FLOW DEPENDENCE OF THE INTRAPULMONARY DISTRIBUTION OF INSPIRED BOLUSES OF $^{133}$Xe IN SMOKERS AND NON-SMOKERS

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SUMMARY

1. Starting at 50% vital capacity, boluses of $^{133}$Xe were inhaled either at very low or maximal flow rates, the inspiration terminating at total lung capacity (TLC). Flow-dependent changes in bolus distribution were examined by measuring regional radioactivity and computing regional time-constants, and also by recording alveolar plateaux during the subsequent vital capacity expiration. Regional residual volumes, as a fraction of regional total lung capacities, were also calculated. Three groups of subjects were studied: young non-smokers, young cigarette smokers, and older non-smokers.

2. All three groups gave similar results in terms of regional time-constants though there was less variation in the results for young non-smokers.

3. Regional residual volumes also gave similar results in all groups although again there was less variation in young non-smokers. In young smokers, residual volumes in some regions depended on the flow rate used in their measurement, which indicated inraregional inhomogeneity of function.

4. In young non-smokers alveolar plateaux after slow and fast bolus inspirations differed little; this was not the case either in older subjects or in smokers. The increased flow-dependence of the alveolar plateau is analogous with the increased frequency-dependence of dynamic compliance and probably indicates obstruction of small peripheral airways.

Key words: smokers, respiratory function, airways obstruction, $^{133}$Xe.

There is evidence that chronic bronchitis first manifests itself as disease of small peripheral airways (Anthonisen, Bass, Oriol, Place & Bates, 1968; Levine, Housley, McLeod & Macklem, 1970; Woolcock, Vincent & Macklem, 1969). Isolated small airway disease is difficult to diagnose; since these airways contribute little to the total airway resistance, their obstruction may not influence commonly used tests of pulmonary function such as expiratory flow rates.

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To date the most useful technique in the study of disease of the peripheral airways has been measurement of changes in dynamic compliance with respiratory frequency: as frequency is increased, compliance declines (Woolcock et al., 1969). This results, of course, from the fact that with increased frequency, lung units with long time-constants (resistance \times \text{compliance}) receive a progressively smaller share of the ventilation. Changes in dynamic compliance reflect changes in the distribution of inspired gas. Measurement of dynamic compliance over a variety of respiratory frequencies, while illuminating, is difficult for both operator and subject and therefore not ideal for widespread application. We have studied the distribution of inspired boluses of $^{133}$Xe as a function of inspiratory flow rate (Robertson, Anthonisen & Ross, 1969), and found this approach capable of delineating difference in time-constants within normal lungs. It seemed rational to extend these studies to populations which might have increased time-constant discrepancies since a simple test which could detect peripheral airway disease would prove useful.

**MATERIALS AND METHODS**

We studied twenty-one subjects, all of whom were physicians or technicians, many of whom were visiting our laboratories and all of whom considered themselves normal. These subjects were separated into three equal groups: (a) non-smokers aged 23–35; (b) cigarette smokers (average consumption, 25 cigarettes/day) aged 25–35, and (c) non-smokers aged 45–63. Five of these seven smokers and five young non-smokers had undergone routine pulmonary function testing within a year of the study; in all cases these results, including lung volumes and expiratory flow rates, were normal (Table 1). No subject gave a history of persistent chest symptoms.

Subjects were studied in the seated position with five or six scintillation counters positioned over each lung for the measurement of regional count rates. These counters had NaI crystals of 2.5 cm diameter and were collimated to examine horizontal slices of lung, each counter being 14 cm behind a sheet of lead which was in contact with the posterior chest; the lead sheet had 2 cm \times 10 \text{cm} windows corresponding to each counter. The output of these counters was stored on magnetic tape, and subsequently replayed through analogue ratemeters (time-constant 1.25 s) to an oscillograph. The subjects breathed through a large mouthpiece which was connected to a lead-shielded plastic cuvette. This cuvette was pierced by a No. 18 needle for injection of $^{133}$Xe boluses, and positioned over the cuvette was an additional shielded scintillation counter.
which had a NaI crystal 3·75 cm in diameter. Events measured by this counter were recorded by a digital ratemeter (Picker) counting over 0·02–0·03 s intervals, the output of which was recorded directly on an XY recorder (Mosely). The total volume of the cuvette was 150 ml. Its washout volume was 200 ml independent of the flow rate. By turning a tap, the cuvette could be connected to either room air or a bag–box spirometer circuit. The volumes of the bag–box system was measured by a Stead–Wells spirometer and recorded potentiometrically on both the tape and the XY recorder. The subject inspired pure O₂ from the bag and expired into the box.

Each subject performed two respiratory manoeuvres illustrated schematically in Fig. 1. To standardize volume history each subject made a vital capacity inspiration, then exhaled to

![Fig. 1. Schematic representation of manoeuvres performed and data gathered. In the upper spiro-meter tracing the subject inspired slowly from RV to 50% VC where a bolus of ¹³³Xe was injected into the mouthpiece. The subject then inspired slowly to TLC and held his breath while regional radioactivity was measured (S₁), then expired to RV while Xe concentration was measured at the mouth (Ps). He then reinhaled room air to TLC and held his breath while regional radioactivity was again measured (S₂). The second manoeuvre (below) was the same as the first except that the bolus was inhaled at maximum flow rates. Relative regional time-constants (T) were calculated as S₁/F₁, regional residual volumes as a fraction of regional TLC (RV₁/TLC₁) as S₂/S₁ and F₂/F₁; finally alveolar plateaux (Ps and Pf) were compared.

residual volume (RV), after which he was turned into the bag–box circuit and inspired slowly to 50% of vital capacity where, during a brief holding of the breath, a bolus of ¹³³Xe (1–2 mCi in 4 ml of air) was injected into the mouthpiece. The subject then inhaled slowly to TLC and held his breath while count rates were recorded from various lung regions (S₁). After this, the subject expired slowly while ¹³³Xe concentration was measured at the mouth and plotted against expired volume resulting in an alveolar plateau (Ps). The subject then inhaled Xe-free air to TLC and again held his breath while regional count rates were recorded (S₂).

The second manoeuvre was the same as the first except that the ¹³³Xe bolus was inhaled at
maximum flow rates. Again regional radioactivity was recorded after the first inspiration (F1), alveolar plateaux recorded during expiration (PF) and regional radioactivity measured a second time after slow inspiration of 133Xe-free air (Fz). The final holding of breath, Fz, was 3−5 s longer than the initial one, S1 (Fig. 1).

Flow rates were controlled by adjusting the flow resistance of the bag-box circuit: added inspiratory and expiratory resistances do not influence Xe distribution (Martin, Wilson, Ross & Anthonisen, 1971b). ‘Slow’ manoeuvres were done through resistances of 10 cmH2O s−1 l−1, and Xe boluses were inhaled at 0.25 ± 0.05 litres/s during these manoeuvres. Low-resistance tubing was used for the inhalation of Xe at high flow-rates, which ranged from 5.0 to 7.5 litres/s. Expiratory flows averaged 0.25 ± 0.04 litres/s; during expiration, flow did not exceed 0.35 litres/s.

Relative time constants for each lung lesion (T) were computed by dividing, after dose correction, the regional count rates measured after slow bolus inhalation by the regional count rates measured after bolus inhalation at maximal flow rates (S1/F1). This computation assumed that at low flow, bolus distribution was directly proportional to regional compliances and that at high flow, bolus distribution was inversely proportional to regional resistances (Robertson et al., 1969). The reproducibility of the results was checked by estimating the variation of dose-corrected count rates present in any region after two boluses inhaled in the same way. The mean variation for all regions in all subjects (ten to twelve regions in twenty-one subjects) was 6%, ranging from 4% in the mid zones to 9% at the apices, where count rates were relatively low.

Regional residual volumes as a fraction of regional total lung capacity (RV/TLCr) were calculated for each manoeuvre by taking the ratio of regional count rates measured during the first and second holding of the breath at TLC, i.e. S2/S1 and F2/F1. This calculation assumes that regional Xe concentrations were not changed during the VC expiration after the first holding of the breath, and that the amount (concentration × volume) of Xe in each region did not change during the subsequent inspiration of 133Xe-free air (Millette, Robertson, Ross & Anthonisen, 1969).

Each subject performed each manoeuvre two or three times, resulting in an approximate maximum radiation dose of 92 mrads to the lung and 10 mrads to the remainder of the body.

RESULTS

Relative regional time-constants (T) are shown for all three groups in Fig. 2. These are presented as a fraction of the mean T as computed for each individual.

This computation of the mean has no effect on the data except to correct them for the dose. T increased from apex to base of the lung in roughly linear fashion in all subjects, with basal value of T being 1.5−2.5 times that of the apex in young non-smokers. The older normal subjects showed a significantly less sharp increase in T from apex to base (P<0.01). The results in young smokers were not strikingly different from those of non-smokers of the same age. In smokers, the value of T increased from apex to base in linear fashion.

Fig. 3 shows RV/TLCr in the three groups as measured after inhalation of boluses at slow flow rates. RV was higher at the lung top than at the bottom and significantly larger in old subjects than in young ones (P<0.01 by variance analysis). In terms of mean RV/TLCr, young smokers were the same as young non-smokers. When RV/TLCr was measured after bolus inhalation at high flow rates, the results were the same in the same non-smokers (Fig. 4a). This
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Fig. 2. Relative regional time-constants (T) in the three groups. T is expressed as % of the mean T value for each subject. The distance is from apex (0 cm) to base (30 cm) of the lung. Data for young non-smokers (●), young smokers (○) and older non-smokers (×) are shown. Each point is a mean value, and the bars represent one standard deviation of the mean.

Fig. 3. Regional residual volumes (RVr/TLCr) in the three groups. The symbols are as defined in Fig. 2.
was not the case in older subjects and young smokers (Fig. 4b and 4c). In each group there was a significant tendency ($P<0.01$ by paired t-test) for $RV_r/TLC_r$ measured after low-flow manoeuvres to exceed that measured after high-flow manoeuvres. This was particularly true of the young smokers, all of whom showed this phenomenon in at least one region of the lung.

Figs. 5(a) and (b) show examples of $Ps$ and $PF$ in a young non-smoker. The curves are virtually identical but $Ps$ showed a slight down-slope and $PF$ was somewhat flatter. Figs. 5(c) and (d) show results from a young cigarette smoker; $Ps$ sloped down more sharply and $PF$ rose as $RV$ was approached. $Ps$ and $PF$ were compared quantitatively over only the lower half of the expired VC, because this part of the VC was less influenced by the dead space, as flows were slightly more reproducible and differences were larger. The plateaux were smoothed by eye and were standardized (and dose corrected) by setting count-rate at 50% VC equal to 100

![Fig. 4. Comparison of $RV_r/TLC_r$ measured after boluses inhaled at low and high flow rates. The data is for young non-smokers (a), older non-smokers (b) and young cigarette smokers (c). In each case the line of identity is shown.](image)
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Fig. 5. Examples of alveolar plateaux; in each panel $^{133}$Xe concentration as measured at the mouth is plotted against expired volume. The traces in (a) and (b) are from a young non-smoker, (a) after a bolus inhaled at low flow rates, and (b) after a high-flow bolus. The two plateaux differ little. The traces in (c) and (d) are from a young cigarette smoker, (c) after a slow bolus, (d) after a high-flow bolus. The differences between the two inhalations are more marked.

Fig. 6. Results of comparison of alveolar plateaux in young subjects. On the ordinate is the dose-corrected difference between plateaux after boluses inhaled at high flow rates ($P_f$) and those resulting from low flow rates ($P_s$). The units are arbitrary and $P_s$ was subtracted from $P_f$ so that values of zero would indicate no difference. The abscissa is expired lung volume from $0 = RV$ to $40\% VC$. The shaded area encloses the mean ($P_f - P_s$) of young non-smokers $\pm SD$ of the mean. The stippled area encloses mean ($P_f - P_s$) $\pm 2 SD$ for young smokers.
and taking count-rates observed at lower lung volumes as % of this value. Standardized Ps count-rates were then subtracted from similarly standardized Pf count-rates, and the differences were plotted against the lung volume at which they were observed. Values of zero would then indicate that Pf and Ps were identical.

Fig. 6 shows the results in young smokers and young non-smokers. Pf - Ps was much larger in smokers; there is little overlap between the two age-matched groups. The seven older non-smokers gave variable results (Fig. 7). Two of them (aged 45 and 48 years) were well within the range for young non-smokers. One of them, aged 58 years, was just outside this range and the other five, aged 48–62 years, were well outside the 95% confidence limits for the younger non-smokers.

**DISCUSSION**

The relative regional T of Fig. 2 agreed with results of other studies (Robertson et al., 1969) and was consistent with the hypothesis that at these lung volumes basal compliances exceeded those at the apex and basal resistances were the same as, or greater than, those at the apex of the lung. The reason for the smaller increase in T from apex to base in older subjects was not clear and awaits further study. The overlap between young and old non-smokers was large enough to preclude separation of individual subjects on the basis of age. The variability of results in old non-smokers was greater than that in young in five of six lung regions; this is indicated by the bars denoting one standard deviation in Fig. 2. This was also true in young smokers; in all lung regions the variability of the results, as expressed by the standard deviation of the mean (Fig. 2), was greater than in young non-smokers. The cause of this greater variation was evident on study of individual results, which indicated that it was not uncommon for young smokers to exhibit one or more lung regions with unusually long or short T values. Examples of these findings with their interpretations have been published by Martin, Wilson & Anthonisen (1971a); their distribution, magnitude and direction were not consistent enough to separate individual smokers from non-smokers.

In non-smokers RVℓ/TLCℓ ratios were in agreement with the results of Milic-Emili, Hender-
son, Dolovich, Trop & Kaneko (1966). Older subjects demonstrated larger RV/TLC ratios than did young ones, and the mean value of RV/TLC was the same in young smokers and young non-smokers. The standard deviations of the mean RV/TLC value were larger in both young smokers and older subjects than in young non-smokers (Fig. 3). This was due to the presence of individual regions with unusually high or low RV/TLC values; combining these data with regional values of $T$ aided interpretation of the latter (Martin et al., 1971a).

In young smokers and to a lesser extent in older non-smokers, the RV/TLC ratio tended to be higher when measured after low flow manoeuvres than after high. We have interpreted this as indicating that intraregional variations of function occurred in these subjects (Martin et al., 1971a). If a number of lung regions each contained two sub-regions, one with a relatively high resistance and a high RV/TLC ratio, such regions would behave like those in Figs. 4(b) and (c). This combination of sub-regions would not afford a unique solution for the phenomenon illustrated in Figs. 4(b) and (c), but is the most reasonable one; these results can only be explained by a relatively long time-constant, and sub-regions with a high value of RV/TLC.

Examination of alveolar plateaux after bolus inhalation at low flow rates ($P_s$) and at high flow rates ($P_f$) was most rewarding. In normal subjects there is good evidence (Clarke, Jones & Glaister, 1969; Jones & Clarke, 1969; Anthonisen, Robertson & Ross, 1970) that during expiration at low flow rates, lower lung regions tend to empty earlier than upper ones, and this phenomenon can be a major influence on the alveolar plateau. Boluses inhaled at low flow rates from 50% VC were distributed more toward the base than the apex of the lung of the erect subject and the subsequent alveolar plateaux sloped downwards (Dollfuss, Milic-Elimi & Bates, 1967). Boluses inhaled at high flow rates from the same lung volume were somewhat more evenly distributed but subsequent alveolar plateaux showed only minimal flattening (Robertson et al., 1969). Our findings in young non-smokers were consistent with these data, and $P_s$ and $P_f$ values were nearly identical in these subjects (Figs. 5 and 6). In young smokers $P_s$ and $P_f$ were clearly not identical; this could be determined by superimposition of the data (Fig. 5); when the plateaux were dose-corrected and smoothed, the data from young smokers showed very little overlap with those of non-smokers of the same age (Fig. 6). On the basis of these results, one would expect to be able to separate individual young people according to their smoking habits. These results indicated that the distribution of inspired gas was dependent on flow rate, or frequency, to a greater extent in smokers than in non-smokers. This agrees with the data of Ingram & O'Cain (1971) who found smokers to have frequency dependence of compliance. Only two of our young smokers underwent this test; one of them did demonstrate a decrease in compliance with increasing respiratory frequency, one did not.

It would appear from Fig. 7 that frequency dependence of the distribution of inspired gas tends to increase with age in at least some non-smokers. There are few data on the effect of age on frequency-induced variations in dynamic compliance, but one of our subjects who was well outside the limits shown for young non-smokers did demonstrate decreased compliance with increasing breathing frequency. This subject was a life-time non-smoker with normal expiratory flow rates.

Regional $T$ values did not show striking systematic differences among our groups and measurements of the RV/TLC ratio indicated the presence of intraregional variations in function in groups that showed large differences between $P_f$ and $P_s$. These findings suggested that flow-dependent variations in the alveolar plateaux might not have been regional in nature. However, a reasonable hypothesis explaining the $P_f - P_s$ difference could be advanced, based on the
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proposition that primarily basal regions were affected. During slow expiration apical lung regions empty somewhat later than basal regions in young normal subjects (Anthonisen et al., 1970; Clarke et al., 1969) and since this sequence is dependent mostly on static elastic properties, it is possible that it was present in our other two groups. Ps tended to be flatter in young non-smokers than in our other two groups, implying that the latter may have had lower apical pre-expiratory Xe concentrations. This would have been the case if these subjects had also had a relatively large amount of airway closure at the base. If basal airway closure were greater than normal, a disproportionate degree of expansion of patent, apical alveoli would occur during inflation from RV to 50% VC, at which point all airways would be open. If a bolus were then administered at 50% VC, it would tend to be distributed away from the expanded, stiff apex and toward the recently opened, compliant base, giving a relatively steep top-to-bottom concentration gradient and a Ps which sloped down sharply. Pf sloped up in some subjects, but not in all. When Pf was flat the regional hypothesis would argue that resistances were, as in young non-smokers, relatively even from top to bottom. When Pf sloped upward, the regional interpretation would postulate relatively high resistances in basal regions with resulting apical accumulation of isotope. In favour of this regional explanation for variations in plateau morphology with age and smoking was the good correlation between the onset and extent of airway closure and the steepness of Ps noted in a study of smokers (R. R. Martin, P. T. Macklem & N. R. Anthonisen, unpublished work). Against the regional hypothesis was the failure in the present study of (Pf - Ps) to correlate with apex-to-base differences in T.

Whatever its genesis, it would appear that assessment of flow-dependent changes of the alveolar plateau might be a test of considerable discriminatory power. It was reproducible, simple to perform and gave a minimal radiation dose. Other inert gas boluses could be substituted for the $^{133}$Xe we used. Finally, the basic results, the alveolar plateaux, were recorded on-line with simple equipment and analysed easily. Indeed, cursory examination of our plateaux was in most instances adequate to separate young non-smokers from the other two groups.

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