Ventilation Inhomogeneity Using Multibreath Nitrogen Washout: Comparison of Moment Ratios and Other Indexes[1-4]

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SUMMARY

In this study we compared a variety of indexes of ventilation inhomogeneity based on multibreath nitrogen washout of the lungs. We studied 40 subjects in 5 clinical groups: 6 normal subjects, 5 "normal" smokers, 6 subjects with asthma, 13 with diffuse interstitial lung disease (DILD), and 10 with chronic obstructive pulmonary disease (COPD). We found that a moment ratio (μ_1/μ_0), which is a mean dilution number (or number of volume turnovers), is superior to other indexes studied with respect to minimal intrasubject variability and maximal diagnostic sensitivity. Even minimal ventilation inhomogeneity could be detected in "normal" smokers, as evidenced by the difference in μ_1/μ_0 values from those found in normal nonsmokers. As a group, asthmatics showed mild ventilation inhomogeneity, with greater variation depending on their functional status at the time of testing. Subjects with DILD tended to have moderate ventilation inhomogeneity, which appeared to increase with age. As expected, the greatest ventilation inhomogeneity occurred in COPD.

Introduction

Intrapulmonary gas distribution and mixing is an important functional property of the lungs and can be characterized by multibreath nitrogen washout. Previously used indexes for quantifying ventilation inhomogeneity by the washout curve have certain limitations. Some of these indexes were computed from few data points or from only part of the curve (1-6), and therefore failed to utilize much of the information contained by the entire washout curve. Alternatively, to analyze the entire washout, curve-fitting models were applied from which many parameters were estimated (7-13). Problems with this approach included nonunique parameter estimates, poor parameter sensitivity, and costliness of clinical implementation.

The approach we used to analyze multibreath washout involved normalization of the data to account for different breathing patterns and lung volumes among the subjects (14). The entire normalized washout curve was quantified by the ratio of first-to-zeroth moments, i.e., a mean value of the washout curve. In terms of a two-alveolar space model, this moment ratio could be interpreted as the relative volume-flow ratio of the poorly ventilated space in the presence of significant ventilation inhomogeneity (15). With the use of a small computer, continual changes in the breathing pattern could be taken into account to allow the washout to be performed with spontaneous breathing. Furthermore, data processing and moment analysis could be accomplished quickly,

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so that the results were available within seconds after the completion of the washout (16).

Methods

Population. We studied 40 subjects, representing 5 clinical categories of respiratory function in order to assess a full spectrum of gas distribution and mixing properties of the lung. There were 6 subjects who were normal by pulmonary function, absence of cardiopulmonary disease by history, chest roentgenogram, and physical diagnosis. These 6 subjects had never smoked cigarettes, in contrast to 5 subjects who fitted the above criteria except for a history of cigarette smoking. There were 10 patients with nonasthmatic chronic obstructive pulmonary disease, with pulmonary function documentation of moderate to severe airways obstruction and clinical dyspnea of a 5-to-30-yr duration. Six asthmatics were studied. These 6 were clinically stable with a history of atopy, confirmed extrinsic allergens, elevated IgE and total eosinophil counts, as well as laboratory documentation of highly reversible obstruction to airflow. Thirteen patients had diffuse interstitial lung disease confirmed by lung biopsy, which included 8 patients with sarcoidosis and 5 patients with diffuse interstitial fibrosis.

Pulmonary function. Lung mechanics were assessed by spirometry (17), flow-volume relationships (18), and whole body plethysmography (19, 20). Functional residual capacity (FRC) was estimated by N_2 washout, and the results were compared with the predicted values (21). Transpulmonary gas transport was assessed by steady-state CO-diffusing capacity (22).

Multibreath nitrogen washout was performed twice with each subject breathing spontaneously. The gas at the mouth was sampled continuously by a nitrogen analyzer (Med Science 505, Med-Science Electronics, Inc., St. Louis, Mo.). The flow signal was obtained with a screen pneumotachometer coupled to a differential pressure transducer (Validyne MP 45), the output of which was amplified and demodulated (Validyne CD19, Validyne Engineering Corp., Northridge, Ca.). Both nitrogen and flow signals were recorded continuously on FM tape and monitored simultaneously with a strip-chart recorder. Volume changes were computed by integration of flow, using a continuously revised calibration factor to account for variation in gas composition and temperature (16). The mixed-expired N_2 fraction was calculated by multiplying flow and synchronized N_2 signals. Data were processed by a digital computer (PDP 11/45, Digital Equipment Corp., Maynard, Mass.).

Methods of analysis. Our method of analyzing the washout curve required that the data be appropriately scaled. First, the end-tidal N_2 fraction F(k) on any breath k is normalized with respect to the initial N_2 fraction: $Y(k) = F(k)/F(0)$. Second, instead of breath number k as the independent variable (abscissa of the washout curve), a dilution number (η_k) at the end of breath k was used (14). This dilution number was the ratio of cumulative expired volume (CEV) at the end of breath k to the functional residual capacity (FRC): $\eta_k = CEV(k)/FRC$. By this scaling of the abscissa of the washout curve, effects caused by differences in FRC and breathing pattern could be minimized (14, 15). With the transformed variables, Y(k) and η_k, we defined the zeroth and first moments as

$$\mu_0 = \sum_{k=0}^{N} Y(k)\,[\eta_k - \eta_{k-1}]$$

and

$$\mu_1 = \sum_{k=0}^{N} \eta_k Y(k)\,[\eta_k - \eta_{k-1}]$$

where N is the number of breaths at which the dilution number exceeds 10 (16). The moment ratio μ_1/μ_0 is the mean dilution number or number of volume turnovers of the washout curve, and, in terms of a two-alveolar space model, it could be interpreted as the relative volume-flow ratio of the poorly ventilated space (15).

For comparison with the moment ratio, we also computed several indexes of the washout curve previously reported in the literature: Becklake Index (1), Lung Clearance Index (2), Five-Breath Index (3, 23), Ventilatory Efficiency or E_{90} (4), Mixing Ratio (5), and Index of Alveolar Ventilation (6).

For all indexes, we derived intrasubject variability from the repeated washouts of each subject as the relative difference:

$$RD = |Z_1 - Z_2|/\langle Z\rangle$$

where Z_1 and Z_2 were the value of any index Z for the 2 washouts, and <Z> was the average value. Diagnostic sensitivity was evaluated by the mean and standard deviation of <Z> of all subjects in each group.

Results

Characteristics of the patients in each category are illustrated in table 1. Pulmonary functions were normal in all normal nonsmoking and "normal" smoking subjects. Five of six asthmatics demonstrated reduced forced expiratory flow rates; 4 of them had elevated specific airway resistance, and 3 had hyperinflation of resting lung volumes. Ten of thirteen patients with DILD demonstrated classic restrictive patterns in lung volumes, and 8 had reduced CO-diffusing capacities. Eight of the thirteen also demonstrated mild reductions in flow rates, and 5 had small increases in specific airway resistance. All 10 patients with COPD had moderate-to-severe obstructive ventilatory patterns, and 8 had reduced diffusing capacities.

The moment ratio (μ_1/μ_0) appeared to have detected mild as well as severe ventilation inhomogeneity in our clinical groups (figure 1). The mean and standard deviation of μ_1/μ_0 showed a tight clustering of values (2.02 ± 0.14) for normal non-

TABLE 1

FUNCTIONAL CHARACTERISTICS*† IN 40 SUBJECTS*

Subjects	Age (yr)	Smoking (pack-yr)	Disease Duration (yr)	FVC (L)	FEV_1/FVC (%)	FEF_{25-75} (L/s)	SRaw (cmH_2O/s)	Vtg‡ (L)	TLC (L)	DLco (ml/min/mmHg)
Normal nonsmokers, n = 6	33.5 ± 9.3	0	0	4.37 ± 1.10 (100)†	86.2 ± 5.5	4.47 ± 0.99 (99)	4.12 ± 1.01 (99)	2.66 ± 0.77 (100)	6.21 ± 1.37 (109)	26.2 ± 10.0
Normal smokers, n = 5	34.6 ± 5.5	15.2 ± 9.7	0	4.36 ± 1.01 (102)	84.4 ± 3.4	4.71 ± 1.22 (114)	3.98 ± 1.13 (103)	2.92 ± 0.66 (109)	5.62 ± 1.54 (105)	21.0 ± 5.2
Asthmatics, n = 6	44.8 ± 14.0	14.6 ± 27.2	13.5 ± 5.9	3.96 ± 1.15 (99)	60.7 ± 22.0	1.83 ± 1.48 (44)	12.34 ± 9.09 (285)	3.31 ± 0.96 (137)	6.01 ± 1.58 (110)	19.2 ± 4.8
DILD, n = 13	47.8 ± 15.9	18.2 ± 36.1	6.8 ± 8.0	2.95 ± 0.54 (74)	77.2 ± 13.8	2.44 ± 1.31 (61)	5.38 ± 3.24 (124)	2.21 ± 0.42 (91)	4.34 ± 0.81 (75)	11.4 ± 5.6
COPD, n = 10	53.2 ± 7.7	42.6 ± 14.8	13.7 ± 8.0	2.35 ± 0.80 (56)	34.1 ± 6.3	0.33 ± 0.13 (10)	25.49 ± 10.15 (566)	5.39 ± 1.61 (207)	6.06 ± 1.21 (97)	10.5 ± 2.3

* mean ± SD.

† The numbers in parentheses represent the mean value for results when each is expressed as a percent of predicted. (References for predicted values are cited in *Methods*.)

‡ Volume of thoracic gas measured in the plethysmograph at the end of a quiet expiration (FRC).

smokers and a mild increase in "normal" smokers (2.38 ± 0.14). A large variation in this index was seen in asthmatics (2.48 ± 0.28), consistent with their functional status when studied. One asthmatic with a normal moment ratio was normal by all other pulmonary functions and, therefore, in a true remission. In the patients with DILD, there were moderate increases ranging from 15 to 50 % higher than normal and averaging 65 % that of patients with severe COPD. These values were higher in the older (61.6 ± 9.9 yr) patients with diffuse interstitial fibrosis (2.83 ± 0.31) than in the younger (39.1 ± 12.5 yr) patients with sarcoidosis (2.67 ± 0.24). As expected, the greatest ventilation inhomogeneity occurred in COPD, where the values of μ_1/μ_0 (3.10 ± 0.31) ranged from 32 to 75 % higher than the normal mean.

To standardize comparison among the various indexes, we used the values of our normal group as a reference. These normal values agreed closely with those reported in the literature (table 2), with the exception of the Becklake Index, where our values were lower than those originally reported by Becklake (1), yet somewhat higher than those reported later by Becklake and Goldman (24). Our values for the Lung Clearance Index (LCI) were well within the normal range described by Bouhuys (2), but were slightly higher than those reported for nonsmokers by Orzalesi and coworkers (25). The reason for these discrepancies was not clear, but they might have occurred because we placed no constraints on breathing patterns in this study. Bouhuys has previously reported, for example, that normal values for LCI increase substantially when patients breathe at smaller tidal volumes (26).

The sensitivities of the various indexes are shown in figures 2 and 3. The LCI compared well with μ_1/μ_0 (figure 2) and was capable of detecting dysfunction in all the "normal" smokers. Al-

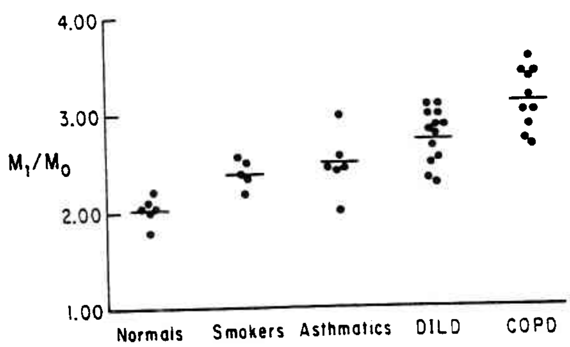

Fig. 1. Moment ratio (μ_1/μ_0) values for clinical groups. Circles represent average of 2 values per subject; bars denote mean value for each group.

TABLE 2

INDEXES OF MULTIBREATH WASHOUT: NORMAL VALUES*

Index	Literature†	This Study
Moment Ratio, μ_1/μ_0	—	2.02 ± 0.14
Five-Breath Index	87.5–100 (3)	88.78 ± 2.04
Ventilatory Efficiency Index	76.3 ± 6.6 (4)	76.61 ± 4.96
Becklake Index	3.65 ± 0.76 (24)	4.25 ± 0.30
Index of Alveolar Ventilation	70 – 97 (6)	85.07 ± 6.09
Mixing Ratio	1.57 ± 0.22 (5)	1.50 ± 0.10
Lung Clearance Index	7.1 ± 1.3 (25)	8.40 ± 0.40

* Mean ± SD.

† The numbers in parentheses cite the References.

though the separation between normal subjects and mild asthmatics was not as distinct, the LCI failed to show ventilation abnormality in only 1 patient with DILD. The diagnostic sensitivity of the remaining indices was less reliable. The Five-Breath Index, Becklake Index, Index of Alveolar Ventilation, and the Mixing Ratio each failed to identify 5 patients with mild or moderate ventilation inhomogeneity, as indicated by μ_1/μ_0. The least sensitive index of ventilation inhomogeneity was the Ventilatory Efficiency Index, which failed to discriminate 8 patients identified by moment analysis, including 4 patients with DILD and 1 with COPD.

Intrasubject variation was computed for all subjects and was smallest for μ_1/μ_0 (5.0 ± 3.2 %). By definition, therefore, μ_1/μ_0 was the most precise of the indexes evaluated. A comparable mean variation was present for the Five-Breath Index (5.4 ± 7.6), but several patients demonstrated substantial variations, as shown by the large standard deviation (figure 4). Variability was relatively larger for other indexes: Ventilatory Efficiency Index (9.5 ± 6.8 %), Becklake Index (9.8 ± 8.5 %), Index of Alveolar Ventilation (10.9 ± 8.8 %), and Mixing Ratio (11.0 ± 9.4 %). Interestingly, Lung Clearance Index, which demonstrated good diagnostic sensitivity, showed the greatest intrasubject variability (13.5 ± 17.2 %) and was, therefore, the least precise index of ventilation inhomogeneity studied.

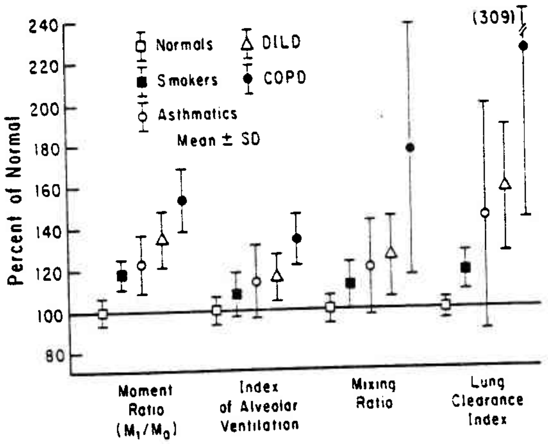

Fig. 2. Comparison of sensitivity of the moment ratio (μ_1/μ_0) to indexes measured at 2% end-tidal N_2. Mean and SD values within each group are plotted as a percentage of the mean value for the normal group.

Discussion

When multibreath nitrogen washout is performed during relaxed, spontaneous breathing, it requires no breath-holding or forced maneuvers and places no constraints on breathing patterns or flow rates. For those indexes that required 2 % end-tidal N_2, performance time was unduly long in patients with COPD (168 ± 78 breaths). Moment analysis, however, which is completed when the dilution number (CEV/FRC) reaches 10, required many fewer breaths (77 ± 18). In fact, a dilution number of 8 appears to be sufficient (16), which would reduce performance time another 20 %. The performance time required for patients with DILD was considerably less, requiring only 30 ± 7 breaths to reach a dilution number of 10. In con-

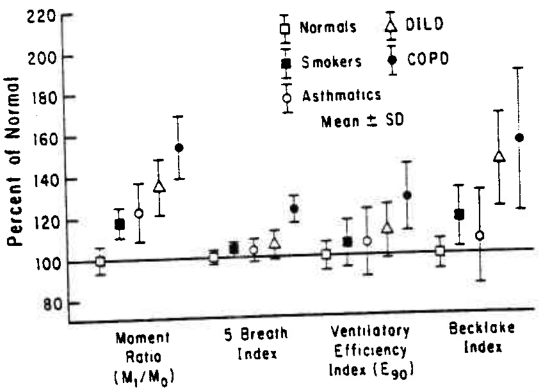

Fig. 3. Comparison of sensitivity of the moment ratio (μ_1/μ_0) with other indexes. Legend is the same as that for figure 2.

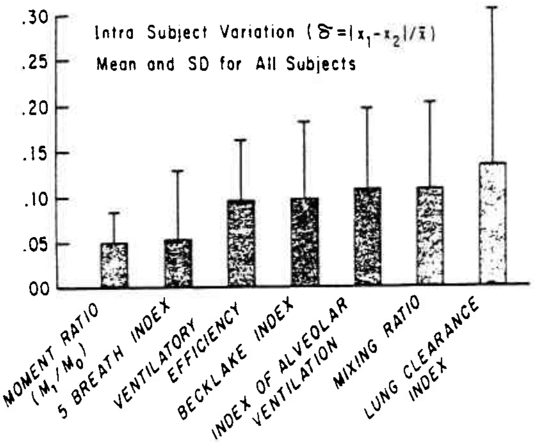

Fig. 4. Comparison of the mean and standard deviation of intrasubject variability of all subjects among indexes of multibreath washout.

trast, to reach 2 % end-tidal N_2, our patients with DILD required 40 ± 11 breaths (range, 20 to 61 breaths).

From these studies of patients with DILD, ventilation inhomogeneity appeared to be more significant than is commonly recognized. Many earlier multibreath N_2 washout studies in this group of patients relied on measurement of the end-tidal N_2 percentage after 7 min of washout. In most patients with DILD previously studied, this index was normal (27-35), although Sharp and associates (36) did find abnormal values in one third of 44 nonobstructed patients with DILD. Curve-fitting methods have previously detected abnormal washout curves in most patients with DILD (7, 37). As demonstrated in this study, μ_1/μ_0 provided a single quantitative index that described the entire washout curve, yet did not require any assumptions regarding the significance or number of exponential components used in curve-fitting.

In patients with DILD, measurement of gas transport, e.g., alveolar-arterial O_2 gradients, provides a sensitive means to assess longitudinally disease activity and the effect of steroids (38). Part of this over-all effect may be attributed to changes in ventilation inhomogeneity.

The use of inert gas clearance studies, such as multibreath N_2 washout, provides a noninvasive method of characterizing pulmonary gas transport. A decrease in intrasubject variability and an increase in sensitivity between diagnostic groups were obtained by (*1*) analyzing all of the breaths of the nitrogen washout curve, (*2*) scaling the data to minimize the effects of breathing pattern variation and operating point (FRC), and (*3*) using a quantitative index (moment ratio) that is a weighted integral measure that reduces variability caused by measurement noise. All of these factors helped to improve diagnostic clustering. With standard instruments in the pulmonary function laboratory, and the availability and modest cost of digital computation, the methods presented here can be readily implemented for clinical use.

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