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Ventilation distribution and density dependence of expiratory flow in asthmatic children

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COOPER, DAN M., ROBERT B. MELLINS, AND ANTHONY L. MANSELL. *Ventilation distribution and density dependence of expiratory flow in asthmatic children*. *J. Appl. Physiol.: Respirat. Environ. Exercise Physiol.* 54(4): 1125–1130, 1983.—Of 114 asthmatic children, 21% had abnormally steep phase III slopes from a modified single-breath oxygen (SBO₂) procedure. We hypothesized that the steep slopes reflect inequality of time constants caused by obstruction of peripheral airways and tested this by using a bronchodilator to reduce overall time constants in subgroups of 10 children with steep slopes (SS) and 20 children with normal slopes (NS). Maximum expiratory flow increased by equivalent degrees (0.65–0.70 l/s) in both groups, but slope decreased significantly only in the SS group. Moreover, the single-breath mixing efficiency of inspired oxygen with resident nitrogen was normal in the NS group but significantly low in the SS group. Density dependence of maximum expiratory flow (DD) was abnormally small in the SS group [$15 \pm 6\%$ (SD) increase compared with $57 \pm 13\%$ increase in a separate group of normal children] and was independent of the anatomical dead space. In contrast, DD was normal and varied inversely with anatomical dead space ($r = 0.62$, $P < 0.01$) in the NS group. These results indicate that 1) steep SBO₂ slopes found in asthmatic children between acute episodes reflect unequal time constants caused by obstruction of peripheral airways and 2) part of the variation in DD among asthmatic children is caused by variation in convective accelerative pressure losses in major airways.

peripheral airways; lung growth; single-breath nitrogen washout

IN ASSESSMENT OF ASTHMATIC CHILDREN between acute episodes, we have observed that some have abnormally steep slopes of phase III of the single-breath oxygen test (SBO₂), whereas others have slopes well within the normal range. Previous work in this laboratory (2) has indicated that the small slope of phase III in normal children is produced primarily by the vertical interregional gradient of ventilation. However, Fowler (8) proposed thirty years ago that the steep slopes observed in some adults with chronic obstructive pulmonary disease resulted from inequality of time constants in peripheral airways. More recently, obstruction of peripheral airways has been associated with maldistribution of a tracer gas in excised lungs (16). Furthermore, morphological studies of asthma from postmortem specimens (7) and from lung biopsies in children (4) have shown that there may be obstruction of peripheral airways by mucous plugs, mucosal edema, and desquamated epithelial cells.

Therefore we hypothesized that the steep phase III

slopes detected in asthmatic children reflect unequal time constants caused by obstruction of peripheral airways. We tested our hypothesis in three ways: 1) the effect of bronchodilator on the slope of phase III—we reasoned that reduction in flow resistance by a bronchodilator might reduce slopes produced by inequality of peripheral time constants but should not reduce slopes produced by the vertical gradient of ventilation; 2) the single-breath mixing efficiency, an index of trapped resident nitrogen after a single breath of pure oxygen—we reasoned that slopes caused by obstruction of peripheral airways would result in increased amounts of trapped gas and reduced mixing efficiencies, whereas slopes caused by the vertical interregional gradient of ventilation would be associated with normal mixing efficiencies; and 3) density dependence of maximum expiratory flow—Despas et al. (5) have proposed that elevated resistance of peripheral airways in asthmatic adults can be detected as a reduction in density dependence of maximum expiratory flow.

In addition, we used an index of anatomical dead space from the single-breath nitrogen washout to determine whether variability in the size of central airways contributes to variability in density dependence of maximum expiratory flow in asthmatic children, as predicted from recent studies of expiratory flow limitation (1, 14, 15).

METHODS

Subjects. We studied 30 asthmatic children, aged 6–18 yr, who were asymptomatic at the time of testing. They had been referred from an outpatient clinic for assessment of pulmonary function. Each child had taken one or more medicines as treatment for asthma on a regular basis. Any current medicines were stopped at least 12 h before the study. We made up the group of asthmatic children to include 10 whose slopes of phase III of the SBO₂ were greater than two standard deviations of normal values (SS group) and 20 whose slopes were in the normal range (NS group) (Fig. 1). Neither maximum expiratory flow nor apparent clinical severity of the asthma was considered in selection of the patients. Another group of 20 normal children, aged 7–18 yr, served as controls for density dependence of maximum expiratory flow (DD). The three groups were well matched for age and height (Table 1). In addition, we measured ratios of residual volume to total lung capacity (RV/TLC) and functional residual capacity to total lung capacity (FRC/

TABLE 1. *Characteristics of normal and asthmatic children studied*

Group	n	Ht, cm	Age, yr	MMEF, % pred	$\Delta\dot{V}_{\max_{50\% \text{ VC}}}$, %	Viso $\dot{V}$, %
Normal	20	152 $\pm$ 15	12 $\pm$ 3	103 $\pm$ 16	57 $\pm$ 13	17 $\pm$ 6
Asthmatic						
NS	20	154 $\pm$ 18	13 $\pm$ 3	73 $\pm$ 21*	46 $\pm$ 18	16 $\pm$ 8
SS	10	151 $\pm$ 18	12 $\pm$ 4	28 $\pm$ 8*	15 $\pm$ 6*	36 $\pm$ 14*

Values are means $\pm$ SD; n, no. of children per group. NS, normal slope; SS, steep slope; MMEF, maximum midexpiratory flow; $\Delta\dot{V}_{\max_{50\% \text{ VC}}}$, increase in maximal expiratory flow at 50% vital capacity; Viso $\dot{V}$, volume of isoflow. * Differed from normal children and other asthmatics: $P < 0.01$ by analysis of variance and modified t test.

TLC) in 35 more SS asthmatic children and 65 more NS asthmatic children.

Because we had predetermined the numbers of asthmatic children with normal and steep phase III slopes, we also surveyed all asthmatic children referred for assessment of pulmonary function in 1980 ($n = 114$) to find the percentage of those with steep slopes.

Single-breath oxygen test. The SBO₂ was performed with a bag-in-box apparatus and wedge spirometer to allow measurement of the inspired volume of oxygen. We have previously found in children that the slope of phase III is more reproducible when the inhalation of oxygen begins at FRC rather than at RV (2). We therefore used the slopes from the FRC maneuver for the present study, although we found no qualitative differences in our results when we analyzed the data from the RV maneuver. On the basis of a previous study of the effect of expiratory flow rates on the SBO₂ in children (2), we kept expiratory flow rates between 0.5 and 1.5 l/s, as measured by a flow transducer connected to the wedge spirometer. There was no difference in expiratory flow rates between the two groups of patients. We measured the slope of phase III from the best-fit line through the linear portion of the alveolar plateau.

We compared the amount of nitrogen exhaled, i.e., the area under the nitrogen-volume curve, with that predicted assuming complete mixing of inspired oxygen with resident nitrogen. The proportion of observed to predicted volumes of nitrogen was expressed as percent and is identified as the single-breath mixing efficiency. Our methods for calculating mixing efficiency from plethysmographic measurements of lung volume and the SBO₂ have been published elsewhere (2).

For an estimation of the volume of major airways, we measured the anatomical dead space (V_D) from SBO₂ tracings by the method of Fowler et al. (see Ref. 3). Results are from maneuvers where oxygen was inspired from FRC to TLC and are expressed as the proportion of V_D to TLC in percent. To establish standard values, we calculated V_D from the SBO₂ tracings of 39 normal children, aged 6–18 yr.

Lung volumes and maximal expiratory flow rates. We measured thoracic gas volume at FRC using a pressure-type plethysmograph. A panting frequency of approximately once per second was used to avoid spurious elevations of FRC and to avoid overestimation of thoracic gas volume. We then measured inspiratory capacity and a slow expired vital capacity (VC) with a water spirometer and combined these with the plethysmographic mea-

surements to calculate TLC and its subdivisions.

A wedge spirometer and X-Y recorder were used to measure maximum expiratory flow-volume (MEFV) curves. We recorded at least three forced VC maneuvers for each subject and used the largest flows and expired volumes for analysis. For measurements of DD, MEFV curves were repeated after the subjects breathed an 80% helium-20% oxygen mixture. To ensure that the gas mixture was well distributed within the lungs, we measured expired nitrogen concentration. FVC maneuvers were not performed until the final nitrogen concentration was 5% or smaller. We used for comparison only those maneuvers in which the VC after helium-oxygen breathing differed by less than 5% from the VC after room air breathing. DD was calculated as the percent increase in flow at 50% VC ($\Delta\dot{V}_{\max_{50\% \text{ VC}}}$) and the volume of isoflow (Viso $\dot{V}$) in percent of VC.

Bronchodilator. After the control measurements of lung volume, maximum expiratory flow, DD, and the SBO₂, nebulized isoproterenol was administered by a face mask. The amount given was 2.5 mg diluted in 2 ml of isotonic saline. It was inhaled during tidal breathing over a 4- to 5-min period. We repeated measurements of lung volume, maximum expiratory flow, and the SBO₂ 10–20 min later. All measurements were completed by 20 min after inhalation of the bronchodilator.

Retrospective study. Hospital and clinic records of all 30 asthmatic children were reviewed with attention to the 1-yr period prior to testing. We recorded hospitalizations for status asthmaticus and the number of emergency room visits in which one or more injections of epinephrine had been given.

Statistical methods. We used standard techniques of statistical analysis, including paired and unpaired t tests for comparing two population means, analysis of variance and modified t test for comparison of more than two means, and correlation of two variables by linear regression analysis (13).

RESULTS

Single-breath oxygen test. In our survey of 114 asthmatic children referred for assessment of pulmonary function, we found that 21% had slopes of phase III greater than 2 SD of normal values. The slopes of the 30 children studied are shown in Figs. 1 and 2. Note that the distribution of slopes in the NS group was indistinguishable from that of normal children. The slopes in the NS group all fell below 3.5% N₂/l and within the normal range, and those in the SS group were above 4.3% N₂/l and outside the normal range. Even after administration of the bronchodilator, there was very little overlap between the two groups (Fig. 2). In addition, slope behaved differently in the two groups when the bronchodilator was given. It reduced slopes in all 10 subjects with steep slopes [by a mean $28 \pm 16\%$ (SD), $P < 0.001$ by paired t test]. In contrast, 7 slopes increased and 13 decreased in the subjects with normal slopes, and there was no significant change for the group as a whole. For these reasons, we have maintained the separation between subjects with normal slopes and those with steep slopes in presentation of our data.

Mixing efficiency from the SBO₂ increases as a function

FIG. 1. Slope of phase III in $\%N_2/L$ as a function of height. Single breath of O_2 was taken from functional residual capacity. Closed circles represent values from 30 asthmatic children. Shaded area represents mean ± 2 SD from measurements in 54 normal children (2).

FIG. 2. Slope of phase III in $\%N_2/L$ in 30 asthmatic children before and after inhalation of standard dose of isoproterenol. Closed circles represent 20 children with normal values for slope before isoproterenol. Open circles represent 10 children with abnormally steep slopes before isoproterenol.

of height during childhood (2). Values in the asthmatic children with normal phase III slopes were a mean 96% of that predicted according to height, and values from the children with steep phase III slopes were a mean 85% of that predicted ($P < 0.025$). In the 30 asthmatic children as a group, mixing efficiency decreased significantly as the phase III slope increased ($r = -0.44$, $P < 0.025$, Fig. 3).

The ratio of V_D to TLC decreased significantly with

increasing height in the group of 39 normal children, as described by the regression equation $V_D/TLC = -3.3 \times 10^{-4}$ (height in cm) + 0.104 ($r = -0.37$, $P < 0.02$). As shown in Fig. 4, values from the asthmatic children fell within 2 SD of the mean values of the normal children.

In an additional 35 SS patients, RV/TLC was $34 \pm 13\%$ (SD) and FRC/TLC was $57 \pm 8\%$ (SD). In an additional 65 NS patients, RV/TLC was $22 \pm 7\%$ (SD) and FRC/TLC was $50 \pm 6\%$ (SD). Both RV/TLC and FRC/TLC were significantly higher in the SS group than in the NS group ($P < 0.05$).

Maximum expiratory flow and density dependence. Maximum expiratory flow was significantly low in the asthmatic children regardless of phase III slope. In 20 of the 30 asthmatic children, the maximum midexpiratory flow (MMEF) was below 2 SD of values predicted according to height in the group of 20 normal children (Fig.

FIG. 3. Mixing efficiency, calculated from single-breath O_2 procedure, as a function of phase III slope. Preinspiratory lung volume was functional residual capacity. Since normal values for both mixing efficiency and slope depend on size of subject, values from 30 asthmatic children are compared with values predicted according to height. Mixing efficiency is expressed as percent predicted, and slope values are expressed as observed minus predicted in $\%N_2/L$. Shaded area represents ± 2 SD of values from 54 normal children (2). Symbols as in Fig. 2.

FIG. 4. Ratio of anatomical dead space (V_D) to total lung capacity (TLC) as a function of height. V_D was measured from single-breath O_2 procedure and is expressed as $\%TLC$. Shaded area represents ± 2 SD of values from 39 normal children aged 6-18 yr. V_D/TLC decreases significantly with age in normal children. Symbols as in Fig. 2.

5). However, the extent of flow reduction was much more severe in the subjects with steep phase III slopes than in those with normal slopes (Table 1, Fig. 5). With inhalation of the bronchodilator, MMEF increased by a mean 23% of values predicted for height (or by a mean 0.70 l/s) in the SS group and by a mean 23% of values predicted for height (or by a mean 0.65 l/s) in the NS group. After the bronchodilator, 9 out of the 10 SS patients still had MMEF values below 2 SD of normal values (Fig. 5).

DD is expressed both at $\Delta V_{\max 50\% VC}$ and as the $\text{Viso}\dot{V}$ in Table 1. Since we found $\Delta V_{\max 50\% VC}$ the less variable of the two indices, we use it for the following comparisons. Reduction in DD was associated with reduction in maximum expiratory flow and elevation in the phase III slope. In the 20 normal children, the $\Delta V_{\max 50\% VC}$ ranged from 31 (−2 SD) to 83% (+2 SD), and 14 of the 30 asthmatic children were below 2 SD. Of these 14 subjects with abnormally low DD, 13 had abnormally low MMEF and 10 had abnormally steep phase III slopes (Fig. 6). Of the remaining 16 with normal DD, there was no association between the $\Delta V_{\max 50\% VC}$ and maximum expiratory flow or the phase III slope. However, within this wide range of normal DD, we found the lowest values for $\Delta V_{\max 50\% VC}$ in subjects with largest ratios of V_D to TLC (Fig. 7). There was no association between these two variables in the 14 patients with low DD.

Retrospective study. The group of asthmatic children with abnormally steep phase III slopes and abnormally low DD had a more severe course over the year preceding our study than the group with normal slopes. Over twice as many were admitted to hospital at least once for treatment of asthma ($P < 0.05$ by chi-square test), frequency of hospitalization was over three times as great ($P < 0.05$ by unpaired t test), and use of epinephrine

injections for emergency treatment was over twice as frequent ($P < 0.05$ by unpaired t test) in this group.

DISCUSSION

We found distinctly steep slopes of phase III in an appreciable number of asthmatic children (21% of 114). Administration of the bronchodilator decreased overall time constants in both the children with steep slopes and the children with normal slopes, judging from the equivalent increases in expiratory flow that occurred in the two subgroups (Fig. 5). However, the bronchodilator caused a significant decrease in slope only in the SS patients. We considered the possibility that this decrease in slope resulted from a decrease in lung volume at FRC. In normal children, decreasing preinspiratory lung volume from FRC to RV consistently decreases the slope of phase III, presumably because dependent airway closure at RV diminishes the vertical gradient of ventilation (2). However, the FRC in the SS patients was abnormally high, and we have shown that raising preinspiratory lung volume above the normal FRC reduces rather than increases the phase III slope (2). Therefore reduction of FRC from an elevated to a normal value would be expected to increase rather than decrease the slope. Furthermore the values of slopes in the SS patients were much higher than the highest values encountered in normal children (2), and they remained so despite their reduction following the bronchodilator (Fig. 2). We conclude that the decrease in slope following the bronchodilator did not reflect an effect of lung volume on the vertical regional distribution of ventilation; the decrease in slope is more consistent with a diminution of differences among intraregional peripheral time constants.

FIG. 5. Maximum midexpiratory flow (MMEF) as percent predicted according to height in 30 asthmatic children before and after inhalation of a standard dose of isoproterenol. Shaded area represents ± 2 SD of values for 20 normal children matched to subjects according to height. Symbols as in Fig. 2.

FIG. 6. Density dependence of maximum expiratory flow as a function of maximum expiratory flow in 30 asthmatic children. Density dependence is expressed as percent increase in maximum expiratory flow at 50% of expired vital capacity ($\Delta\dot{V}_{\text{MAX}50\% \text{ VC}}$). Maximum midexpiratory flow (MMEF) is expressed as percent predicted according to height. Cross represents means ± 2 SD from 20 normal children matched to subjects according to height. Symbols as in Fig. 2.

The single-breath mixing efficiency is an index of trapped resident nitrogen following the inspiration of pure oxygen. Although we found high ratios of RV/TLC in the SS group, indicating excessive gas trapping near end expiration, it is noteworthy that the breath of oxygen for the single-breath mixing efficiency was taken from FRC. Therefore the low values for mixing efficiency in the SS patients (Fig. 3) indicate gas trapping at the end-tidal lung volume in these patients. These findings suggest obstruction of peripheral airways at FRC, i.e., the preinspiratory lung volume from which the steep slopes were detected.

Patients with steep slopes invariably had reduced density dependence of maximum expiratory flow (Table 1, Fig. 6). Although reduced DD is consistent with obstruction of peripheral airways, it is also to be expected on the basis of reduced convective accelerative pressure losses at low flow rates, as demonstrated by Mink et al. (14, 15) from studies in excised lungs. Therefore the sites of increased resistance responsible for the flow reduction are not necessarily identified by the finding of reduced DD.

The range of DD in our normal subjects was wide (Fig. 6), as found in previous studies (1, 12). In the asthmatic children who fell within the lower limits of this normal range, phase III slopes were normal and maximum expiratory flow rates were no lower than in asthmatic children with greater DD. We considered geometry of major airways as another possible source of variability in DD. From studies of airway conductance in vivo and in excised lungs (6, 9, 11, 17), it is now generally accepted that conductance of central airways is relatively large in early childhood. That is, central conductance per volume of lung decreases with growth during childhood. As an

independent confirmation of this pattern of growth, we show here that V_D per volume of lung decreases with growth as well (Fig. 4). We have not examined V_D as a determinant of DD in normal children, but the asthmatic children who fell within the lower limits of normal DD had higher V_D per volume of lung than asthmatic children with greater DD (Fig. 7). To the extent that V_D/TLC reflects variation in geometry at the flow-limiting segment, relatively small convective accelerative pressure losses must occur in the children with relatively large V_D/TLC . Therefore the observation that DD falls as V_D/TLC increases may be explained by relatively large cross-sectional areas in central airways, as indicated from studies by Mink et al. (14, 15).

In summary, we have demonstrated a pattern of physiological findings, i.e., steep phase III slope, reduced single-breath mixing efficiency, and reduced density dependence of maximum expiratory flow, present in some asthmatic children but absent in others who nevertheless show a wide range of expiratory flow limitation. The two patterns of airway obstruction that we found in asthmatic children differ quantitatively from those found by Despas et al. (5) in asthmatic adults. With regard to DD, our "nonresponders" generally had much more severe expiratory flow obstruction than the "responders" (Fig. 6). The two groups identified by Despas et al. had equivalent degrees of obstruction. On retesting our children after inhalation of isoproterenol, we still found a virtually complete separation of phase III slopes in the two groups, suggesting a persistent involvement of peripheral airways in the patients with steep phase III slopes. We do not have data regarding the consistency of either pattern over a period of time. However, the group with abnormally steep phase III slopes, abnormally low DD, and more severe flow reduction followed a significantly more

FIG. 7. Density dependence of maximum expiratory flow as a function of anatomical dead space in 16 asthmatic children whose density dependence was within normal limits. Density dependence is expressed as percent increase in maximum expiratory flow at 50% of expired vital capacity ($\Delta\dot{V}_{\text{MAX}50\% \text{ VC}}$). Anatomical dead space (V_D) is expressed as percent of total lung capacity (%TLC). Density dependence decreases significantly with increasing dead space, as indicated by regression line ($r = -0.62$, $P < 0.01$).

severe clinical course than the other group over the year preceding our study. Since a steep phase III slope in young adults may predict significant chronic airflow obstruction later in life (18), the methods evaluated here might be used to relate the natural history of chronic airflow obstruction to specific patterns of reactive airway disease during childhood.

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