Real-time moment analysis of pulmonary nitrogen washout

JAFAR SANIE, GERALD M. SAIDEL, AND EDWARD H. CHESTER
Departments of Biomedical Engineering and Medicine, Case Western Reserve University and Veterans Administration Medical Center, Cleveland, Ohio 44106

SANIE, JAFAR, GERALD M. SAIDEL, AND EDWARD H. CHESTER. Real-time moment analysis of pulmonary nitrogen washout. J. Appl. Physiol.: Respirat. Environ. Exercise Physiol. 46(6): 1184–1190, 1979.—A real-time moment analysis was applied to multibreath nitrogen-washout dynamics of the lung. Because the analysis accounts for breathing pattern variations, subjects could perform the washout with spontaneous breathing. The real-time digital processing of the nitrogen and flow signals incorporates filtering, delay compensation, and corrections for the effects of gas composition and temperature changes. In our study, moment analysis of the multibreath washout was evaluated for 37 subjects: 6 normal nonsmokers, 4 “normal” smokers, 6 asthmatics, 12 with diffuse interstitial disease, and 9 with chronic obstructive pulmonary disease. Moments were computed from end-tidal and breath-averaged nitrogen fractions. The ratio of 1st-to-0th moments was found to yield distinctions among subjects with different degrees of ventilation inhomogeneity, even between normal nonsmokers and “normal” smokers. With minimal computational facilities, this moment analysis not only provides a sensitive index of ventilatory dysfunction, but also a cost-effective tool.

EXPERIMENTAL METHODS

Clinical subjects. We studied 37 subjects who represented five separate categories: 1) normal nonsmoker with no history of chronic or recurrent lung disease, respiratory symptoms, or history of smoking; 2) “normal” smoker with no history of chronic or recurrent lung disease, respiratory symptoms, but a history of cigarette smoking greater than 5 pack-yr; 3) diffuse interstitial lung disease (DILD) with diffuse chronic inflammatory disease of lung parenchyma (e.g., interstitial fibrosis); 4) bronchial asthma with episodic wheezing and dyspnea with intervals free of clinical symptoms; and 5) chronic obstructive pulmonary disease (COPD), which is not asthmatic, with persistent chronic obstruction to airflow (e.g., emphysema and/or bronchitis).

Pulmonary function was assessed in all subjects by spirometry, dilution lung volumes, and body plethysmography (Table 1). In addition, steady-state carbon monoxide diffusing capacity (D\textsubscript{LCO}) was evaluated. There were six normal nonsmoking subjects and four “normal” smokers who averaged 15 pack-yr of cigarette smoking each and were normal by all these pulmonary functions tests. The six asthmatic patients were all asymptomatic, but five of them had reduced forced expiratory flow rates from 25 to 75% of the total forced vital capacity (FEF\textsubscript{25–75}). Four of the six also had increased specific airway resistance (SRaw) in the body plethysmograph, and three were hyperinflated. All six had a normal diffusing capacity. Only one was normal by all parameters tested and therefore in a true remission, i.e., no detectable physio-
logical abnormalities at that time. Obviously, such a patient would still have evidence of bronchial hyperactivity to bronchial provocation testing with methacholine. Twelve subjects had a histologically verified diffuse interstitial lung disease, seven with sarcoidosis and five with diffuse interstitial fibrosis. Ten of these 12 subjects had classical restrictive patterns manifested by reductions in total lung capacity, and seven of the 12 had decreased DLo. In addition, eight of the 12 had reduced FEVs and five had increased SRaw. Classical extreme patterns of ventilation inhomogeneity were shown in nine patients with chronic obstructive pulmonary disease, all of whom had moderate-to-severe obstructive ventilatory patterns and eight of nine had decreased DLo.

**Testing procedure and apparatus.** Subjects are tested in the following manner: in a relaxed, spontaneous fashion, the subject inhales and exhales through a pneumotachometer open to ambient air. After he becomes adjusted to the situation, he inhales fully to the total lung capacity, seven with sarcoidosis and five with diffuse interstitial fibrosis. Ten of these 12 subjects had classical restrictive patterns manifested by reductions in total lung capacity, and seven of the 12 had decreased DLo. In addition, eight of the 12 had reduced FEVs and five had increased SRaw. Classical extreme patterns of ventilation inhomogeneity were shown in nine patients with chronic obstructive pulmonary disease, all of whom had moderate-to-severe obstructive ventilatory patterns and eight of nine had decreased DLo.

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The washout data are analyzed in terms of moments. Furthermore, higher moments are more subject to the poor signal-to-noise ratio in the tail region of the washout curve. An appropriate independent variable is the dilution number, which is defined as the ratio of cumulative expired volume (CEV) to FRC as described by Saidel et al. (11). In terms of the time-varying volume flow rate Q(t) integrated over expirations E(j) for j = 1, 2, ..., k, the dilution number at the end of any breath k is

\[ \eta_k = \int_{E(k)} Q(t)dt / FRC \]

where \( N \) is chosen to be sufficiently large that no significant information is lost, i.e., \( Y(N) \sim 1 \). As a practical limitation, the signal-to-noise ratio can also lead to error for large \( N \). Moments higher than the second need not be computed, because most of the information in the unimodal washout curve is contained in the first few moments. Furthermore, higher moments are more subject to the poor signal-to-noise ratio in the tail region of the washout curve.

Moments computed from the mixed-expired \( N_2 \) fraction of successive breaths can also be used to characterize the \( N_2 \) washout dynamics. Consequently, we define these moments as

\[ \langle \mu_r \rangle = \sum_{k=0}^{N} \eta_k^r \langle Y(k) \rangle \{ \eta_k - \eta_{k-1} \}; \quad r = 0, 1, 2, \ldots \]

where

\[ \langle Y(k) \rangle = \int_{E(k)} Y(t)Q(t)dt / \int_{E(k)} Q(t)dt \]

**Signal processing**

The nitrogen fraction and flow (pressure difference) signals are digitized with 12-bit accuracy in real time. Samples of these signals taken at 40 Hz are processed and retained in memory only long enough to compensate for the delay between the nitrogen and flow signals. Figure 1 is a functional diagram of data processing that includes the following blocks: 1) input: calibration factors and sampled input signals; 2) signal conditioning: filtering, delay compensation, and flow correction; 3) variables on each breath: tidal volume, end-tidal nitrogen fraction, and average nitrogen fraction; and 4) derived quantities: lung volumes, dilution number, and moments.

**Calibration.** When there are zero inputs to the nitrogen analyzer and pressure signal amplifier, outputs are recorded for a few minutes before the washout test to

### Table 1. Pulmonary function studies

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>PEF% , l/s</th>
<th>FRC liters</th>
<th>TLC liters</th>
<th>SRaw cmH2O/1</th>
<th>DLo mL/min-Torr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>4</td>
<td>4.4</td>
<td>3.0</td>
<td>6.2</td>
<td>4.1</td>
<td>26</td>
</tr>
<tr>
<td>Nonsmokers</td>
<td>±0.9</td>
<td>±0.9</td>
<td>±1.4</td>
<td>±1.0</td>
<td>±10</td>
<td></td>
</tr>
<tr>
<td>&quot;Normal&quot;</td>
<td>4</td>
<td>4.7</td>
<td>2.9</td>
<td>5.6</td>
<td>4.0</td>
<td>21</td>
</tr>
<tr>
<td>Smokers</td>
<td>±1.2</td>
<td>±0.8</td>
<td>±1.5</td>
<td>±1.1</td>
<td>±5</td>
<td></td>
</tr>
<tr>
<td>Asthmatics</td>
<td>6</td>
<td>1.8</td>
<td>3.1</td>
<td>6.0</td>
<td>12.3</td>
<td>19</td>
</tr>
<tr>
<td>DILD</td>
<td>12</td>
<td>2.4</td>
<td>1.9</td>
<td>4.3</td>
<td>5.4</td>
<td>11</td>
</tr>
<tr>
<td>COPD</td>
<td>9</td>
<td>0.3</td>
<td>4.4</td>
<td>0.1</td>
<td>25.5</td>
<td>11</td>
</tr>
</tbody>
</table>

Values are means ± SD, n, no. of subjects. See text for abbreviations.
flow compensation for the DC offsets. The nitrogen signal is calibrated by assuming the $N_2$ fraction in the ambient air and in the lung before washout is 0.796 (dry). The flow signal is calibrated using a reciprocal pump (Harvard), which provides an oscillatory flow of ambient air through a pneumotachometer at 0.25 Hz with a cycle volume ($\Delta V$) of 1.000 liter. The relationship between the measured pressure drop, $\Delta P(t)$, across the pneumotachometer and the flow rate, $Q(t)$, is given by

$$Q(t) = \frac{K}{v} \Delta P(t)$$

where $K$ is the volume calibration coefficient and $v$ is the viscosity of air at ambient temperature (e.g., $v = 185 \times 10^{-6}$ poise at $23^\circ$C). Integration of this equation over one-half a cycle yields

$$K = v \Delta V / \int \Delta P(t) dt$$

To get an accurate value of $K$, we calculate its mean value from several cycles. This coefficient is the same for flow in either direction. The criterion of acceptability of the $K$ value is that its coefficient of variation be less than 1%. If this criterion is not met, it is necessary to clean and dry the pneumotachometer screen and recalibrate. The calibration factors are stored on the disk and automatically become available when they are needed in the main program.

**Signal filtering.** In converting flow and nitrogen signals from analog to digital form, we required an appropriate filter to improve the signal-to-noise ratio. For this purpose, we selected a second-order Butterworth low-pass filter with a cutoff frequency of 20 Hz.

**Delay time compensation.** The response time of the nitrogen analyzer to a sudden change in nitrogen concentration can be divided into two parts: delay time and rise time. The time delay for sampled gas to travel from the sampling valve to the ionization chamber and become ionized is approximately 75 ms. Because we use the nitrogen signal for flow signal correction and must obtain the product of nitrogen and volume flow rate at the same time, it is important that the two signals be synchronous. Consequently, we delay the flow signal also by 75 ms.

**Flow-signal correction.** Accurate measurement of vol-
PULMONARY NITROGEN WASHOUT

ume flow rate at the mouth is essential for our data analysis. Consequently, we must correct the flow signal for the effects of changes in composition and temperature of the gas passing through the pneumotachometer. Differences are particularly noticeable between inspired and expired gases. The inspired gas consists of humidified oxygen at ambient temperatures; the gas leaving the mouth, however, is saturated with water at close to body temperature. Unless the screen of the pneumotachometer is heated, water vapor can condense on it to cause a change in resistance, i.e., a change in the calibration coefficient of the pressure signal.

Provided the flow is laminar, we can relate the volume flow rate $Q(t)$ and pressure difference $\Delta P(t)$ across the pneumotachometer screen by

$$Q(t) = K \frac{\Delta P(t)}{\rho(F,T)}$$

where the gas viscosity, $\rho$, is a function of temperature, $T$, and gas composition, $F = (N_2, O_2, H_2, CO_2)$, and $K$ is a geometric constant. Because the mixture of gas species can be considered an ideal gas, the viscosity of the mixture can be formulated as the linear combination of viscosities of pure gas weighted by their fractional concentration $F^\alpha$.

$$\rho(F,T) = \sum_a F^\alpha \rho_a(T)$$

where $\alpha = N_2, O_2, H_2O, CO_2$.

The temperature changes are sufficiently small to allow the viscosities of $O_2, N_2, H_2O, CO_2$ to be related linearly to temperature (2):

$$\begin{align*}
\rho_{N_2}(T) &= 43.93 + 0.453T \\
\rho_{O_2}(T) &= 118.50 + 0.298T \\
\rho_{H_2O}(T) &= -23.00 + 0.570T \\
\rho_{CO_2}(T) &= 16.25 + 0.455T
\end{align*}$$

where $T$ has the units of °K. The fractional concentrations ($F_a$) of $H_2O$ and $CO_2$ in inspired gas, expired gas, and ambient air are assigned reasonable values (Table 2). Consequently, from Table 2 together with Eqs. 1–3, the volume flow rate at body temperature ($T_b$) can be computed by

$$Q(t) = K[F_n(T_b/T)P(t)/(A(T) - B(T)F_{N2}(t))]$$

During inspiration, we set $T = 23^\circ$C, for which $A = 205.3$

| TABLE 2. Fractional concentrations of inspired and expired gas |
|-------------------|-------------------|-------------------|-------------------|
| Species Fraction | Inspiration      | Expired           | Ambient Air       |
| $F_{N2}$          | $F_{N2}(t)$       | $F_{N2}(t)$       | 0.790             |
| $F_{O2}$          | 0.972 – $F_{N2}(t)$ | 0.896 – $F_{N2}(t)$ | 0.200             |
| $F_{H2O}$         | 0.028             | 0.062             | 0.007             |
| $F_{CO2}$         | 0                 | 0.041             | 0.003             |

The only directly measured fraction is $F_{N2}(t)$. The fractional concentration of water vapor, assuming complete saturation, may be approximated by $F_{H2O} = (13.20 - 0.61T + 0.04T^2)/P$, where $T$ is temperature, in °C, and $P$ is pressure in Torr.

and $B = 28.9$. During expiration, we used a mean expired temperature, $T = 34^\circ$C, for which $A = 204.7$ and $B = 27.0$.

**Measured variables.** A zero-crossing technique is applied to discriminate inspiration from expiration. Integration (by the trapezoidal method) of the flow signal allows computation of maximum expiratory volume, maximum inspiratory volume, and also tidal volume during the washout test. The inspiratory and expiratory volumes over the breath $k$ are given by

$$\Delta V(k, I) = \int_{I(k)} Q(t)dt$$

$$\Delta V(k, E) = \int_{E(k)} Q(t)dt$$

where $\Delta V(k, I)$ and $\Delta V(k, E)$ are the magnitudes of the volume changes on inspiration and expiration. The end-tidal nitrogen fraction $F(k)$ is determined by searching for the maximum point in nitrogen signal during the $k$th period. Multiplication of the synchronized nitrogen and flow signals leads to an estimation of averaged expired nitrogen fraction in breath $k$

$$(F)_k = \int_{E(k)} F(t)Q(t)dt/\Delta V(k, E)$$

The accuracy of computer calculation of variables $(F)_k$, $(F)_k$, $\Delta V(k, I)$, and $\Delta V(k, E)$ was verified by several techniques. In particular, $F(k)$ was directly measured from the $X$-$Y$ recorder. Volume amplitudes were checked with pump volumes, and the total amount of nitrogen expired over several breaths was measured from a collection bag. We found that the difference between computer and measured variables in typically ±1%.

**Lung volumes.** Functional residual capacity is derived from measured variables, allowing for different inspiratory and expiratory volume changes on each breath (13)

$$FRC = V(0, E) = \sum_{j=1}^k (F)_j \Delta V(j, I)/[F(0) - F(k)] + \sum_{j=1}^k [\Delta V(j, I) - \Delta V(j, E)]/[F(0)/F(k) - 1]$$

As $k$ gets large, $F(0) \gg F(k)$ so that the second term in this equation becomes negligible. For spontaneous breathing, we make the approximations that $FRC = V(0, E)$ and at the end of expiration $k$ the end-tidal nitrogen fraction leaving the lung is approximately equal to the $N_2$ fraction within the lung. In addition to the FRC, we computed the following volumes: vital capacity (VC), RV, and TLC.

**EVALUATION OF INDICES**

**Statistical measures.** In evaluating indices of ventilation inhogeneity, we examine the sensitivity of the indices to the degree of abnormality and the variability of the indices for a given subject and among subjects in a given diagnostic group. For all indices we computed the inusubject variability from the repeated washouts of each subject as the relative difference
where \( Z_1 \) and \( Z_2 \) are the values of any index \( Z \) for the two washouts and \( AZ \) is their average value. The diagnostic intergroup sensitivity is evaluated by the mean and standard deviation of \( AZ \) of all subjects in each group. The mathematical expressions used are presented in the APPENDIX.

Comparison of indices. Moments were computed from end-tidal and breath-averaged nitrogen fractions at a dilution number (\( \eta \)) of 8 or 10. From these moments, we obtained the 1st-to-0th and 2nd-to-0th moment ratios (Table 3). As previously found by Saidel et al. (11) and evaluated again in this study, the end-tidal moment ratios \( \mu_1/\mu_0 \) and \( \mu_2/\mu_0 \) at a dilution number of 10 are linearly related with a very high correlation coefficient \( (\rho = 0.993) \). At \( \eta = 8 \), these ratios are linearly related (Fig. 2) with nearly the same correlation coefficient \( (\rho = 0.994) \). Within any clinical group, \( \mu_1/\mu_0 \) tends to show less relative spread than \( \mu_2/\mu_0 \) at both \( \eta = 8 \) and \( \eta = 10 \). Similar results are found for the breath-averaged moment ratios \( (\mu_1)/\mu_0 \) and \( (\mu_2)/\mu_0 \). Because the ratios involving second moments yielded no additional information, we shall not consider them further.

The remaining comparisons involve the moment ratios \( \mu_1/\mu_0 \) and \( (\mu_1)/\mu_0 \). As seen in Fig. 3, these moment ratios with \( \eta = 8 \) are also linearly related, having a correlation coefficient \( \rho = 0.944 \); with \( \eta = 10 \), the correlation coefficient is somewhat higher \( (\rho = 0.964) \). The relative variabilities among groups and subjects of these 1st-to-0th moments are also similar (Table 3). Although either of these moment ratios would be adequate for our analysis, we shall arbitrarily choose the end-tidal ratio \( \mu_1/\mu_0 \) for further comparisons. We recognize that there are reasons for the use of mixed expired rather than end-tidal data to study washout dynamics. However, the end-tidal moment ratio has a clear mathematical interpretation (12). Based on a model with two alveolar spaces, one of which is poorly ventilated, the moment ratio \( \mu_1/\mu_0 \) approximately equals the relative volume-flow ratio of that space. A remaining question is whether truncation of the data at dilution number \( \eta = 8 \) is as satisfactory as at \( \eta = 10 \). Although the earlier truncation of the data at \( \eta = 8 \) causes some loss of information, the effect on diagnostic distinction of the subjects appears to be only slightly altered (Fig. 4).

Because characteristic lung volumes and volume ratios can be determined as part of the test with very little extra effort, these also can be used to help make distinctions. In our study, the estimated FRC typically varied less than 8% for repeated tests of a given subject. The difference in the estimates of FRC with dilution 8 or 10 is even smaller than 8%. Consequently, although the FRC tends to be slightly underestimated with the smaller dilution number, the difference is not significant for comparison of among subjects. To help distinguish subjects with COPD from other diagnostic groups, we looked at the volume ratios, e.g., RV/TLC. As shown in Fig. 5, RV/TLC vs. \( \mu_1/\mu_0 \) tends to make this distinction clearer. No additional distinction is apparent from other lung volumes or volume ratios.

![FIG. 2. Comparison of end-tidal moment ratios with dilution number](image)

**Diagnostic differentiation.** With respect to normal

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### TABLE 3. Intergroup sensitivity and intrasubject variability of moment ratios

<table>
<thead>
<tr>
<th>Diagnostic Group</th>
<th>Dilution No. (( \eta ))</th>
<th>( \mu_1/\mu_0 ) Sensitivity</th>
<th>( \mu_2/\mu_0 ) Sensitivity</th>
<th>( \mu_1/\mu_0 ) vs ( \mu_2/\mu_0 ) Sensitivity</th>
<th>( \mu_1/\mu_0 ) vs ( \mu_2/\mu_0 ) Sensitivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal smokers</td>
<td>8</td>
<td>1.74 0.09 1.00-1.84</td>
<td>5.26 0.45 5.64-7.02</td>
<td>1.54 0.10 1.41-1.66</td>
<td>5.38 0.51 4.66-5.53</td>
</tr>
<tr>
<td>Asthmatic subj</td>
<td>8</td>
<td>1.88 0.06 1.74-1.88</td>
<td>7.47 0.57 6.84-8.19</td>
<td>1.64 0.11 1.52-1.76</td>
<td>6.38 0.63 5.30-7.14</td>
</tr>
<tr>
<td>DILD subj</td>
<td>8</td>
<td>2.03 0.25 1.95-2.04</td>
<td>8.80 1.00 7.00-8.08</td>
<td>1.62 0.20 1.55-1.91</td>
<td>5.93 0.70 5.80-7.33</td>
</tr>
<tr>
<td>COPD subj</td>
<td>8</td>
<td>2.00 0.26 1.79-2.04</td>
<td>7.92 1.44 7.18-13.15</td>
<td>1.68 0.26 1.68-2.24</td>
<td>8.31 1.86 8.13-11.30</td>
</tr>
<tr>
<td>All subj</td>
<td>8</td>
<td>2.00 0.26 1.80-2.04</td>
<td>8.68 1.44 7.07-10.40</td>
<td>1.80 0.26 1.87-2.20</td>
<td>8.61 1.86 8.13-11.30</td>
</tr>
</tbody>
</table>

**Variables:**

<table>
<thead>
<tr>
<th>Variability</th>
<th>MRD ± SDRD%</th>
</tr>
</thead>
<tbody>
<tr>
<td>RD =</td>
<td>Z1 - Z2</td>
</tr>
<tr>
<td>Normal smokers</td>
<td>8</td>
</tr>
</tbody>
</table>

Means and standard deviations for intergroup sensitivity are denoted by MZ and SDZ, where Z is one of the following indices: \( \mu_1/\mu_0 \) or \( \mu_2/\mu_0 \). Means and standard deviations for intrasubject variability are denoted by MRD and SDRD.
nonsmokers, the mean values (MZ) of $\mu_1/\mu_0$ are 9% greater for "normal" smokers, 18% greater for asthmatics, 28% greater for DILD subjects, and 57% greater for COPD subjects. By the moment ratios, abnormal subjects including the "normal" smokers are well discriminated from the normal nonsmokers. The symptomatic asthmatics have moment ratios higher than do normals; in remission, however, asthmatics have normal values for all the pulmonary function tests applied, including the indices of $N_2$ washout. Although the mean of $\mu_1/\mu_0$ for COPD subjects is higher than the mean for either asthmatics or DILD subjects by 39 and 29%, respectively, some asthmatics and DILD subjects have moment ratios as high as those of COPD subjects.

Although the moment ratio demonstrates differences among several clinical groups, it is not intended as a diagnostic index for a specific disease state. (Indeed, no single pulmonary function index or parameter can do that.) Rather, we use the clinical groups to give us an indication of the extent of ventilation inhomogeneity. The purpose of the moment ratio is to quantify the degree of ventilation inhomogeneity for any individual regardless of disease state.

In conclusion, with proper signal conditioning and corrections incorporated into a computerized analysis, the washout procedure can be done with spontaneous breathing in a few minutes, even with subjects with severe COPD. By use of on-line computation, the results can be available seconds after the completion of a washout. The ratio of the 1st- to 0th moments of the end-tidal nitrogen fraction dynamics yields a quantitatively informative and clinically feasible index of ventilation inhomogeneity. This moment ratio 1) shows little sensitivity to small measurement errors and random noise, 2) has a relatively small range of values for normal nonsmokers, 3) can even detect mild ventilation inhomogeneity of "normal" smokers, and 4) can distinguish the greater inhomogeneity of subjects with asthma, diffuse interstitial lung disease, or chronic obstructive pulmonary disease.

**APPENDIX**

*Statistical Measures*

Because each subject in these experiments performed the washout procedure twice, we have two values of all indices denoted by $Z_i(I, g, s)$ and $Z_0(I, g, s)$, where $I$ is the index, $g$ is the diagnostic group, and $s$ is the subject in the diagnostic group $g$. For each subject, we compute an average

$$AZ(I, g, s) = \frac{Z_i + Z_0}{2}$$

and a relative difference

$$RD(I, g, s) = \frac{|Z_i - Z_0|}{AZ}$$

As measures of intergroup sensitivity among diagnostic groups, we can define for each group $g$, having $Q(g)$ subjects, a mean

$$MZ(I, g) = \frac{\sum_{s=1}^{Q(g)} AZ(I, g, s)}{Q(g)}$$

and a standard deviation

$$SDZ(I, g) = \left[ \frac{\sum_{s=1}^{Q(g)} (AZ - MZ)^2}{Q(g)} \right]^{1/2}$$

The intrasubject variability of the indices is characterized for all subjects by a mean and standard deviation of the relative difference...
MRD(I) = \frac{\sum_{i=1}^{P} \sum_{j=1}^{Q} RD}{\sum_{i=1}^{P} Q(i)} \\
SDRD(I) = \left[ \frac{\sum_{i=1}^{P} \sum_{j=1}^{Q} (RD - MRD)^2}{\sum_{i=1}^{P} Q(i)} \right]^{1/2}

where \( P \) is the total number of groups.

REFERENCES


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