Changes in Ventilation Homogeneity from Preschool through Young Adulthood as Determined by Moment Analysis of Nitrogen Washout¹

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ABSTRACT. This study was designed to assess potential differences in ventilation homogeneity related to growth. One hundred thirty-three healthy subjects representing four stages of growth were studied: group 1, preschool, ages 34–74 months; group 2, preadolescent, ages 8–10 yr; group 3, postpubertal, ages 15–17 yr; group 4, young adult, ages 26–40 yr. Ventilation homogeneity was assessed by moment analysis of multibreath nitrogen washout with functional residual capacity, the ratio of the 1st to 0th moment (MR 1/0), and the ratio of the 2nd to 0th moment (MR 2/0) being the outcome variables of interest. Across the four groups functional residual capacity increased as a curvilinear function of height. At all heights functional residual capacity was larger in males than females and the slope of the regression was steeper in males than females ($p < 0.001$). Both MRs 1/0 and 2/0 were significantly higher in group 1 than the other groups, indicating that ventilation washout was less homogeneous in the preschool subjects than in older children or adults. Males of group 1 had significantly higher values for both moment ratios (more ventilation nonuniformity) than females. In the other groups there were no significant sex based differences although there was a trend for males to have a lower MR 1/0 than females in the young adults, $p = 0.08$. The results indicate that both age and sex are important determinants of the growth of distribution of ventilation. (*Pediatr Res* 23: 68–71, 1988)

Abbreviations

FRC, functional residual capacity
FN₂, mixed expired nitrogen fraction
D, dilution number
MR 1/0, ratio of 1st to 0th moment
MR 2/0, ratio of 2nd to 0th moment
MANW, multibreath nitrogen washout
D_K, dilution index

Moment analysis of MANW is a relatively new technique of quantifying ventilation inhomogeneity (1, 2). It has advantages over older indices derived from analysis of the shape of the washout curve in that all points of the curve are taken into consideration; intrasubject variability tends to be low relative to

other indices; the results are largely independent of body size, respiratory rate, and tidal volume; and results can be obtained virtually instantaneously using modern computer techniques (1–3). MANW has the sensitivity required to separate out groups of patients with known lung disease and asymptomatic smokers from healthy subjects (2–5). We have previously shown that in young children intrasubject variability of moment ratios derived from MANW was the same as in adults and that there was a quantitative relationship between the clinical degree of lung disease and ventilation non-uniformity in young children with cystic fibrosis (6).

Data from previous studies have suggested that ventilation homogeneity changes with growth such that school age children have somewhat less efficient ventilation than adolescents or young adults (7, 8), but comparative data over a wide age range including preschool children have not been previously published. Since body size (in the form of functional residual capacity) is taken into account in the calculation of moment ratios derived from MANW we hypothesized that the technique could be used to assess potential age and sex related differences in ventilation washout.

METHODS

Subjects. A total of 133 subjects was studied. All were non-smokers, had no history of a respiratory illness in the previous 3 wk, and were healthy insofar as they had no history of chronic heart or lung disease as determined by a modification of the American Thoracic Society—Division of Lung Diseases Pediatric Questionnaire. The subjects were selected to represent four stages of growth and development: group 1, preschool, ages 34–74 months; group 2, preadolescent, ages 8–10 yr; group 3, postpubertal, ages 15–17 yr; and group 4, young adult, ages 25–40 yr. Anthropometrics and sex distribution of the groups are shown in Table 1. This study was approved by the OHSU Human Research Committee and informed consent was obtained from all subjects.

Nitrogen washout. MANW was performed in the sitting position through a soft, leak free, age appropriate face mask (Vital Signs, Inc.). Each subject performed three nitrogen washouts during the test session. The subjects first breathed room air until they were acclimated to the system, and they were then turned into a circuit consisting of an oxygen supply, a one-way valve, and a pneumotachygraph in series. Oxygen breathing continued for 5 min and the subjects were distracted by listening to music of their choice. During the washout nitrogen and flow signals were recorded on FM tape and subsequently computer analyzed in real time. Appropriate corrections were made for the delay between nitrogen and flow signals and the changing gas composition in the pneumotachygraph during the washout. All subjects achieved an end tidal nitrogen concentration of less than 2% before the end of the 5-min period. The subjects rested and

Received July 6, 1987; accepted September 16, 1987.

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Supported by NIH Grant R01 HL3295602.

¹ Presented in part at the annual meeting of the American Thoracic Society, New Orleans, LA, May 1987.

Table 1. *Anthropometrics and sex distribution of subjects*

	Group 1	Group 2	Group 3	Group 4
<i>n</i>	36	46	29	22
Males/ females	19/17	23/23	11/18	11/11
Age				
Mean	58 mo	8.8 yr	16.0 yr	32.3 yr
Range	37–74 mo	8–10 yr	15–17 yr	26–40 yr
Ht				
Mean	107 cm	139 cm	169 cm	170 cm
Range	92–125 cm	121–168 cm	155–187 cm	155–188 cm

breathed room air for 5 to 10 min between runs. For each washout curve FRC was determined by a modification of the method of Darling *et al.* (9) with corrections for the volume of N₂ added by blood to the lungs during the washout, the trace N₂ in the O₂ supply, and the dead space of the system (45 ml). The computer algorithm was designed such that for each washout FRC was calculated first and the moment analysis proceeded subsequently.

Moment analysis. The procedures used in this laboratory for MANW have been described in detail previously (6). MANW is a mathematical means of describing the shape of the nitrogen washout curve. The technique assumes that the curve resulting from a nitrogen washout is a unimodal distribution, and in statistical terms the 0th moment is the area under the washout curve, the 1st moment is the mean of the distribution, and the 2nd moment is the variance. A better intuitive understanding of the results of moment analysis can be achieved through examination of the technique used for calculation. Briefly, the FN₂ for each breath *k* was plotted against the D_k for that breath. D_k was calculated as the cumulative expired volume of the washout at the end of the breath *k* divided by FRC and was simply a method of scaling the *x* axis for intersubject differences in body size, tidal volume, and respiratory rate. The *r*th moment of FN₂ plotted against D_k was defined as:

$$M_r = \sum_{k=1}^X D_k^r [FN_2]_k [D_k - D_{k-1}], \quad r = 0, 1, 2, \dots, n$$

where *X* was a breath number high enough so the *D* was greater than 10. The curves were analyzed out to the point where *D* = 10, *i.e.* the point where the subject had washed out a cumulative expired volume equal to 10 times his/her FRC.

Inspection of the above equation shows that when *r* = 0 the result is the area under the curve defined by FN₂ plotted against D_k. As *r* increases the tail-end of the curve becomes progressively magnified in a mathematical sense since the term D_k^{*r*} becomes much larger especially as *D* approaches 10. It is at the tail-end of the washout curve where one expects to see the earliest splaying out due to ventilation inhomogeneity. Since moments are dimensionless it is useful to reference successively higher moments to the 0th moment, and accordingly ratios of the 1st to 0th and 2nd to 0th moments were calculated for each run (MR 1/0 and MR 2/0). It can be appreciated that as ventilation inhomogeneity increases moment ratios will increase in magnitude (2–6).

Multiple regression analyses using linear and curvilinear models were used to determine the strength of the association between FRC and age, sex, and body size. Among groups, analysis of variance and *t* testing with correction for multiple comparisons were used to determine the effect of age on moment ratios. Within groups sex based comparisons were performed using a 2-tailed *t* test for unmatched samples. For all statistical analyses the 5% level was chosen as the cutoff for significance.

RESULTS

FRC. Results of stepwise regression analyses showed that across the four groups FRC increased as a curvilinear function of height (Fig. 1). The addition of age and/or weight added only

very slightly to the strength of the correlation coefficients. The slope of the regression for males was significantly different than for females (*p* < 0.001).

Moment analysis. Individual points for MR 1/0 and MR 2/0 plotted against height are shown in Figure 2. Regression analysis showed that both MR 1/0 and MR 2/0 demonstrated slight but statistically significant trends to decrease with height (for MR 1/0 *r* = −0.28, *p* < 0.05 and for MR 2/0 *r* = −0.30, *p* < 0.05). When moment ratios among the four groups were compared it was found that group 1 had significantly higher mean values for both MR 1/0 and MR 2/0 than groups 2, 3, and 4 (Table 2), indicating that nitrogen washout was less efficient in the preschool group than in the other groups.

Sex-based comparisons within the four age groups showed that within group 1 males had significantly higher mean values for both moment ratios than females (Table 3). In the other three groups there was a consistent trend for males to have slightly lower mean values for moment ratios than females, with the difference approaching statistical significance for MR 1/0 in group 4. Thus the data indicated that in the preschool age range boys had significantly less efficient ventilation washout than girls but in the older age groups this finding was not present and in fact the data showed a trend in the opposite direction.

DISCUSSION

MANW has been used as a method of assessing ventilation inhomogeneity for more than 35 yr (10). Until recently, however, methods used to quantify the level of ventilation inhomogeneity from washout curves have been time consuming and suffered from relatively high degrees of intra and intersubject variability. MANW is a technique that treats the multibreath nitrogen washout curve as a unimodal distribution (1) and that takes all points of the curve into consideration. Since the mathematically derived moments are dimensionless areas under curves, moment ratios referencing the 1st, 2nd, . . . *n*th moments to the 0th moment (which is simply the area under the raw washout curve) are usually constructed and increasing moment ratios are indicative of increasing ventilation inhomogeneity (1–6).

Some technical considerations in the present study deserve mention. In the past investigators have plotted nitrogen washout curves both as functions of mixed expired and end tidal nitrogen concentration (1, 2, 5, 6, 10–12). In patients with lung disease the use of mixed expired nitrogen may be preferred as a better representation of the overall dynamics of pulmonary washout. We have previously shown that in healthy subjects moment ratios derived from mixed expired nitrogen concentration are slightly lower than those derived from end tidal but that there was no difference in test sensitivity (6). Herein we report moment

Fig. 1. Regression lines for FRC plotted against height in males (solid line) and females (dashed line) of groups 1–4. *r* = correlation coefficient, *p* = significance of slope.

Fig. 2. Individual data points for moment ratios 1/0 and 2/0 plotted against height in groups 1-4.

Table 2. Mean (SD) moment ratios for groups 1-4

	MR 1/0	MR 2/0
Group 1	2.14 (0.17)*	9.34 (1.40)†
Group 2	1.97 (0.24)	8.24 (1.84)
Group 3	1.98 (0.15)	8.07 (1.16)
Group 4	2.04 (0.20)	8.58 (1.58)

* Group 1 different from groups 2-4, $p < 0.005$.

† Group 1 different from groups 2-4, $p < 0.01$.

Table 3. Sex-based comparison of moment ratios within groups 1-4; values for moment ratios are mean (SD)

		MR 1/0	MR 2/0
Group 1	Males	2.19 (0.19)*	9.75 (1.50)†
	Females	2.08 (0.13)	8.87 (1.13)
Group 2	Males	1.96 (0.25)	8.03 (2.02)
	Females	2.01 (0.23)	8.45 (1.66)
Group 3	Males	1.95 (0.19)	7.96 (1.24)
	Females	2.00 (0.13)	8.14 (1.14)
Group 4	Males	1.97 (0.24)‡	8.12 (1.96)
	Females	2.12 (0.13)	9.04 (0.98)

* Group 1 males different from females, $p < 0.01$.

† Group 1 males different from females, $p = 0.05$.

‡ Group 4 males different from females, $p = 0.08$.

ratios as a function of mixed expired nitrogen concentration with curves carried out to a cumulative expired volume of 10 times FRC, *i.e.* a point where dilution number equals 10, in order to facilitate comparison with previously published data (12). Previous studies have shown that there is a high correlation between MR 1/0 and MR 2/0 (2). In terms of test sensitivity most investigators have either found no difference between MR 1/0 and MR 2/0 (4, 6, 12) or a slightly preference for MR 2/0 (5). In the present study both moment ratios showed similar abilities to detect differences among the groups and between sexes.

Best fit regression analysis showed that FRC increased as a curvilinear function of height. Exponents for the equations and values for FRC at all heights were similar to those derived from the summary equations of Polgar and Weng (13). Over the height range reported in the present study the slope of the regression of FRC on height was steeper in males than females and there was no crossover between the curves, findings that are consistent with previously published data (13-15).

Herein we found that distribution of ventilation was less homogeneous in young children than in older children or young adults. To our knowledge there are no data in the literature that would allow direct comparison with those presented here. Michaelson *et al.* (7) performed single and multiple breath nitrogen washout studies in a large group of children 6 to 18 yr of age and used compartment analysis, the lung clearance index, and closing volume as outcome measures. They found definite evidence of increasing homogeneity of lung washout with growth as exemplified by an increasing incidence of single compartment curves, a decrease in lung clearance index, and a decreasing slope of phase III with age. Cooper *et al.* (8) performed single breath oxygen tests in healthy subjects 5 to 41 yr of age and also found that the slope of phase III decreased and mixing efficiency increased with age. Kraemer *et al.* (12) performed MANW in children 7 to 16 yr of age and found a slight but statistically nonsignificant inverse correlation of moment ratios with age. Inspection of their data shows a trend for moment ratios to be higher in the children of smallest stature, suggesting a trend toward increasing ventilation inhomogeneity in the youngest subjects. In that study the youngest subjects would have fallen between our groups 1 and 2 in age.

With the present data and those of previous authors we cannot determine with certainty the reason(s) that ventilation becomes more homogeneous with growth. Ultimately anatomical growth and changes in the mechanical properties of the lungs with age will determine distribution of ventilation. Over approximately the first 8 yr of life there is considerable lung growth with alveoli multiplying about 10-fold and airways growing in length and diameter (16). Beyond the age of completion of alveolar multiplication both airways and alveoli continue to increase in size until late adolescence or early adulthood, although the two types of structures do not necessarily grow in direct proportion to each other (17). It is interesting to note that our data suggest that children achieve adult levels of ventilation uniformity between the preschool and preadolescent ages, the same age range during which alveolar multiplication ceases. During growth some of the changes in lung mechanics that take place include an increase in the static elastic recoil of the lungs, an increase in peripheral airways conductance relative to total conductance, and a decrease in closing volume (17-20). Changes in lung elastic recoil and peripheral airways conductance could influence distribution of ventilation, especially if regional differences existed and the respiratory rate was of an appropriate frequency (21). However, frequency dependence of compliance, which is associated with

ventilation nonuniformity, probably does not occur at normal breathing frequencies in healthy children (22). Thus we would agree with the suggestion of Cooper *et al.* (8) that changes in closing volume with growth are more likely to have an effect on distribution of ventilation in healthy subjects than changes in the mechanical properties of parallel units among peripheral airways whose effect on distribution of ventilation would be largely frequency dependent.

Very few investigators have examined sex based differences in distribution of ventilation, especially as they relate to growth. Hutchison *et al.* (4) performed MANW in a small group of healthy children ages 8 to 14 yr and found that moment ratios in girls tended to be higher than in boys. Kraemer *et al.* (12) found no difference in moment ratios between boys and girls ages 7 to 16 yr and in the present study we found no sex based difference in distribution of ventilation between the males and females of similar age in groups 2 or 3. At the extremes, however, we did find differences with the young boys of group 1 having more ventilation inhomogeneity than young girls and a trend of borderline significance in the opposite direction in the young adults of group 4. Since males and females within groups 1–4 were of the same age, and since MANW takes body size (in the form of FRC) into account in the calculation of moment ratios, we believe that the sex-based differences that were found represent real differences in ventilation homogeneity. Although we cannot comment definitively on the mechanism of these sex-based differences it is of interest to note that they parallel data from flow-volume curve studies over the past several years indicating that young boys have smaller airways relative to their lung volume than young girls but that this trend may reverse in late adolescence or early adulthood (14, 15, 23, 24). Debate continues as to whether these anatomic regional differences in lung growth between males and females really exist, but they could potentially influence distribution of ventilation by causing differences in closing volume.

In summary, we have shown that MANW can be used to describe changes in ventilation homogeneity over a wide age range. The data indicate that: 1) ventilation is less homogeneous in young children than older children or young adults and 2) young boys have more ventilation inhomogeneity than young girls and this trend disappears and may reverse with age.

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