The Use of a Helium-Oxygen Mixture during Maximum Expiratory Flow to Demonstrate Obstruction in Small Airways in Smokers

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ABSTRACT We measured the response to breathing a mixture of 80% helium and 20% oxygen (He) during a maximum expiratory flow-volume (MEFV) maneuver in 66 nonsmokers and 48 smokers, aged 17–67. All of the subjects studied had (forced expiratory volume in 1 s/forced vital capacity [$FEV_{1.0}/FVC$])$\times$ 100 of greater than 70%. While the flow rates of the smokers were within ±2 SD of those of the nonsmokers at 50% VC ($\dot{V}max_{50}$), both groups showed a reduction in flow with age (nonsmokers: $r = -0.34$, $P < 0.01$; smokers $r = -0.52$, $P < 0.001$). Nonsmokers showed no significant reduction with age in response to breathing He, while smokers showed a marked reduction with age ($r = -0.63$, $P < 0.001$ at $\dot{V}max_{50}$). We also measured the lung volume at which maximum expiratory flow ($\dot{V}max$) while the subject was breathing He became equal to $\dot{V}max$ while he was breathing air, and expressed it as a percent of the VC. This was the most sensitive method of separating smokers from nonsmokers. These results indicate that the use of He during an MEFV maneuver affords sufficient sensitivity to enable detection of functional abnormalities in smokers at a stage when $\dot{V}max$ while they are breathing air is normal.

INTRODUCTION

Recently Despas, Leroux, and Macklem reported that maximum expiratory flow rates ($\dot{V}max$)[1] in patients with chronic bronchitis and in some asthmatics did not increase when the patients breathed a mixture of 80% helium and 20% oxygen (He) as compared to air (1). They attributed this to peripheral airways obstruction. We wondered whether a diminished response to He was an early manifestation of peripheral airways obstruction. Thus, in this study, we have endeavored to determine whether the response of $\dot{V}max$ to the breathing of He is a sufficiently sensitive indicator to allow detection of small airways obstruction in smokers at a stage when $\dot{V}max$ while they are breathing air is within normal range.

METHODS

Data were collected from 114 subjects: 66 nonsmokers whose ages ranged from 17 to 60 yr (mean±SD = 42.3± 10.1 yr) and 48 smokers, ages 24–67 yr (mean±SD = 42.6± 11.2 yr). A nonsmoker was defined as an individual who had never smoked more than a few cigarettes and had smoked absolutely none since age 25 or for 5 yr before the study, whichever was the longer. A smoker was defined as one who had smoked more than 20 cigarettes daily for 5 yr or more. Before entering the study, both smokers and nonsmokers were carefully screened to rule out any previous or current significant respiratory disease such as asthma, frequent pneumonias, tuberculosis, bronchiectasis, or upper respiratory infection in the preceding 2 mo. The presence of any of these conditions excluded subjects, since the study was designed to isolate the effects of smoking as closely as possible. A questionnaire administered at the time of the study revealed that nonsmokers were virtually symptomless, while a large number of the smokers admitted to one or more of cough, sputum, wheezing, or shortness of breath. 60 of the nonsmoking subjects were office workers recruited by the health department of a large local utilities company; there were 10 men and 10 women in each of the 10-yr age groups between the ages of 30 and 60. The remaining nonsmokers, ages 17–30, were laboratory personnel. 30 of the smoking subjects were recruited from a smokers' cessation clinic and the remainder from a per-

Received for publication 21 March 1974 and in revised form 25 November 1974.

[1] *Abbreviations used in this paper:* EPP, equal pressure point; FEV_1/FVC, forced expiratory volume in 1 s/forced vital capacity; MEFV, maximum expiratory flow-volume; P_L, transpulmonary pressure; Rus, resistance between alveoli and EPPs; RV, residual volume; TLC, total lung capacity; VC, vital capacity; $\dot{V}isov$, isoflow-volume; V_L, absolute lung volume; $\dot{V}max$, maximum expiratory flow.

sonnel department and laboratory staff. All smokers accepted into the study had a forced expiratory volume in 1 s/forced vital capacity (FEV_1/FVC) of 70% or greater.

With the subjects breathing air, measurements were made of the subdivisions of lung volume and maximum expiratory flow-volume (MEFV) curves. Volume was measured in an Emerson Model BP volume displacement plethysmograph (Emerson Apparatus Company, Melrose, Mass.). Absolute lung volume (V_L) was measured by the gas compression technique based on Boyle's law (2). Flow was measured by a Fleisch #4 pneumotachygraph and an H.P. 270 differential pressure transducer (Hewlett-Packard Corp., Palo Alto, Calif.). The response of the flow-measuring system was linear to 12 liter/s.

The pneumotachygraph was calibrated for air and for He by passing the gases through it at a variety of constant flow rates into the plethysmograph. The rate of change of volume of the plethysmograph was determined from the slope of the volume-time tracing on a strip chart recorder. The plethysmograph was calibrated from a 3-liter syringe. It was pressure-compensated and had a flat frequency response to 12 cycle/s. MEFV curves were obtained by displaying flow against volume on the x-y coordinates of a Tektronix storage oscilloscope (Tektronix, Inc., Beaverton, Ore.) during forced expiration from total lung capacity (TLC) to residual volume (RV). The curves were stored and traced with an oscillotracer (Waters Mfg. Inc., South Sudbury, Mass.). Each MEFV curve was repeated until three or more that were virtually indistinguishable were obtained. Only those with a consistent vital capacity (VC) between tracings (agreeing within 5%) were used in the calculation. The subject expired to RV and then performed three VCs, breathing He, after which an MEFV curve was obtained from TLC. Despas et al. (1) had equilibrated their subjects on He for 10 min before performing an MEFV maneuver breathing He. However, it was our objective to establish a simple method for screening. This was investigated in a pilot study and it was found that maximum expiratory flow at 50% VC ($\dot{V}max_{50}$) when subjects breathed He was 4.7% less after three VC breaths than after a 10-min equilibration in smokers, whereas it was 3.6% less in nonsmokers. Thus the response to He that we measured may in part be determined by evenness of ventilation distribution.

The response to breathing He was calculated by determining the air and the He flow rates at 50% of VC and at 25% of VC ($\dot{V}max_{25}$) and expressing the increased flow while subjects breathed He as a percent of the flow while they breathed air: $\Delta\dot{V}max_{50} = [(\dot{V}max_{50}\ He - \dot{V}max_{50}\ air)/\dot{V}max_{50}\ air] \times 100$. An additional method[2] of evaluating the response to He is illustrated in Fig. 1. The flow-volume curves for air breathing and those for He breathing were superimposed visually, and the volume where the flow rates for the two gases became identical was determined and expressed as a percent of VC. We have termed this the "isoflow-volume" (Visoẏ). Where the flow-volume curves did not have identical VC, they were superimposed from RV. Differences in VC should be random between TLC and RV and between He and air curves. Any error introduced by matching at RV will thus be random in those who do not have identical VC.

[2] We are grateful to Dr. N. Zamel for this suggestion.

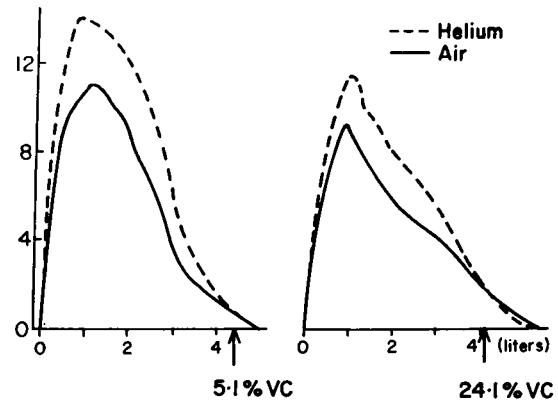

FIGURE 1 Examples of MEFV curves during air breathing (solid lines) and during the breathing of an 80% helium–20% oxygen mixture (He) (broken lines), superimposed to demonstrate the point where the curves either become identical (left) or cross (right) (the isoflow-volume: Visoẏ). Ordinate: flow in liters per second. Abscissa: volume in liters.

RESULTS

$\dot{V}max_{50}$ for the nonsmokers and smokers breathing air is shown in Fig. 2. The regression equation for the nonsmokers indicates that flow rates are higher in younger individuals and decrease with age as follows: -0.038 age (yr) $+ 6.091 \pm 1.08$ ($r = -0.34$, $P < 0.01$). When flow rates for individual smokers are plotted on the regression and 95% confidence limits of the nonsmokers, most of the smokers are seen to have normal airflow rates (-0.067 age [yr] $+ 6.759 \pm 1.16$), but the negative correlation with age is greater in the smokers ($r = -0.55$, $P < 0.001$) and the mean values between smokers and nonsmokers are significantly different from one another ($P < 0.05$). At 25% of VC (Fig. 3), the nonsmokers breathing air decline with age as follows: -0.039 age (yr) $+ 3.133 \pm 0.44$ ($r = -0.68$, $P < 0.001$). Again it is seen that the airflow rates of most smokers are within normal limits at this lung volume (-0.045 age [yr] $+ 3.088 \pm 0.52$; $r = -0.70$, $P < 0.001$), but the mean values between smokers and nonsmokers are not significantly different ($P > 0.05$). Figs. 4 and 5 demonstrate that expressing flow as a function of TLC only slightly improved the separation of smokers from nonsmokers when airflow rates were used as a criterion. In addition, expressing flow rates in VC/s did not materially reduce scatter, an observation also made by Green, Mead, and Turner (3).

However, MEFV curves recorded while the subjects were breathing He showed a greater separation of smokers from nonsmokers. Fig. 6A shows the $\Delta\dot{V}max_{50}$ for the nonsmokers. The mean increase in flow is 47.3% ± 27.4 (2 SD), and there is no significant change with age ($-0.245 + 57.644 \pm 13.56$; $r = -0.13$,

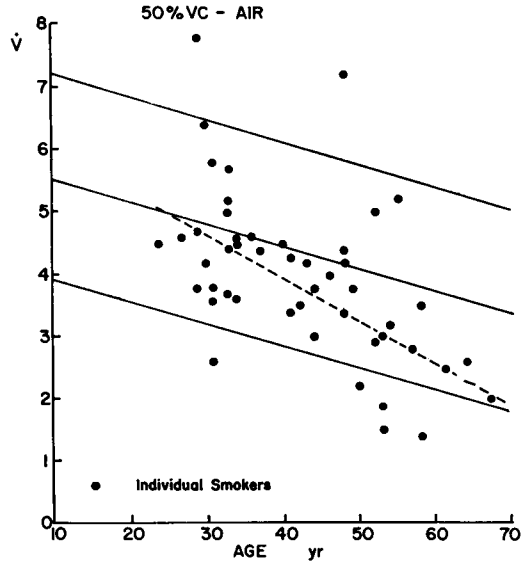

FIGURE 2 Maximum expiratory flow at 50% of vital capacity ($\dot{V}max_{50}$). Solid lines are the regression ±2 SD for the nonsmokers ($r = -0.34$, $P < 0.01$): broken line is regression for smokers ($r = -0.55$; $P < 0.001$). Ordinate: flow in liters per second. Abscissa: age in years.

$P > 0.1$). The individual data points for the smokers are shown in Fig. 6B superimposed on ±2 SD of the nonsmokers. The fall in response to He with age is marked: −0.891 age (yr) + 61.784±12.21 ($r = -0.63$, $P < 0.001$) and the P value between the means of the

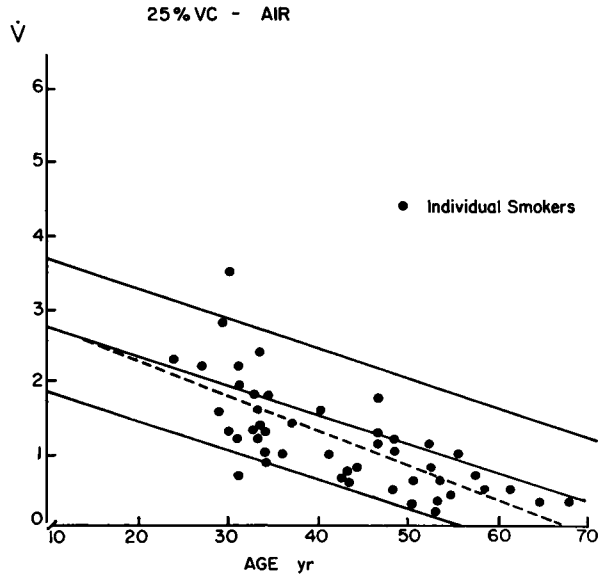

FIGURE 3 Maximum expiratory flow at 25% of vital capacity ($\dot{V}max_{25}$). Solid lines are regression ±2 SD for the nonsmokers ($r = -0.68$); broken line is regression for smokers ($r = -0.70$). Ordinate: flow in liters per second.

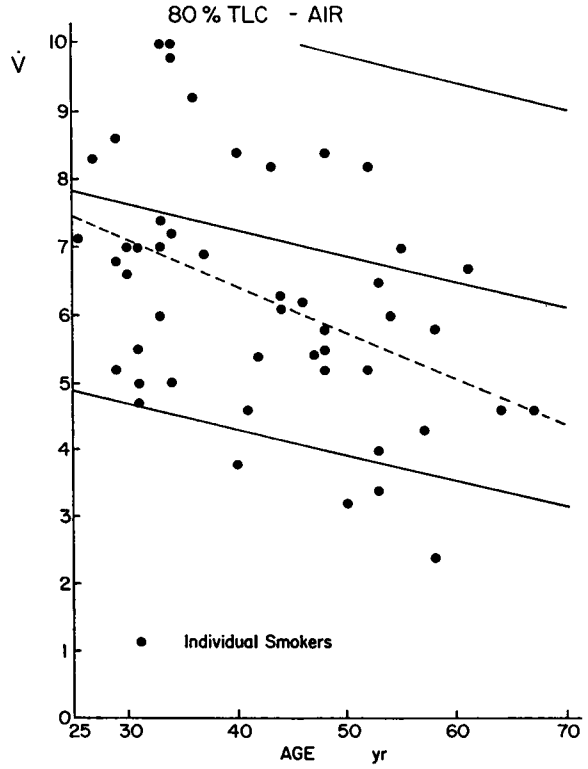

FIGURE 4 Maximum expiratory flow at 80% total lung capacity while subjects breathed air. Solid lines are regression ±2 SD for nonsmokers ($r = -0.25$; $P < 0.05$); broken line is regression for smokers ($r = -0.45$; $P < 0.01$). Ordinate: flow in liters per second.

smokers and nonsmokers is less than 0.001. Seven smokers failed to increase their flow at all with He, and 19 (39.5%) had $\Delta\dot{V}max_{50}$ that fell below 2 SD of the nonsmokers (i.e. lower limit of normal nonsmokers = 19.9%). The percent increase breathing He at 25% VC ($\Delta\dot{V}max_{25}$) is illustrated in Fig. 7, which shows the mean ±1 SD (29.1%±23.4) for the nonsmokers (−0.019 age [yr] + 37.912±23.18; $r = -0.08$, $P > 0.2$), and the individual smokers are plotted. Since the variability was great, −2 SD would fall well below 0. Yet 31 smokers, as compared to 11 nonsmokers, failed to show any response to He at 25% VC, and while in the nonsmokers $\Delta\dot{V}max_{25}$ did not change significantly with age, the smokers' $\Delta\dot{V}max_{25}$ fell with age (−0.063 age [yr] + 35.660±12.15; $r = -0.49$, $P < 0.001$). No smoker over the age of 50 had any response to He at 25% VC and the significance of the differences between the mean values for smokers and nonsmokers was $P < 0.001$.

The Visov̇ is shown for the nonsmokers in Fig. 8A. The scatter is much less than for $\Delta\dot{V}max_{50}$ and $\Delta\dot{V}max_{25}$, and there is a significant rise with age: 0.291 age (yr) + 4.917±6.88 ($r = 0.40$, $P < 0.001$). Fig. 8B shows that Visov̇ rises more steeply with age in smokers

(0.861 age [yr] − 3.079±11.30; $r = .65$, $P < 0.001$). 25 of the smokers (52.1%) had a Visov̇ that fell above +2 SD of the nonsmokers and the means between the smokers and nonsmokers were different ($P < 0.001$). The number of smokers with functional abnormalities was not increased when Visov̇ was expressed as a percent of TLC.

DISCUSSION

It is apparent that a good proportion of otherwise healthy smoking subjects respond quite differently to breathing He during an MEFV maneuver than apparently healthy nonsmokers of similar age and with similar airflow rates. The influence of gas density on lung function has long been of interest to respiratory physiologists. Barach described a beneficial effect of breathing helium-oxygen mixtures in asthma (4–6), and it was subsequently demonstrated that pulmonary resistance fell in normal subjects and in a small group of mild asthmatics breathing He (7, 8). Other workers failed to document increased flow in severe asthmatics (9) but demonstrated reduced resistance in patients with emphysema when He was used (10). Schilder, Roberts, and Fry were the first to describe the use of He during an MEFV maneuver, and they found that while He was breathed there was an increase of about 50% in flow in normal subjects at high lung volumes (due to reduced gas density), while at low lung volumes flow fell below that of air (due to increased gas viscosity) (11). Barnett made the observation that experimental obstruction in large airways failed to affect the response to breathing He but that constriction of small airways caused a marked reduction in the He response (12).

The equal pressure point (EPP) theory of Mead, Turner, Macklem, and Little presented a framework in which the response to He could be more rigorously evaluated (13). According to this concept, the segment upstream from EPPs at a given lung volume has a fixed driving pressure (the elastic recoil pressure of the lung at that volume). Because flow is constant at any given lung volume, the resistance between alveoli and EPPs (Rus) must also be constant. The pressure drop between alveoli and EPPs is composed of frictional losses resulting from turbulence and laminar pressure drops and from convective acceleration. Formulas for each of these forms of pressure losses (14) show that when the pressure drop is due entirely to convective acceleration, V̇max varies as the square root of density (13), whereas when the drop is due entirely to turbulence, V̇max varies as density to the −0.43 power. If fully developed laminar flow accounted entirely for Rus, pressure losses would be independent of density. Since EPPs in normal lungs are at the segmental or the lobar bronchi, where the total cross-sectional area is approximately

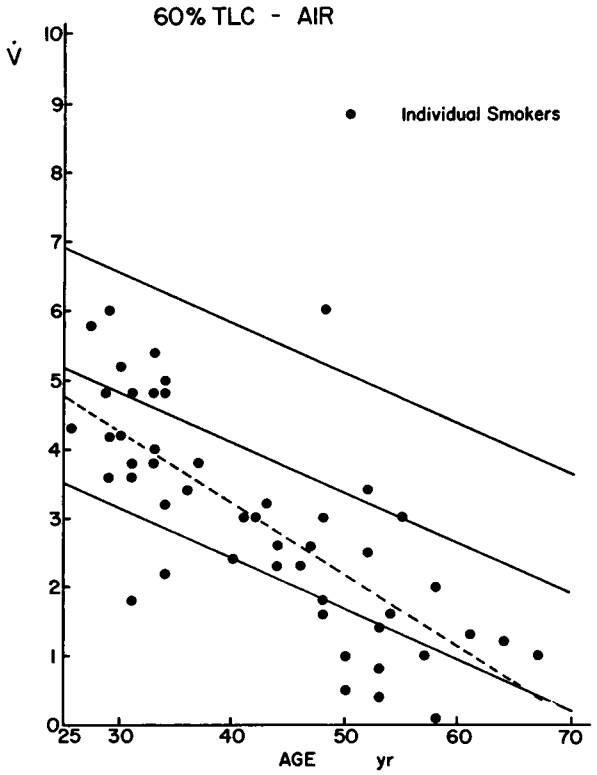

FIGURE 5 Maximum expiratory flow at 60% total lung capacity while subjects breathed air. Solid lines are regression ±2 SD for nonsmokers ($r = -0.52$; $P < 0.001$); broken line is regression for smokers ($r = -0.71$; $P < 0.001$). Ordinate: flow in liters per second.

equal to that of the trachea, resistance due to convective acceleration is the major component of Rus at high lung volumes (15). Wood and Bryan used these concepts in relating the MEFV curve to various ambient pressures and thus gas densities during air breathing. They concluded that flow upstream from EPPs was nonlaminar at volumes above 25% VC and that at higher lung volumes, Rus was almost entirely due to turbulence and/or convective acceleration (16). Thus breathing He during an MEFV maneuver will increase Vmax at those lung volumes where EPPs are in larger airways where Reynolds' numbers and pressure losses due to convective acceleration are large, and therefore the flow regime is dependent on gas density. However, when EPPs are in smaller airways, with lower Reynolds' numbers, flow in the upstream segment may be laminar and thus independent of gas density.

It is obvious that the size of airways at which EPPs are located at a particular lung volume is crucial. Normal subjects tend to have EPPs in larger airways throughout much of their lung volumes, and so they respond to He until about 25% VC, when EPPs move peripherally. In the presence of obstruction in small air-

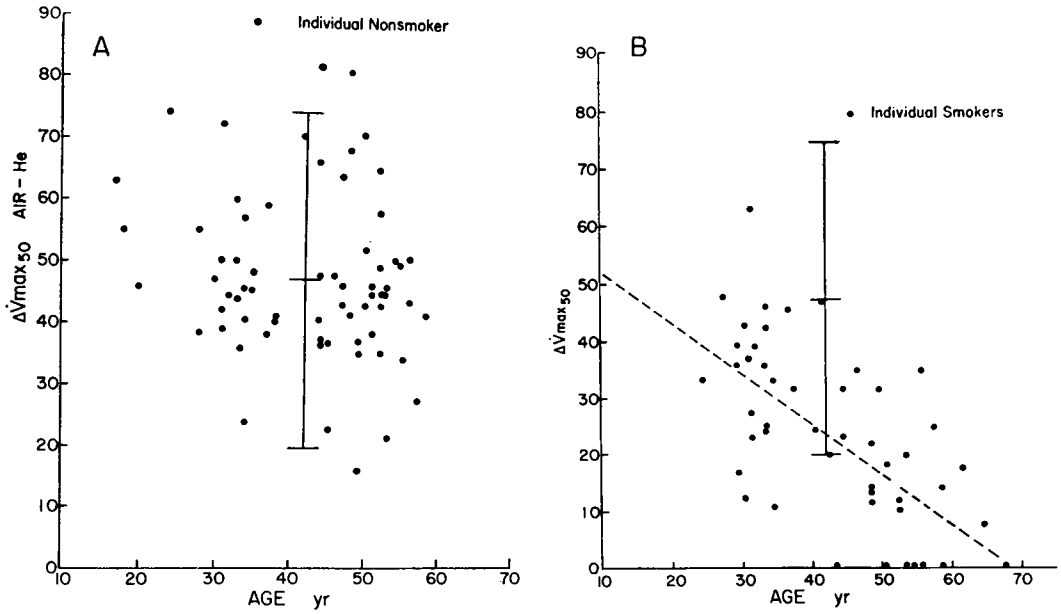

FIGURE 6 (A) Percent increase in $\dot{V}max_{50}$ while breathing He as compared to air. $\Delta\dot{V}max_{50} =$ [(flow with He − flow with air)/flow with air] × 100. Closed circles are individual nonsmokers. Means±2 SD (——) are shown. There is no significant change with age. (B) Parameters are identical to those of Fig. 6A with substitution of individual smokers (closed circles) and regression for smokers (broken line). Means±2 SD of nonsmokers from Fig. 6A are shown. $r = -0.63$; $P < 0.001$.

ways, one of two possibilities must result. If EPPs were to remain at the same site as in normal individuals, Rus would be increased and $\dot{V}max$ during air breathing would be decreased. The response to He would be unchanged. On the other hand, if EPPs were to be displaced upstream as a result of the obstruction, the decrease in Rus because of shortening of the upstream segment would tend to counterbalance the increase in Rus resulting from airway narrowing, thus tending to maintain $\dot{V}max$ during air breathing. If this were the case, however, EPPs would be located in smaller airways, where the total cross-sectional area is larger and the Reynolds' numbers lower. The response to breathing He would therefore be diminished. Because the $\dot{V}max_{50}$ and the $\dot{V}max_{25}$ while the subjects were breathing air were within the normal range, whereas the response to He was markedly diminished, the second alternative must have occurred in the lungs of smokers. Thus $\dot{V}max_{50}$ and $\dot{V}max_{25}$ during air breathing are insensitive to peripheral airways obstruction until it is relatively far advanced, but assessment of the response to He is quite sensitive, particularly when the $\dot{V}isov$ is measured (Fig. 8B). Although differences in ventilation distribution between smokers and nonsmokers could have influenced the response to He, the differences in the He response between the two groups were so great that this factor is not likely to play an important role.

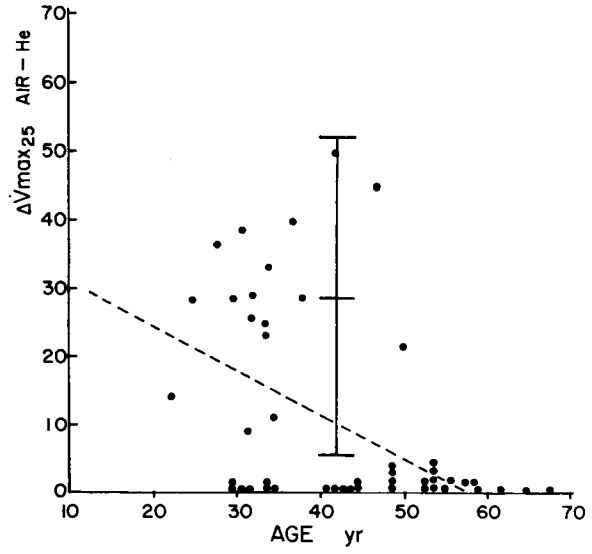

FIGURE 7 Percent increase while breathing He as compared to air at 25% of vital capacity ($\Delta\dot{V}max_{25}$). Closed circles are individual smokers. Broken line is regression for smokers. Mean ±1 SD of nonsmokers is shown. $r = -0.49$; $P < 0.001$.

Stated simply: the failure to increase $\dot{V}max$ while breathing He indicates a laminar flow regime upstream from EPP; a large increase in $\dot{V}max$ with He indi-

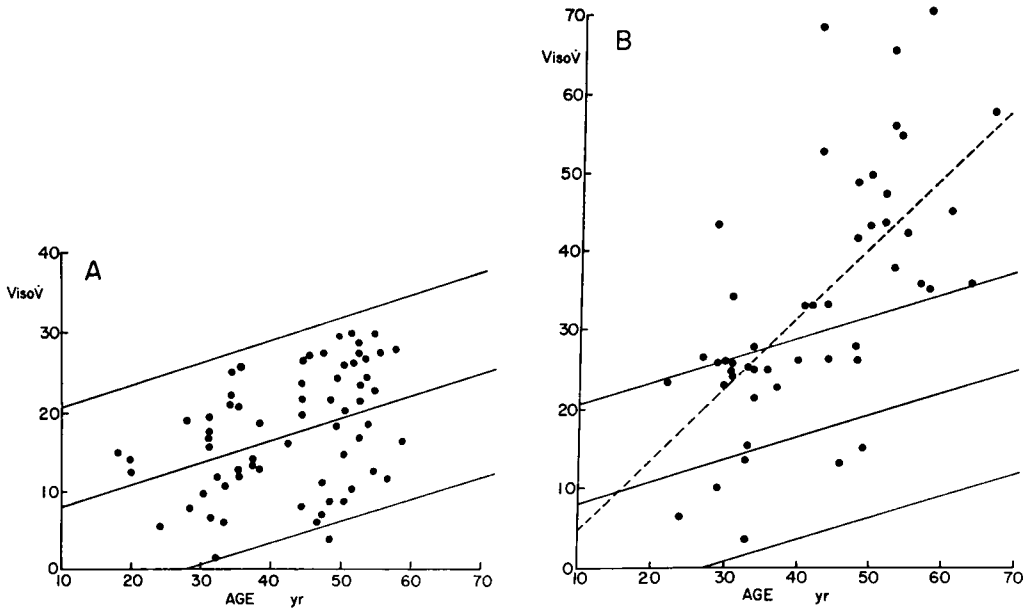

FIGURE 8 (A) Isoflow-volume (Visov̇) for nonsmokers. Solid lines are regression ±2 SD for nonsmokers. Ordinate is Visov̇ expressed as a percent of vital capacity. $r = 0.40$; $P < 0.001$. (B) Visov̇ for smokers (●) and nonsmokers. Solid lines are regression ±2 SD for nonsmokers; broken line is regression for smokers. Visov̇ is expressed as percent of vital capacity. $r = 0.65$; $P < 0.001$.

cates that the major flow regime in the upstream segment is convective acceleration and/or turbulence (1, 13, 16); and the gradation between these two extremes in a population of smokers with normal airflow rates must indicate the shift of EPP (at a given lung volume) from airways whose caliber is large to airways whose size is smaller. That the EPP concept can be applied to lungs with nonuniform ventilation distribution is supported by the work of Takashima et al. (17), who demonstrated that during an MEFV maneuver the lungs tended to behave as a single compartment, even in patients with chronic obstructive pulmonary disease.

It might be argued that a comparison of $\dot{V}$max during air breathing at given percentages of TLC rather than VC would prove to be a more sensitive method of detecting functional abnormalities in smokers. However, Figs 2 and 5 indicate that while the smokers' correlation coefficient of flow vs. age was −0.71 with flow at 60% TLC and −0.55 with flow at 50% VC, only four additional smokers fell clear of −2 SD of the nonsmokers' data when we used TLC as compared to VC. This is probably because the mean RV between smokers and nonsmokers was not significantly different ($P > 0.2$). At 50% TLC, airflow rates in some smokers became so low that it was difficult to interpret them accurately, so this lung volume is not suitable for screening.

We argue (see Appendix) that because $\Delta\dot{V}max_{50}$ does not fall with age in nonsmokers, whereas elastic recoil pressure at 50% VC does, therefore $\Delta\dot{V}max_{50}$ is uninfluenced by loss of elastic recoil. Thus, the response to helium is probably relatively specific for the caliber of the small airways. The Visov̇ may not be as specific for airway caliber, because loss of elastic recoil may well have an influence on this measurement (18. See Appendix.). Further support that these tests are determined by properties of the small airways is that upon cessation of smoking both $\Delta\dot{V}max_{50}$ and Visov̇ improved, without any change in elastic recoil (19).

Although the main purpose of this investigation was to compare the influence of gas density on $\dot{V}$max in smokers and nonsmokers, the single-breath N_2 curve and compliance at different frequencies were also measured in most of the subjects. Of the smokers, 25.0% were frequency-dependent, 35.4% had an abnormal slope of the alveolar plateau, and 38.9% had an abnormal closing capacity and/or closing volume. Abnormal $\Delta\dot{V}max_{50}$ was found in 39.5%, and 52.1% had an abnormal Visov̇. The Visov̇ was abnormal in all smokers over the age of 50. Thus, in our hands, if one wishes to determine whether a smoker has functional abnormalities, the measurement of Visov̇ is the most sensitive test.

This is probably more than an academic point. It is likely that one cannot detect functional abnormalities from symptoms such as cough and sputum, because the available evidence suggests that the correlation between the two is poor (20–22). Yet not all smokers have

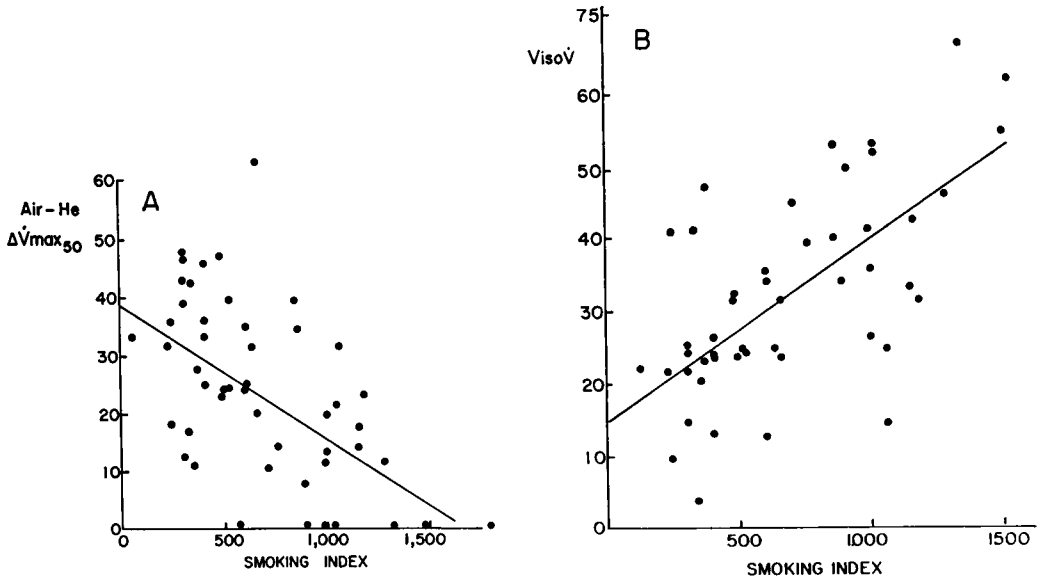

FIGURE 9 (A) Smoking index, calculated by multiplying number of cigarettes smoked per day by smoking years. Closed circles are individual smokers. Solid line is regression. $r = -0.53$; $P < 0.001$. (B) Smoking index at isoflow-volume (Visov̇). Closed circles are individual smokers. Solid line is regression with smoking index. $r = 0.66$; $P < 0.001$.

functional abnormalities. However, smokers with functional abnormalities may represent a high-risk group. Although the long-term health significance of these functional abnormalities is unknown (and long-term prospective studies will be necessary to determine the significance), the abnormalities are similar to, but less than, those found in chronic bronchitis and emphysema. Characteristic pathophysiological abnormalities in these diseases are loss of elastic recoil (23), abnormalities of ventilation distribution, as reflected in a steeply sloping alveolar plateau of the single-breath N_2 test (24), frequency dependence of compliance (25), alterations in regional distribution of inspired gas (26), abnormalities in gas exchange, as reflected in alveolar-arterial oxygen tension differences (27) and dead-space tidal volume ratios (28), decreased diffusion capacity (29), and a diminished or absent response of Vmax while breathing helium (1). The majority of these abnormalities have now been described in some smokers (20, 21, 30–34). Thus, although the final proof is not yet at hand, the circumstantial evidence is accumulating that by using simple tests of lung function one can detect smokers at high risk to develop irreversible disease.

If this is so, there should be a correlation between the amount smoked and the functional abnormalities, because the development of irreversible airways obstruction is so correlated. When the exposure to cigarettes for our subjects was expressed as a smoking index derived from number of cigarettes per day times smoking years, the results (Fig. 9A) showed a reduction in response to He at $V\text{max}_{50}$ with increasing smoking index ($r = -0.53$, $P < 0.001$), which was remarkably similar to reduction with age ($r = -0.63$, $P < 0.001$). It was also true for Visov̇, which showed a marked rise (Fig. 9B) with smoking index ($r = 0.66$, $P < 0.001$), similar to the rise with age ($r = 0.65$, $P < 0.001$). That the members of our sample had similar smoking habits explains this; i.e., most subjects began smoking in their late teens and smoked 20–25 cigarettes/day from then on.

APPENDIX

Since the He MEFV curve appears to be a simple, sensitive indicator of early functional abnormalities suggestive of peripheral airways obstruction, we examined the physiological determinants of $\Delta\dot{V}\text{max}_{50}$ and Visov̇. In particular, we wished to assess the relative influence of loss of elasticity and peripheral airways obstruction on these measurements.

Of the subjects in this study, elastic recoil measurements were carried out on 61 of the nonsmokers and 46 of the smokers. Transpulmonary pressure (P_L) was measured with an esophageal balloon (10 × 3.5 cm; P.E. 200 tubing, 100 cm) and a Sanborn 267 B differential transducer (Sanborn Div., Hewlett-Packard Co., Palo Alto, Calif.) that subtracted mouth pressure to record P_L, from which expiratory static $V_L - P_L$ curves were constructed. From this data the resistance of the upstream segment was calculated (13) as the ratio of elastic recoil pressure to Vmax at 50% VC when breathing He ($Rus_{50}He$). Upstream resistance was also calculated at Visov̇ (Rus[Visov̇]) by dividing the elastic recoil at the appropriate lung volume by the maximum expiratory flow rate at the same lung volume.

Fig. 10A shows that there was no change with age in $\Delta\dot{V}max_{50}$ in nonsmokers ($r = -0.08$) but that in smokers $\Delta\dot{V}max_{50}$ fell significantly ($r = -0.62$, $P < 0.001$). Both groups showed a fall in $\dot{V}max_{50}$ with age (Fig. 10B): nonsmokers: $r = -0.31$, $P < 0.01$; smokers: $r = -0.55$, $P < 0.001$. While the smokers as a whole had lower $\dot{V}max_{50}$ than nonsmokers, most fell within ±2 SD of the nonsmokers. P_L at 50% VC (P_{L50}) for the two groups (Fig. 10C) was similar in the younger subjects but fell somewhat more quickly in smokers (nonsmokers: $r = -0.33$, $P < 0.01$; smokers: $r = -0.42$, $P < 0.002$). $Rus_{50}He$ (Fig. 10D) did not change significantly with age in nonsmokers ($r = 0.20$) but rose in smokers ($r = 0.44$, $P < 0.002$). Fig. 10E demonstrates that $Visô$ rose more quickly for smokers ($r = 0.63$, $P < 0.001$) than for nonsmokers ($r = 0.36$, $P < 0.01$), and Fig. 10F shows that while $\dot{V}max$ at $Visô$ ($\dot{V}max$ [$Visô$]) did not change with age in nonsmokers ($r = 0.10$), it rose in smokers ($r = 0.32$, $P < 0.02$). P_L at $Visô$ (P_L[$Visô$]) (Fig. 10G) also did not change with age in nonsmokers ($r = 0.18$) but rose in smokers ($r = 0.39$, $P < 0.01$). Rus ($Visô$) did not change in smokers ($r = -0.03$) or in nonsmokers ($r = 0.18$) (Fig. 10 H). The significance of the differences of the mean values of each of the variables between smokers and nonsmokers was as follows: 10A, $P < 0.001$; 10B, $P < 0.05$; 10C, NS; 10D, $P < 0.001$; 10E, $P < 0.001$; 10F, $P < 0.001$; 10G, $P < 0.001$; 10H, NS.

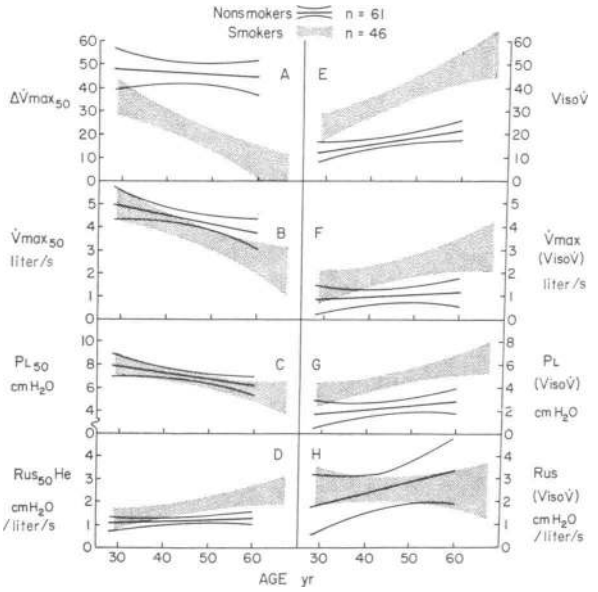

FIGURE 10 Regression with age ±SE regression line (smokers and nonsmokers). A: percent change in $\dot{V}max_{50}$ with He at 50% VC ($\Delta\dot{V}max_{50}$). $P < 0.001$ for smokers; NS for nonsmokers. B: maximum expiratory flow breathing air at 50% VC ($\dot{V}max_{50}$). $P < 0.001$ for smokers; < 0.01 for nonsmokers. C: transpulmonary pressure at 50% VC (P_{L50}). $P < 0.002$ for smokers; < 0.01 for nonsmokers. D: upstream resistance with He at 50% VC ($Rus_{50}He$). $P < 0.002$ for smokers; NS for nonsmokers. E: isoflow volume ($Visô$). $P < 0.001$ for smokers; < 0.01 for nonsmokers. F: maximum expiratory flow at $Visô$ ($\dot{V}max$[$Visô$]). $P < 0.02$ for smokers; NS for nonsmokers. G: transpulmonary pressure at $Visô$ (P_L[$Visô$]). $P < 0.01$ for smokers; NS for nonsmokers. H: upstream resistance at $Visô$ (Rus[$Visô$]). P is NS for both smokers and nonsmokers. P values refer to significance of change with age.

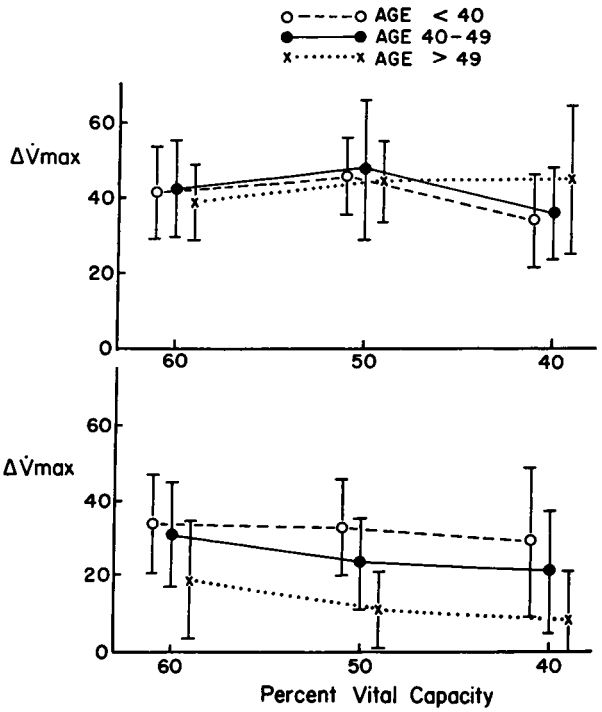

FIGURE 11 Increase in maximum expiratory flow rate when subjects breathed an 80% He–20% O_2 mixture compared to air ($\Delta\dot{V}max$) at 60, 50, and 40% VC ±1 SD for various age groups of nonsmokers (upper panel) and smokers (lower panel).

When $\dot{V}max$ is independent of gas density, the resistance upstream from EPP (13) is also independent of gas density. As fully developed laminar flow is the only known pressure-flow regime independent of gas density, and as this regime occurs only in small airways, a poor response to He-O_2 would indicate that the peripheral airways constitute most of the Rus. This is not the case in normal lungs at volumes greater than 25% VC (16). Thus, the cause of an abnormally low He-O_2 response is thought to be peripheral airways narrowing (1). However, it is possible that loss of elastic recoil could result in the displacement of EPP toward the alveoli (13) so that laminar flow resistance would contribute more to the total Rus. Thus it seems theoretically possible that the He-O_2 response could result both from peripheral airways narrowing and from loss of elasticity.

For two reasons, we think that loss of elastic recoil does not influence the $\Delta\dot{V}max_{50}$. First, in nonsmokers there is a moderate decrease in elastic recoil pressure at 50% VC with age but no change in $\Delta\dot{V}max_{50}$. Second, Wood and Bryan (16) showed that the response of $\dot{V}max$ to changes in gas density is independent of V_L from peak flow to functional residual capacity (FRC). We have analyzed our own data in this regard. The percent increase in flow when breathing He was unchanged in all groups between 60 and 40% VC (Fig. 11). However, over these volumes there are substantial changes in elastic recoil pressure. In spite of these changes, EPPs move little over these lung volumes

(13). It therefore appears that $\Delta\dot{V}max_{50}$ is uninfluenced by moderate changes in elastic recoil. For these reasons, we do not think that the slightly decreased $P_{L_{50}}$ in the total population of smokers is responsible for their lower $\Delta\dot{V}max_{50}$ (Fig. 10C). Indeed, the striking fall in $\Delta\dot{V}max_{50}$ with age in smokers is associated with a rise in $Rus_{50}He$ with age. We conclude that $\Delta\dot{V}max_{50}$ is a relatively specific test of small airways caliber.

The same cannot be said for the $Visov\dot{}$. This test may well reflect the V_L where EPP move rapidly toward the alveoli (13). With peripheral shift in EPP, the laminar component of Rus would increase substantially. That, coupled with the decrease in flow as volume decreases, would result in lower Reynolds' numbers in the upstream segment. Elastic recoil pressure certainly plays a role in the decrease in flow and may well be responsible for the shift in EPP. Thus the influence of elastic recoil on $Visov\dot{}$ may be mediated both through its effect on $\dot{V}max$ and its effect on the site of EPP. If elastic recoil is the major determinant of $Visov\dot{}$, then P_L at $Visov\dot{}$ should not change with age. This is the case in nonsmokers. If its influence is mediated through its effect on $\dot{V}max$, one could expect that $\dot{V}max$ at $Visov\dot{}$ would not change with age either. This too is the case in nonsmokers. Thus we interpret our data in nonsmokers as indicating that the rise in $Visov\dot{}$ with age is probably a reflection of a reduction in $\dot{V}max$ secondary to loss of recoil.

If the higher $Visov\dot{}$ in smokers was due to loss of elasticity, then their P_L at the $Visov\dot{}$ should be similar to that of nonsmokers. In fact, as shown in Fig. 10G, mean transpulmonary pressure at $Visov\dot{}$ in smokers was significantly higher than in nonsmokers ($P < 0.001$). Thus the increased $Visov\dot{}$ cannot be attributed entirely to loss of elasticity. The most likely explanation for identical $\dot{V}max$ at a given lung volume breathing air and breathing He is that Reynolds' numbers in the segment upstream from EPP are so low that the pressure-flow regime is independent of gas density. If we neglect differences in gas viscosity, Reynolds' numbers at $Visov\dot{}$ will be low to the extent that flow in the upstream segment is low and the total tube diameter is large; thus in the segment upstream from EPP, Reynolds' numbers will fall as EPP are displaced towards the alveoli and the total cross-section increases. Therefore $Visov\dot{}$ may be increased by a given site of EPP and/or a reduction in $\dot{V}max$. It may then be argued that a high $\dot{V}max$ ($Visov\dot{}$) implies that in the upstream segment Reynolds' numbers have decreased because EPPs have moved upstream. In the nonsmokers we have argued that at $Visov\dot{}$ Reynolds' numbers are low because of low $\dot{V}max$ secondary to loss of recoil at a given lung volume; in the smokers we argue that the higher $Visov\dot{}$ in the presence of high $\dot{V}max$ must be due at least in part to low Reynolds' numbers in the upstream segment secondary to peripheral shift of EPP with peripheral airways obstruction.

In addition, we have obtained additional information on 10 subjects who stopped smoking (19). While P_L was unchanged after cessation, $\Delta\dot{V}max_{50}$ was increased and $Visov\dot{}$ reduced, indicating an improvement in small airways obstruction. These observations support the theory that increased $Visov\dot{}$ in smokers is due at least in part to airways disease.

ADDENDUM

Since the preparation of this paper, Hutcheon, Griffin, Levison, and Zamel also have described the isoflow-volume and have shown the sensitivity of this test in detecting functional abnormalities in smokers (35).

ACKNOWLEDGMENTS

Mrs. Bernice Lurie assisted with recruitment of the smoking subjects and Mrs. M. Hammer with the preparation of the manuscript.

This study was supported by NIH grant no. 73-2902 (r) and a grant from the Medical Research Council of Canada.

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