. Total lung capacity (TLC) was measured in a body plethysmograph. At entry into the longitudinal study mean values for K and static recoil pressure in the 39 smokers available for follow up were similar to those obtained in the original group of 101 smokers (73 men), mean age 42 (SD 11) years, in the cross sectional study. Over the interval of the study, ln K and TLC increased and FEV_1 decreased at rates greater than those found in a previous longitudinal study of 34 non-smokers (24 men), mean age 42 (SD 15) years. In the longitudinal study of smokers the observed changes in K and in recoil pressure over the interval of study were greater than the values obtained from the regression slopes found in the cross sectional study of smokers. On the basis of the regression model used previously in the longitudinal study of non-smokers, the age coefficient for ln K was greater than that found in the non-smokers ($p < 0.01$). The regression model also showed that the slope of ln K on age increased in older subjects. Because K is related to peripheral airspace size, a rapid rate of increase in K identifies smokers in whom airspace size is increasing abnormally rapidly. In this study the rate of increase in K and the variation between subjects was sufficient to explain the magnitude of the increased pulmonary distensibility found in cigarette smokers who present with emphysema.

According to the elastase hypothesis for the development of emphysema,[1][2] a relative increase in elastolytic degradation of lung connective tissue produces an increase in the size of peripheral airspaces and breakdown of alveolar tissue. The observations of Thurlbeck[3][4] and others[5][6] show that increases in lung volume and in peripheral airspace size are found in lungs with minor or equivocal evidence of tissue destruction, from which it has been inferred that the increase in volume is independent of the "lesions of emphysema"[6] (which are defined partly in terms of alveolar wall destruction). An alternative view is that in the process leading to the anatomical changes recognised as "emphysema" an increase in the size of airspaces precedes the breakdown of alveolar tissue. If

the latter were true, it should be possible to show that an increase in the size of airspaces occurs at an accelerated rate in some smokers. We expect also that an increase in the size of airspaces would be likely to begin in some smokers within the first few years of smoking and would progress at different rates for different individuals.

The size of airspaces in the lungs is the major determinant of pulmonary distensibility.[7][8] By studying pulmonary distensibility therefore the gradual increase in airspace size in cigarette smokers can be followed. Pulmonary distensibility is quantified by exponential analysis of static pressure-volume (PV) data obtained during deflation of the lungs.[9] The exponent K is an index of distensibility, which is independent of lung size and independent of sex.[10] The index K relates directly to a morphometric estimate (mean linear intercept, Lm) of average airspace size in excised human lungs, whether normal or emphysematous, as well as in the lungs of several other mammals.[8] Through its influence on surface forces the

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size of airspaces is the major determinant of K.[8] This hypothesis was supported by the finding in healthy subjects that the rate of increase in K with age corresponds to the rate of increase in Lm with age in excised human lungs.[11] In a previous cross sectional study of cigarette smokers who were not disabled K increased with age more rapidly than in non-smokers, suggesting that the size of airspaces also increased at an unusually rapid rate.[12]

The present longitudinal study of smokers was undertaken to obtain a direct estimate of the rate of increase in K (and therefore of Lm) in individual smokers and to test the following hypothesis. If the increase in the size of airspaces in the lungs is a gradual process extending over many years, as is implicit in the elastase hypothesis,[13 14] then K should increase abnormally rapidly in some smokers and at a rate sufficient to account for values obtained in patients presenting with emphysema in their sixth decade. In other smokers, presumably those who maintain a normal elastase-antielastase balance or who can repair elastin damage more effectively, the rate of increase in K should be similar to that found in healthy non-smokers.

Methods

SUBJECTS

The 39 subjects (24 men and 15 women) included in the present study were regular cigarette smokers without established lung disease and all were able to maintain normal activity. They were selected from 101 subjects who had been included in a cross sectional study.[12] Of these 101 subjects, 10 had become ex-smokers, three refused to take part in a second study, and one had died from an accident. The remaining 48 subjects from the cross sectional study did not reply or could not be traced. All subjects smoked more than 15 cigarettes a day, with a mean consumption of 33 (SD 14, range 15–80) cigarettes a day, starting from the age of 18 (SD 4, range 9–32) years. The interval between the first and the second study averaged 3·5 (SD 0·5, range 2·8–5·2) years. All subjects freely consented to these studies.

PRESSURE-VOLUME DATA

Static pressure-volume data were obtained during several interrupted deflations of the lungs from total lung capacity (TLC) with a computerised measurement system.[15] Transpulmonary pressure (PL) was measured with an oesophageal balloon (length 10 cm, gas volume 0·5 ml) and a Statham differential strain gauge (PM131TC). For both studies in a given subject the distance from the external nares to the tip of the balloon was the same. The change in lung volume from TLC was obtained by electrical integration of flow at the mouth with correction for gas

compression near TLC but not at lower lung volumes.[10] After each deflation pressure-volume data were displayed on a graphics terminal (Tektronix 4006).

A single exponential function of the form

$$V = A - Be^{-KP}, \tag{1}$$

where V is lung volume, P is static recoil pressure, and A, B, and K are constants, was fitted to the pressure-volume data from TLC to a lower volume limit, usually in the range of 50–60% TLC (mean 56%, SD 5% TLC), in such a way as to exclude data points systematically shifted to lower pressures relative to an exponential curve.[9] On average, 32·3 (SD 5·5) pressure-volume points were used to define the exponential function. In all studies in a given subject the exponential function was fitted to pressure-volume data over the same volume range.

The exponential constant K describes the shape of the pressure-volume curve independently of TLC, A is the volume asymptote, and B is the difference between A and the volume at zero recoil pressure. The distribution of the original pressure-volume data about the derived curve was quantified by the ratio of residual variance divided by the total variance for volume. Average residual variance was 1·0% (SD 0·6%) in the initial study and was similar in the second study.

PL during a sustained maximum inspiratory effort at full inflation (maintained for approximately one second, PLmi) was measured directly and was the mean of the four highest values. Static recoil pressure at 90% of TLC (PL$_{90}$) was derived from the exponential function.

LUNG VOLUMES

TLC and the maximum expiratory flow-volume curve (MEFV) were obtained with a body plethysmograph and associated electronic equipment (Pulmostar Compact, Fenyves and Gut, Basel) connected via an analogue to digital converter to the computerised measurement system.[10] In this pressure-flow plethysmograph gas flow between the box and its surroundings and gas flow at the mouth were measured with Fleisch pneumotachometers (No 3). When this was tested with an oscillating flow, the signals representing mouth volume and box volume (obtained by electrical integration of flow) were in phase up to 10 Hz. To correct for non-linearity of the Fleisch pneumotachometer the volume obtained by integration of forced expiratory flow was decreased by 2%. Thoracic gas volume was obtained by a Boyle's law method with computerised sampling and a breathing frequency of about 1 Hz.[12] Immediately after the measurement of thoracic gas volume, the subject inspired maximally and the inspired volume was added to thoracic gas volume to obtain TLC. The final value used for TLC was the mean of three or four measurements.

For analysis of the increase in ln K with age we used the statistical model developed by McGilchrist et al,[17][18] which has the following form:

$$\ln K = a + b_1 \times age + b_2 \times age \times \varDelta\, age + C + E, (2)$$

where a is a constant, b_1 is the age coefficient, age is the age in years at entry to the study, $\varDelta$ age is the elapsed time since entry, b_2 shows whether the age coefficient changes over the period of observation, C is a random variable representing the contribution to ln K peculiar to an individual subject, and E is the individual error term. The ratio of the variance of C to the variance of E tests whether the difference between subjects exceeds the variance attributable to an individual. This is a mixed model solved by maximum likelihood. It resembles a mixed ANOVA with two random effects. The advantage of this model is that it allows for a variable number of observations in different individuals to be included as well as for a significant difference in ln K between individuals. For these reasons we used it previously to analyse the change in ln K in a longitudinal study of healthy non-smokers.[11] Each observation is entered as ln K and related to age and the years since entry to the study. We used this model to define how ln K changes with age and not to imply causal relationships.

For all lung volumes the BTPS value was used. Linear regression, covariance analysis of linear regression, determination of R, and Student's *t* test were performed as described by Snedecor.[16] Results are compared with those obtained in a cross sectional study of smokers[12] and in a longitudinal study of healthy non-smokers.[11] Where the hypothesis being tested is that a difference between smokers and non-smokers for a given parameter arises because smoking increases the change a single tailed *t* test has been used. In cross sectional studies of smokers[12] and non-smokers[10] there was no sex difference for K or for the slopes of the regressions on age for PLmi and PL_{90}; in the present study therefore these values for men and women have been combined.

Results

At the time of the first study (table 1) the 39 smokers to be studied longitudinally were similar in age to the non-smokers studied longitudinally[11] and, on average, a little older than the 101 smokers previously studied cross sectionally. At entry to the present study mean values obtained for K, ln K, and static recoil pressure (table 2) were similar to values obtained in the smokers in the cross sectional study. For each measurement the change over the interval of study was highly significant (p < 0.005). Individual values for K are shown in fig 1. The rate of increase in K or decrease in recoil pressure over the interval of study was greater than the values obtained from the respective regression slopes in the

Table 1 *Anthropometric data (means with standard deviations in parentheses) at entry for longitudinal studies in smokers (present study*) and in non-smokers[11] and in a cross sectional study of smokers[12] (numbers of subjects in square brackets)*

	Longitudinal				Cross sectional	
	Smoker		Non-smoker		Smoker	
Sex						
Age (y)						
M	[24]	47† (9)	[24]	44 (15)	[73]	42 (11)
F	[15]	45 (7)	[10]	37 (15)	[28]	43 (8)
M + F	[39]	47† (8)	[34]	42 (15)	[101]	42 (11)
Ht (cm)						
M		177 (9)		178 (5)		176 (8)
F		163 (6)		164 (8)		163 (5)
Wt (kg)						
M		78 (13)		76 (10)		77 (12)
F		58 (8)		64 (10)		61 (9)

*The smokers in the longitudinal study are a subsample of the cross sectional study of smokers.
†p < 0.05: significance of the difference from the value for the cross sectional study.

Table 2 *Exponential analysis of pressure-volume data (means with standard deviations in parentheses) for 39 smokers studied twice (present study) and for a cross sectional study of 101 smokers[12]**

	Longitudinal studies		Cross sectional study
	Initial	Final	
K, (kPa^{-1})	1.62 (0.68)	1.84 (0.81)	1.59 (0.61)
ln K, (kPa^{-1}) × 10	4.08 (0.38)	5.35 (0.37)	4.05 (0.34)
PLmi (kPa)	3.30 (1.17)	2.89 (0.98)	3.37 (1.10)†
PL_{90} (kPa)	1.34 (0.40)	1.21 (0.36)	1.37 (0.37)†

*The change from the initial to the final study (over an average of 3.5 (SD 0.5) years was significant in each case (p < 0.005). Values for the initial study and the cross-sectional study are similar.
†For 73 men.
K—index of lung distensibility; PLmi—static recoil pressure at maximum inspiration; PL_{90}—recoil pressure at 90% of total lung capacity.
Conversion: SI to traditional units—1 kPa = 10.2 cm H_2O.

cross sectional study of smokers (table 3). The rate of increase in K and ln K and the rate of decrease in PLmi were also greater than the values found in the longitudinal study of non-smokers, but the rate of decrease in PL_{90} was similar in the two studies.

The final form of the regression model used to estimate the increase in ln K with age (table 4) was reached after we had tested several possible models. The term age × $\varDelta$ age (equation 2) decreased the -2 ln (likelihood) estimate from the 126.92 obtained with a regression on age alone to 109.15. The decrease of 17.77 was highly significant (χ^2 test with one degree of freedom, p < 0.005) and therefore improved the fit of the model. The addition of the term $b_3 \times \varDelta$ age to equation 2 gave a value for b_3 (5.31 × 10³, SEM 41.6
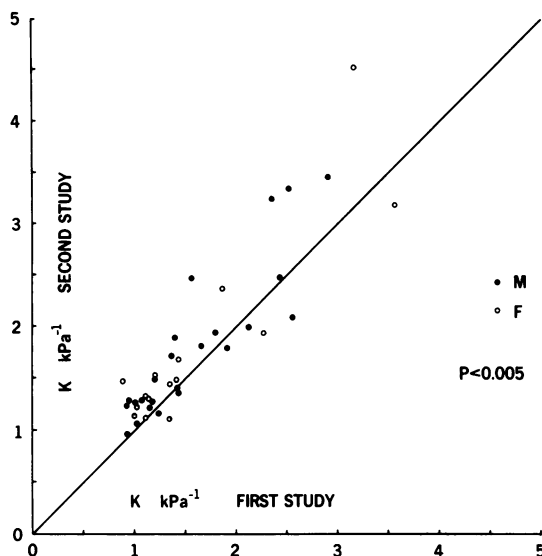
Fig 1 *Values for pulmonary distensibility (K) for 24 male (M) and 15 female (F) smokers for the first study (abscissa) and the second study (ordinate). K increased significantly over the interval between these studies. The line of identity is shown.*

$\times$ 10^3; p $>$ 0·5) that was insignificant; it changed the estimate of the coefficient for the age $\times$ Δ age term (b_2) from 7·68 $\times$ 10^{-4} to 8·80 $\times$ 10^{-4}, which was less than one standard error of the estimate for b_2. The Δ age term was therefore omitted from the final regression model.

In the smokers the estimate for the rate of increase in ln K with age at entry to the study (2·26 $\times$ 10^{-2}/year— age coefficient, b_1 in table 4) was greater than the corresponding value obtained in the longitudinal study of non-smokers[11] (9·02 $\times$ 10^{-3}/year, SEM 1·77 $\times$ 10^{-3}, p $<$ 0·01), but it did not differ significantly from the age coefficient in the cross sectional study of

smokers (p $>$ 0·1) or from Δ ln K/year in smokers (p $>$ 0·1; table 3). The coefficient (b_2) for the interaction term was also significant and shows that in older subjects ln K increased at a slightly greater rate than that given by b_1. The significant variance ratio (table 4) shows that values for ln K differed significantly between subjects.

The regression coefficient obtained from linear regression of the pooled values for ln K (two observations per subject) in the longitudinal studies of smokers and of non-smokers was greater in smokers (2·43 $\times$ 10^{-2}/year, SEM 0·469 $\times$ 10^{-2}/year) than in non-smokers (1·02 $\times$ 10^{-2}/year, SEM 0·136 $\times$ 10^{-2}/year; p $<$ 0·005) and close to the value given for b_1 in table 4. This estimate of the regression coefficient from the longitudinal study of smokers was also greater than that obtained in the cross sectional study of smokers (table 3). After allowance has been made for age, the value of ln K did not show a significant relationship to the duration of smoking (F = 0·872).

Individual values for TLC in the two studies are shown in figure 2. Over the interval of study FRC and TLC increased; VC, FEV_1, the ratio of FEV_1 to FVC, and maximum mid expiratory flow decreased (table 5). The changes were similar in men and women and only the pooled results are given. The rate of increase in TLC and decrease in FEV_1 were greater in the smokers in this study than in the longitudinal study of non-smokers[11] (p $<$ 0·05 and $<$ 0·001 respectively), but the changes in FRC and VC did not differ significantly in the two studies. The remaining values in table 5 could not be compared with findings in the non-smokers.

Discussion

The subjects included in our previous cross sectional study of cigarette smokers appeared to be representative of a working population of smokers without overt disability,[12] and the subsample available for the present longitudinal study showed values similar to those obtained in the larger, cross sectional study. By

Table 3 *Annual changes in pulmonary distensibility in longitudinal and cross sectional studies (means with standard errors in parentheses)*

	Longitudinal*		Cross sectional smokers (regression slopes)
	Smokers (difference/y)	Non-smokers (difference/y)	
K (kPa^{-1}) $\times$ 10^2	6·63†§ (1·89)	2·94 (0·65)	2·25 (0·54)
ln K (kPa^{-1}) $\times$ 10^2	3·67‡§ (0·81)	1·83 (0·40)	1·17 (0·30)
PLmi (kPa) $\times$ 10	− 1·21†§ (0·24)	− 0·72 (0·16)	− 0·41 (0·1)‖
PL$_{90}$ (kPa) $\times$ 10^2	− 3·98§ (0·69)	− 3·20 (0·55)	− 1·68 (0·33)‖

*For the longitudinal studies the difference per year between the final and the first study was calculated for each individual and the mean obtained.
†p $<$ 0·05.
‡p $<$ 0·01: significance of the difference from the corresponding value in non-smokers (single tail test).
§p $<$ 0·05, from corresponding regression slope in smokers (two tail test).
‖For 73 men.
Abbreviations as in table 2.

Table 4 *Regression of ln K (kPa^{-1}) on age (years) at entry into the longitudinal study**

	Estimate	SE	p
a × 10	−6·42	3·08	< 0·05
b_1 × 10^2	2·26†	0·653	< 0·001
b_2 × 10^4	7·68‡	1·64	< 0·001
(Var C)/(Var E)	6·53§	2·3	< 0·01
(Var E) × 10^2	1·44		

*Values from ln K = a + b_1 × age + b_2 × age × Δ age + C + E, where b_1 is the age coefficient, Δ age is the elapsed time since entry, b_2 tests whether the age coefficient changes with time, C is the contribution to ln K peculiar to an individual subject, and E is the individual error term.
†Significantly greater than the value obtained for a longitudinal study of 34 non-smokers, p < 0·01 (single tail test).
‡The age coefficient for ln K increases over the years of study.
§Values for ln K differ significantly between individual smokers.
Var—variance.
Conversion: SI to traditional units—To convert kPa^{-1} to cm H_2O^{-1} subtract ln 10·2 from the value given for a.
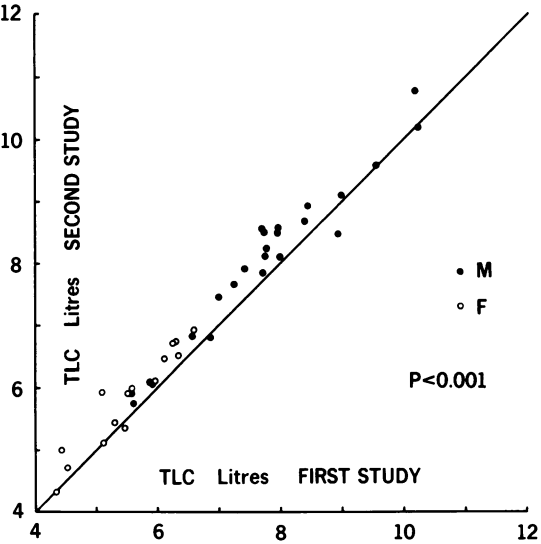

Fig 2 *Values for total lung capacity (TLC) for 24 male (M) and 15 female (F) smokers for the first study (abscissa) and the second study (ordinate). TLC increased significantly over the interval between these studies. The line of identity is shown.*

excluding subjects with established lung disease, however, we have probably underestimated the effects of heavy smoking in a random sample of the population.

The rate of decrease in FEV_1 in the present study was greater than that obtained in a longitudinal study of non-smokers[11] and similar to that reported for smokers (> 15 cigarettes/day) by Fletcher and Peto.[19] The decrease in VC was relatively smaller than the decrease in FEV_1—a result consistent with an increase in TLC.[20] The rates of increase in TLC and in FRC reported here are similar to those found by Corbin *et al* in their longitudinal study of smokers.[21] The increase in TLC documented here is unlikely to be related to technical factors, because all tests were performed with the same equipment. It is consistent with the increased TLC found in cigarette smokers with emphysema.[3 6]

Pulmonary distensibility increased and elastic recoil pressures decreased more rapidly in the present group of smokers than in the non-smokers studied previously.[11] Static recoil pressure is inversely related to K, so the decreases in PLmi and PL_{90} complement the observed increase in K. The rate of decrease in PL_{90} was greater in smokers than in non-smokers but the difference did not reach statistical significance (table 3). This result suggests that point estimates of recoil pressure are less discriminatory for a change in pulmonary elastic properties than is K, which reflects the relative changes in recoil pressure and lung volume over the upper half of lung volume.

In their longitudinal study Corbin *et al*[21] reported a rate of decrease in PL_{90} (calculated by the present authors from table 3 of ref 21) of 11·0 × 10^{-2} kPa/year in smokers and 9·2 × 10^{-2} kPa/year in non-smokers. These rates, similar to each other, are about three times the rates of decrease in PL_{90} shown for our subjects in table 3. Corbin *et al*[21] acknowledge that, because of systematic differences in their analysis of recoil pressure in the initial and in the final study, they may have overestimated the rate of decrease in PL_{90}. Estimates for the increase in K may also be obtained from their values for h—the half inflation pressure (K

Table 5 *Lung volumes and FEV_1 (means with standard deviations in parentheses and percentages of predicted values in square brackets) for 39 smokers studied twice*

	Study 1	Study 2	Difference/y
TLC (l)	6·87 (1·54) [102·2 (11·3)]	7·18 (1·56) [106·8 (11·2)]	0·086* (0·081) [1·30* (1·26)]
FRC (l)	4·13 (0·98) [112·4 (17·4)]	4·38 (1·05) [119·6 (21·0)]	0·074* (0·089) [2·12* (2·55)]
VC (l)	4·34 (1·18) [96·9 (12·7)]	4·24 (1·11) [96·6 (12·5)]	−0·031* (0·063) [−0·08 (1·66)]
FEV_1 (l)	3·27 (0·89) [98·7 (16·8)]	3·01 (0·85) [93·7 (16·2)]	−0·076* (0·063) [−1·48* (1·87)]
FEV_1/FVC (%)	77·5 (8·0)	74·9 (10·2)	−0·84* (1·56)
MMEF (l s^{-1})	2·94 (1·10) [90·7 (31·4)]	2·61 (1·14) [80·0 (32·0)]	−0·099* (0·135) [−3·23* (4·35)]

*p < 0·005: significance of the difference over the interval of study (mean 3·5 (SD 0·5) years).
TLC—total lung capacity; FRC—functional residual capacity; VC—vital capacity; FEV_1—forced expiratory volume in one second; MMEF—maximum mid expiratory flow.

= $\ln 2/h$)—and, although their absolute values are systematically lower (owing to a different method of analysis) than for our own subjects, the rates of increase in K of 6.4×10^{-2} kPa^{-1}/year in smokers and 3.2×10^{-2} kPa^{-1}/year in non-smokers are similar to the values given in table 3.

The results obtained in our longitudinal study of non-smokers[11] showed that K increased as a function of its initial value, suggesting the use of an exponential, or logarithmic, model for expressing its increase with time. In the analyses given here the rate of increase in ln K is greater in smokers than in non-smokers. The average obtained for $\Delta\ln$ K/year over the interval between the two studies (table 3) is greater than other estimates, but is probably a biased estimate and is limited in its application. Our statistical model (see table 4 and also under "Methods") used the absolute values for ln K and also allowed for significant variability between subjects. The estimate obtained for the annual increase in ln K using this statistical model provides a weighted average value of the slope related to age; it was nearly twice the estimate obtained in the cross sectional study of smokers, although owing to a relatively large variance in both cases this difference did not reach significance. The significant b_2 age $\times \Delta$ age term (table 4) affects the slope of the linear regression of ln K on age. As subjects become older this slope increases and is detected here because precision of comparison within subjects is greater than cross sectional comparisons between subjects.

In the comparison of longitudinal and cross sectional data for smokers inherent differences between these studies need to be considered. Smokers are a heterogeneous group, as shown by the significant between subject variation for ln K; and individuals would be expected to show different rates of change for any given parameter. In our cross sectional study of smokers individuals were selected who were not disabled. Thus subjects disabled because of smoking induced lung disease (predominantly older subjects) were excluded. This method of selection decreases the rate of change in lung function seen over time in a cross sectional study. It is therefore not surprising that the present longitudinal study of smokers showed a greater rate of change for distensibility and elastic recoil than was found in the cross sectional study of smokers. So far as their lung function was concerned, the 39 subjects included in the longitudinal study were representative of the original 101 subjects in the cross sectional study, and the relatively short interval between the two studies should have minimised loss of subjects because of the development of serious disability. But we cannot estimate how the data may have been affected had a larger proportion of the original subjects been studied twice.

The analysis given in table 4 is the basis for a model showing the increase in K as an exponential function of time (fig 3). The age coefficient from the logarithmic regression model (b_1 in table 4) is the reciprocal of the time constant—44 years—while the SEM allows calculation of the 95% range from the shortest (28 years) to the longest (105 years) time constant. The range for healthy non-smokers is from a cross sectional study of 124 subjects,[10] because this study covered a wider age range and included nearly four times as many subjects as in the longitudinally studied non-smokers. In an average cigarette smoker K will be outside the normal range by his mid 40s, and a high initial value at the age of 20 years, or a shortened time constant, means that during the sixth decade he or she will achieve a value for K within the range found for patients with emphysema (diagnosed on clinical and radiological grounds—Colebatch, unpublished observations). Because we excluded smokers with established pulmonary disease, we are likely to have underestimated the rate of increase in K in some smokers. The limits of the model (shortest time constant with highest initial value and vice versa) are not, however, given in figure 3. The range of time constants is such that some smokers would retain normal values for K throughout their lifespan.

The analysis given in figure 3 suggests how smokers who are susceptible to the emphysema inducing effect of cigarette smoke might be identified. To determine the time constant in an individual would require several measurements of K over an interval of 5–10 years. The exponential model suggests a simpler approach. Subjects with increased values for K have already identified themselves as having shortened time constants, and younger subjects who have K values in the upper normal range are also likely to be in the susceptible group. (The distribution of the residuals of K in smokers supports the view that older subjects with increased values for K are recruited predominantly from subjects whose K values in their youth initially lay in the upper normal range.[12]) It should also be noted that, because smoking does not decrease K, values for K in the lower normal range in figure 3 represent subjects who in their 20s also had values in the lower normal range. The finding of an increased value for K would need to be confirmed in a subsequent study and, where possible, by additional studies covering several years.

Various observations support this model of a continuous increase in lung distensibility in cigarette smokers, a process that has emphysema as the end result. In postmortem studies Thurlbeck[14] found an increase in the maximum lung volume and in airspace size in lungs graded as showing only a trace of emphysema. He suggested that airspace enlargement may precede the destruction of alveolar tissue recognised as "emphysema." The observations of Silvers *et*
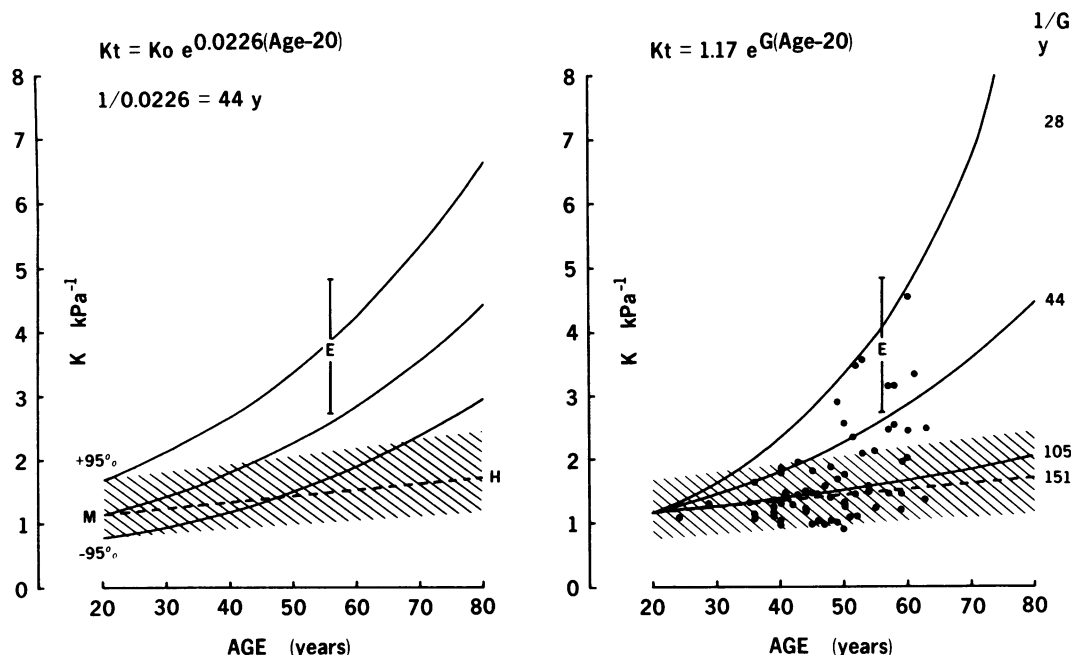
$$Kt = Ko\ e^{0.0226(Age-20)}$$

$$1/0.0226 = 44\ y$$

$$Kt = 1.17\ e^{G(Age-20)}$$

Fig 3 *A model of the increase in the index of pulmonary distensibility (K) as an exponential function of time. The interrupted line is the mean time constant for 124 healthy non-smokers[10] and the shaded area the 95% confidence interval derived from the regression of ln K on age for these subjects. The range and standard deviation of values for K found in 93 subjects with emphysema (E) is shown (unpublished observations—see text). In the left hand panel curves are shown with the same time constant (44 years) and different initial values of K at age 20 years (Ko). In the right hand panel the curves originate at the mean value for K at age 20 years, and show the 95% range of time constants (1/G) for smokers as well as values for individual smokers in both studies. K at any given time (Kt) is calculated according to the equations. M—mean. For further discussion see text.*

al[5] and of Berend *et al*[6] are also consistent with an increase in lung distensibility preceding the development of emphysema. In addition, an asymptomatic increase in distensibility has been found in a cross sectional study of smokers.[12] This process of increasing distensibility implies—as detailed analysis elsewhere has shown[20][22]—that airways disease and emphysema are not causally related.

An increase in peripheral airspace size (that is, a decrease in the surface:volume ratio of the lungs) decreases the contribution of surface forces to lung recoil and thereby increases distensibility (increase in K). Surface forces normally dominate the distensibility of air filled lungs and differences in tissue elasticity (as assessed in saline filled lungs) have no discernible effect on total lung distensibility.[8] Thus increased distensibility in emphysema is likely to be directly related not to decreased tissue recoil or to the tissue destruction itself but to the accompanying enlargement of peripheral airspaces, an enlargement that is part of the definition of emphysema.[23] In this respect, to use the term emphysema only when there is

tissue destruction—the lesions of emphysema[6]—may be misleading. In the assessment of emphysema there is a difference, in principle, between picture grading methods (which emphasise the most abnormal areas) and measurements of Lm[7] (which exclude bullous lesions larger than 2 cm in diameter and include the more "normal" airspaces). Large emphysematous spaces in excised lungs remain inflated for days at very low transpulmonary pressure.[7] Thus bullae probably contribute little to lung function during life other than as air filled, space occupying lesions and, in relating structure to distensibility, measurements of Lm appear to be preferable to measurements that reflect gross destructive lesions.

An increase in airspace size reflects changes to the fibrous framework of the lungs, probably caused by a relative increase in elastolytic activity in lung connective tissue.[1] This could occur, without any change in the total quantity of elastin or collagen, through a rearrangement of fibres that may reflect a greater turnover of elastin,[24] as well as the normal stresses to which lung tissue is exposed throughout life. As is seen

from the increase in Lm with age,[11] a similar process, but developing at a slower rate, takes place in normal aging. The development of imbalance between elastase and antielastase activity[2] in smokers will be a chronic process,[13 14] resulting in a gradual increase in airspace size and therefore in K. Consequently the increase in airspace size, and therefore in K, should be revealed as a continuous change over many years, as is suggested by the findings in the present study.

Because of its direct relationship with airspace size, K provides an appropriate index for identifying the development of emphysema during life.[22] High values for K identify smokers with large airspaces—the antecedent of emphysema. Moreover, longitudinal studies can identify smokers in whom K is increasing abnormally rapidly and who are therefore at risk of developing clinical emphysema.

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