

Multi-breath and single breath helium dilution lung volumes as a test of airway obstruction

C.M. Roberts, K.D. MacRae*, W.A. Seed

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ABSTRACT: Total lung capacity (TLC) and residual volume (RV) measurements derived from multi-breath and single breath helium dilution methods were combined to produce four indices of gas mixing: single breath volume/multi-breath volume ratio (TLCr, RVr) or multi-breath volume minus single breath volume difference (TLCd, RVd). The reproducibility of these indices and their sensitivity and specificity in discriminating between normal subjects and those with mild asthma and severe chronic obstructive pulmonary disease (COPD) was assessed. The total lung capacity ratio (TLCr) was the superior variable overall, providing a single range for both sexes with a specificity and sensitivity similar to that of the forced expiratory volume in one second (FEV₁) in the diagnosis of airflow obstruction. Despite the similar sensitivity, correlation between TLCr and FEV₁ was only moderate ($r = 0.56$). This may reflect greater influence of peripheral rather than central airflow obstruction on TLCr. Combining both tests improved sensitivity in the detection of airways obstruction in the asthmatic and COPD groups studied.

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Multi-breath (MB) and single breath (SB) helium dilution measurements of lung volume are in common use in lung function laboratories. Correlation between volume measurements derived from the two different methods is excellent in normal subjects [1-3]. However, this correlation falls when subjects with airflow obstruction are tested, the single breath method tending to be lower than the multi-breath value [4-6]. The difference between the two measured volumes has been shown to correlate with the degree of spirometric abnormality [7] and it has been suggested that it is related to incomplete gas mixing in the lungs and could be used to detect and assess airways obstruction [8-10]. This abnormality of gas mixing has been recorded for both residual volume (RV) [11-14] and total lung capacity (TLC) (or alveolar volume) [7, 9, 15, 16] and has been expressed in terms of absolute difference (MB-SB) or as a ratio (SB/MB \times 100), providing four different variables.

Despite the fact that MB and SB lung volume measurements are made during lung function testing, use of the volume differences does not appear to have been widely adopted as a formal test of gas distribution or airway obstruction. No study has yet compared the sensitivity and specificity of these variables in the detection of airways obstruction or produced widely acceptable normal ranges. The purpose of the present

study was to establish normal ranges and within-subject reproducibility for these four alternative volume relationships in a normal population group and compare their specificity and sensitivity for detecting airway obstruction with conventional spirometric measurements in patients with obstructive lung disease (asthma and chronic obstructive pulmonary disease (COPD)) and parenchymal lung disease (cryptogenic fibrosing alveolitis (CFA) and scleroderma). The latter group were included because uneven mixing might be a consequence of uneven pulmonary compliance whilst in the former group it would be dominated by uneven distribution of airways resistance.

Methods

Subjects

179 normal subjects (96 male, 83 female; mean age, 45 yrs, range 18-86) were recruited from the hospital catchment area in response to advertisements placed in the hospital foyer and fracture clinics. Normal subjects were lifelong nonsmokers (not more than 1 cigarette per day for 1 year) with no history of respiratory or other serious illness, who gave negative replies to a simplified British Medical Research Council respiratory health

questionnaire which covered current respiratory symptoms, previous medical history, time loss from work and smoking history. In order to examine intra-subject variability 30 of these subjects (mean age 33 yrs range 20–64) were tested a second time within one week of the original test.

100 nonsmoking subjects with asthma (mean age 43 yrs, range 18–75) and 100 current or ex-smokers with COPD (mean age 67 yrs, range 46–84) were selected retrospectively from lung function laboratory records of tests carried out concurrently with those on the normal subjects. Asthmatics were selected on the basis of clinical history and evidence of reversible airflow obstruction (greater than 20% increase in forced expiratory volume in one second (FEV₁) following bronchodilator administration). COPD patients were selected on the basis of clinical history and impairment of FEV₁ with less than 20% response to bronchodilator inhalation.

Asthmatics with a positive smoking history or chest X-ray abnormality other than overinflation, and COPD patients with chest X-ray abnormality other than overinflation or evidence of emphysema, were excluded. Apart from these exclusions, the patients formed a consecutive series concurrent with the studies of the normal subjects. In addition, 38 nonsmoking patients with CFA or scleroderma, diagnosed clinically by accepted criteria [17], were also selected. All these subjects had radiological evidence of respiratory involvement and an increased alveolar-arterial oxygen gradient (range 2.9–6.0 kPa).

Measurements

Subjects had their age, height and weight recorded and underwent full lung function testing, consisting of multi-breath helium dilution (lung volumes), single breath carbon monoxide transfer factor (including single breath helium dilution), and spirometry. Either a Gould (model CPI 5000 IV) lung function computer or combination Morgan lung function and transfer apparatus (model C) and Hewlett Packard Vertek pneumotachograph (model 5000 VR) were used to measure these values.

Closed circuit multi-breath helium dilution was used to measure the functional residual capacity (FRC) during a 5–8 min tidal volume rebreathing period which was terminated after the helium concentration had remained stable for a minimum period of 60 s. During this period two inspiratory vital capacity (IVC) manoeuvres were performed. The test was repeated in each subject at 15 min intervals until two FRC determinations within 200 ml of each other were obtained. The RV was derived from the FRC minus the expiratory reserve volume. The TLC was calculated from the RV plus the higher inspiratory vital capacity value. The mean of the results from the two tests was taken.

The single breath helium dilution lung volume was measured during the carbon monoxide transfer factor estimation. The subject was instructed to expire to RV and then take a maximal inspiration to TLC followed by a breath hold of approximately 10 s before expiration.

The first 750 ml of the expirate was discarded and the following litre of the vital capacity collected for analysis. A minimum of two attempts were made and were accepted if the IVC fell within 10% of the previously performed multi-breath IVC.

The spirometric measurements were taken from the first three maximum forced expiratory vital capacity manoeuvres performed with acceptable technique and maximum effort. The highest values for FEV₁ and FVC were taken independently from these three tests.

Statistics

All data were transferred to the University of London Computing Centre (Amdahl 5890) and analysed using the Statistical Package for Social Sciences (SPSS Inc. Chicago, Illinois). The dependence of the mixing indices on the independent variables age, height, weight and absolute lung volume measured (TLC or RV) was examined with scatterplots, correlation coefficients, and regression lines.

Values for the four new mixing indices - total lung capacity ratio (TLCr), total lung capacity difference (TLCd), residual volume ratio (RVr), and residual volume difference (RVd) - were calculated for each of the 179 normal subjects and their distributions examined for skewness and kurtosis. The difference between sexes was assessed using the Kolmogorov-Smirnov distribution test.

Table 1. - Descriptive statistics for mixing indices in normal subjects

Mixing index	Mean	SD	Skew	Kurtosis
Males				
TLCr %	93.6	7.56	1.22	4.23
TLCr* %	93.0	6.50	0.23	-0.27
TLCd l	0.49	0.47	-0.19	0.17
RVr %	85.2	14.04	-0.12	-0.29
RVd l	0.32	0.32	0.89	0.79
Females				
TLCr %	94.1	6.75	-0.30	0.30
TLCd l	0.32	0.36	0.50	0.50
RVr %	87.7	15.39	0.11	-0.23
RVd l	0.22	0.27	0.84	1.26
Combined				
TLCr %	93.9	7.12	0.52	2.42
TLCr* %	93.7	6.65	0.06	-0.50
TLCd l	0.39	0.45	-0.18	1.18
RVr %	86.7	14.89	0.04	-0.25
RVd l	0.26	0.30	0.91	1.10

*: one outlying value removed; TLCr: total lung capacity ratio; TLCd: total lung capacity difference; RVr: residual volume ratio; RVd: residual volume difference.

The normal range for each mixing index was calculated from the mean value and a one sided 95% distribution (mean - 1.645 SD). A one sided distribution was chosen because a single breath value higher than a multi-breath value is physiologically nonsensical, only a low ratio being indicative of a mixing defect. The

Table 2. – Between subject and within subject variability of mixing indices (30 normal subjects tested twice)

A. Between subjects: mean values for each test performed twice on same day			
Mixing index	Mean	SD	*CV%
TLCr 1	95.7	5.3	5.5
TLCr 2	96.3	5.4	5.6
TLCd 1	0.27	0.36	–
TLCd 2	0.25	0.34	–
RVr 1	90.3	15.5	18.2
RVr 2	91.4	17.8	19.5
RVd 1	0.19	0.26	–
RVd 2	0.20	0.32	–

B. Within subject: mean values for each test performed twice on separate days

	Paired variables					
	Mean	SD	t	p	r	**CV%
TLCr (1-2)	-0.53	7.07	-0.72	0.48	0.72	7.3
TLCd (1-2)	-0.02	0.24	0.37	0.71	0.78	–
RVr (1-2)	-2.94	9.66	-1.67	0.11	0.84	10.7
RVd (1-2)	-0.01	0.23	-0.10	0.92	0.71	–

*CV%: SD/mean; **CV%: SD of differences/mean value of the two tests; t: value of t-test; p: statistical probability; r: correlation coefficient. For other abbreviations see legend to table 1.

Table 3. – Spirometric variables for asthma and COPD subjects expressed as mean (SD) percent of predicted value and mixing indices expressed in absolute terms as percentages (ratios) or litres (differences)

Variable	Asthma		COPD	
	Males n=42	Females n=58	Males n=64	Females n=36
FEV ₁	88.2 (25.2)	64.0 (25.3)	64.1 (25.4)	42.4 (19.1)
FVC	83.8 (15.9)	79.1 (19.1)	64.9 (18.0)	61.4 (19.0)
FEV ₁ /FVC	73.9 (15.1)	77.8 (19.1)	59.4 (15.2)	65.8 (17.0)
TLCr %	83.5 (11.4)	84.0 (10.0)	76.2 (9.4)	77.9 (14.4)
TLCd l	1.22 (0.91)	0.80 (0.53)	1.63 (0.77)	1.28 (1.09)
RVr %	72.0 (18.4)	73.6 (20.0)	61.6 (13.6)	64.4 (16.6)
RVd l	0.88 (0.83)	0.66 (0.52)	1.47 (0.74)	1.27 (0.93)

COPD: chronic obstructive pulmonary disease; FEV₁: forced expiratory volume in one second; FVC: forced vital capacity. For other abbreviations see legend to table 1.

following definitions were used in statistical analysis: specificity = true negatives/(true negatives + false positives) × 100; sensitivity = true positives/(true positives + false negatives) × 100; positive predictive value = true positives/(true positives + false positives) × 100; negative predictive value = true negatives/(true negatives + false negatives) × 100.

The specificity of the mixing indices was examined within the normal group by looking for concordance of abnormal values between the four variables. Discriminant analysis, which calculates both specificity

and sensitivity, was used to test the power of the four indices to classify the normal and asthmatic groups into their correct diagnostic categories. Sensitivity was further assessed in the groups of asthmatics and COPD subjects, an abnormal value being defined as one which lay below the lower limit of the predicted normal range (*ie.* more than 1.645 standard deviations below the predicted value). Such a criterion implies a fixed specificity of 95%. The change in sensitivity of spirometric and mixing index tests when combined was assessed in a similar manner. The sensitivity and positive

Table 4. — Discriminant power of mixing indices and FEV₁ applied to normal (group A) and asthmatic (group B) subjects

	FEV ₁	TLCr	TLCd	RVr	RVd <i>l</i>	
					<i>l</i>	%
Group A						
Mean	3.42	93.6	0.40	86.4	0.32	0.22
sd	0.95	6.6	0.42	14.8	0.32	0.27
Group B						
Mean	2.12	83.3	0.98	72.9	0.89	0.66
sd	0.97	10.6	0.74	19.2	0.83	0.52
Sensitivity %	70	62	56	67	55	64
Specificity %	71	80	77	67	84	80
Positive-predictive power %	58	63	58	50	61	66
Negative-predictive power %	81	79	75	78	78	78
Discriminant power +	-	1.0	0.97	0.71	0.75 (sexes combined)	

+ : discriminant power relative to TLCr. For all other abbreviations see legend to table 1.

predictive value of each variable was calculated for both the mixing indices and the spirometric tests and compared. The correlation between individual spirometric and mixing index variables was calculated using correlation coefficients derived from linear regression analysis. Within-subject reproducibility of mixing indices was determined using paired t-tests (and coefficient of variation where appropriate) in 30 subjects tested twice on two separate days within the same week.

Results

Mean values and statistical characteristics of the mixing indices TLCr, TLCd, RVr and RVd derived from the normal subjects are given in table 1. None of these variables had a significant correlation with age, height or weight. There was a significant relationship, as expected, for both RV variables with multi-breath RV (for RVd, $R^2 = 0.42$; for RVr, $R^2 = 0.19$). However, this was much less apparent for the TLC-derived values when correlated with multi-breath TLC (for TLCd, $R^2 = 0.07$; for TLCr, $R^2 = 0.01$).

The only variable for which there was a sex difference when examined by the Kolmogorov-Smirnov Z score and two-tailed probability test was RVd ($p=0.002$). The sexes were therefore combined for all other variables to determine normal ranges and coefficients and skew and kurtosis but were examined individually for RVd. The high kurtosis coefficient for TLCr (table 1) was due to a single extreme outlying value in a male subject. When this was removed the recalculated skew and kurtosis were consistent with a normal distribution [18].

Table 5. — Sensitivity (%) of mixing index and spirometric variables applied to subjects with asthma, COPD, and parenchymal lung disease

Variable	Asthma	COPD	Parenchymal Disease
	n=100	n=100	n=38
TLCr	48	74	11
TLCd	35	60	6
RVr	24	51	3
RVd	36	79	8
FEV ₁	47	61	19
FEV ₁ /FVC*	65	91	8
TLCr + FEV ₁	62	83	25
TLCr + FEV ₁ /FVC	74	96	19

*: ratio below predicted mean -1.645 sd. For all other abbreviations see legend to table 1.

The reproducibility of the mixing indices is shown in table 2 for the 30 normal subjects undergoing two sets of tests at the same time of day on two separate days within the same week.

When the one sided 95% normal range for each mixing index was applied to the normal subject group, a total of 20 individuals were identified as abnormal. In 6 cases a subject was classified as abnormal by only a single test (TLCd(3) RVd(2) RVr(1)). In all other subjects an abnormal result was corroborated by one or more other abnormal result.

Table 3 describes the spirometric and mixing index data for the asthmatic and COPD groups. Table 4 describes the results of discriminant analysis using the mixing indices and FEV₁ to differentiate between the asthmatic and normal subjects. A ranking order

(discriminant power) is provided for correct allocation of subjects to their true diagnostic groups. The positive and negative predictive values for each of these variables is given and compared with those derived from FEV_1 .

In Table 5 the sensitivities of the mixing indices and spirometric variables in subjects with asthma, COPD or parenchymal lung disease are tested.

Discussion

The study indicates that TLCr is the most sensitive and specific of the mixing indices tested (tables 4 and 5). It is also independent of the absolute volume measured, provides a single normal range for both sexes, and has a better reproducibility within individuals than the other mixing indices. Both the sensitivity and specificity of TLCd is lower than that of TLCr.

The use of residual volume indices suffers from their dependence upon the absolute volume measured and their poorer reproducibility than the TLC indices. Both of these problems may be related to the greater difficulty many subjects have in expiring to RV compared with inspiring to TLC [12,13]. The RV values are also smaller volumes than TLC values and any systematic error in measurement will cause a greater percentage error in RV than in TLC.

In measurement of both RV and TLC a proportion of subjects recorded a higher single breath than multi-breath volume. This has been attributed to insufficient expiration to RV, or an inspiration to TLC which begins before the subject is switched into the helium/CO system, in the single breath test. An air leak during the single breath test, or an effort difference causing the single breath IVC to exceed the multibreath IVC would also produce this result.

There is little data on the normal range of TLCr in the literature. In this study the lower limit of the normal range was 82.8% (table 1), which is similar to the 85% suggested by LYONS *et al.* [16] for the VA/VA, but lower than the 90% suggested by TECULESCU [15] although this latter figure is the author's estimate of the normal range and its derivation is not given. A range below 100% is to be expected because the single breath method is likely to underestimate the true lung volume, since perfect gas mixing is improbable even in normal adults. In addition, regional inhomogeneity of pulmonary ventilation may contribute further to an underestimation of true lung volume from a single breath dilution test. Apical lung units will contain lower concentrations of helium than basal units [20, 21] and as they will empty last [22] may not be included in the one litre expirate collected at the mouth before the sample is complete. Any imperfection of gas mixing caused by uneven distribution of airway resistance or lung compliance will affect a single breath measurement more than a multi-breath one.

The potential usefulness of a mixing index in detecting abnormal airways depends upon its sensitivity and specificity. The sensitivity of FEV_1 and TLCr used alone is similar, but their combined sensitivity rises by 10–20% (table 5). It is therefore likely that this combination will

improve the sensitivity of lung function tests in detecting mild airways obstruction when used in a prospective clinical setting.

The relative sensitivity of the TLCr and FEV_1 , however, depends upon 2 main factors. The first is the clinical severity of the airways disease. In this study the asthmatic group had mild disease with 35 subjects having normal FEV_1/FVC ratios. This accounts for the apparently low sensitivity of all the indices evaluated for the detection of airway obstruction. The second factor is the choice of prediction equations for normal values for the FEV_1 . We have used our own recently derived values from a nonsmoking, healthy population [23]. Many lung function laboratories currently use older values, some derived from groups that included cigarette smokers and others from groups which were not carefully screened for respiratory disease. The sensitivities of FEV_1 values from such groups are likely to be less than that in the present study and the TLCr may then provide additional information.

In the subjects with obstructive airways disease the TLCr and FEV_1 show only moderate correlation (correlation coefficient $r=0.56$, $p<0.001$, in asthmatics and $r=0.55$, $p<0.001$, in COPD). More detailed analysis of the asthmatic patients revealed that 33 had abnormal values for both TLCr and FEV_1 , 15 of the 53 subjects with a normal FEV_1 had an abnormal TLCr and 14 of the 52 with a normal TLCr had an abnormal FEV_1 . These results suggest some shared but also some separate influencing factors on the TLCr and FEV_1 measurements. Gas mixing may be predominantly influenced by small airways function, whereas FEV_1 is dominated by the large airways. Thus in subjects with predominantly small airway obstruction FEV_1 might remain normal in the presence of uneven gas mixing [24], whilst large airway obstruction in the absence of small airways damage would produce an abnormal FEV_1 but a normal TLCr. Alternatively, large and small airway obstruction may coincide. All of these combinations have been found histologically in at least one extensive postmortem study [25].

The parenchymal lung disease subjects showed a much lower prevalence of abnormal TLCr values than the obstructive airway group (table 5). Previous studies of gas mixing in parenchymal lung disease using single and multi-breath washout tests have demonstrated abnormalities in most subjects [26–28]. These studies however, included cigarette smokers and studied predominantly patients with sarcoidosis, which may itself result in endobronchial obstruction. In studies using multi-breath washout in nonsarcoid patients the prevalence of abnormality has been much lower [29, 30]. Our observations suggest that TLCr is much less sensitive to parenchymal lung disease and more specific to airways disease. As gas mixing should be disturbed by both uneven compliance as well as airway resistance, the explanation for the results in this group is not clear. It may imply that compliance change in these patients was evenly distributed or may suggest that peripheral airflow obstruction is the dominant determinant of gas mixing in the lung.

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Les volumes pulmonaires par dilution de l'hélium en respiration multiple ou unique comme tests, de l'obstruction des voies aériennes. C.M. Roberts, K.D. MacRae, W.A. Seed.

RÉSUMÉ: Des mesures de capacité pulmonaire totale (CPT et de volume résiduel (VR), dérivées de méthodes de dilution de l'hélium en respiration multiple ou unique, ont été combinées pour obtenir quatre indices de la mixique des gaz: le rapport volume en respiration unique/volume en respiration multiple (TLCr, RVd) ou la différence entre le volume à respiration multiple et le volume en respiration unique (TLCd, RVd). La reproductibilité de ces indices et leur sensibilité, ainsi que leur spécificité, pour discriminer des sujets normaux et ceux atteints d'asthme léger ou de bronchopneumopathie chronique obstructive sévère, ont été étudiées. Le rapport des capacités pulmonaires totales (TLCr) s'avère la variable globalement la plus valable, qui donne des valeurs similaires pour les deux sexes, avec une spécificité et une sensibilité similaires à celles du VEMS pour le diagnostic de l'obstruction des voies aériennes. Malgré une sensibilité similaire, la corrélation entre TlCr et VEMS n'est que modérée ($r=0.56$). Ceci pourrait être le reflet d'une influence plus marquée de l'obstruction périphérique par rapport à l'obstruction centrale sur TlCr. La combinaison des deux tests améliore la sensibilité pour la détection de l'obstruction des voies aériennes dans les groupes étudiés de sujets asthmatiques et de bronchopneumopathies chroniques obstructives.

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