



SERIES “ATS/ERS TASK FORCE: STANDARDISATION OF LUNG FUNCTION TESTING”

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Interpretative strategies for lung function tests

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KEYWORDS: Bronchodilator, diffusing capacity, lung volume measurements, obstructive, spirometry, reference values

BACKGROUND

This section is written to provide guidance in interpreting the pulmonary function tests (PFTs) to medical directors of hospital-based laboratories that perform PFTs, and physicians who are responsible for interpreting the results of PFTs most commonly ordered for clinical purposes. Specifically, this section addresses the interpretation of spirometry, bronchodilator response, carbon monoxide diffusing capacity (DL_{CO}) and lung volumes.

The sources of variation in lung function testing and technical aspects of spirometry, lung volume measurements and DL_{CO} measurement have been considered in other documents published in this series of Task Force reports [1–4] and in the ATS interpretative strategies document [5].

An interpretation begins with a review and comment on test quality. Tests that are less than optimal may still contain useful information, but interpreters should identify the problems and the

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direction and magnitude of the potential errors. Omitting the quality review and relying only on the numerical results for clinical decision making is a common mistake, which is more easily made by those who are dependent only upon computer interpretations.

Once quality has been assured, the next steps involve a series of comparisons [6] that include comparisons of test results with reference values based on healthy subjects [5], comparisons with known disease or abnormal physiological patterns (*i.e.* obstruction and restriction), and comparisons with self, a rather formal term for evaluating change in an individual patient. A final step in the lung function report is to answer the clinical question that prompted the test.

Poor choices made during these preparatory steps increase the risk of misclassification, *i.e.* a falsely negative or falsely positive interpretation for a lung function abnormality, or for a change in lung function. Patients whose results are near the thresholds of abnormality are at a greatest risk of misclassification.

REFERENCE EQUATIONS

General issues

Interpretation of PFTs is usually based on comparisons of data measured in an individual patient or subject with reference (predicted) values based on healthy subjects. Predicted values should be obtained from studies of “normal” or “healthy” subjects with the same anthropometric (*e.g.* sex, age and height) and, where relevant, ethnic characteristics of the patient being tested. Ideally, reference values are calculated with equations derived from measurements observed in a representative sample of healthy subjects in a general population. Reference equations can also be derived from large groups of volunteers, provided that criteria for normal selection and proper distribution of anthropometric characteristics are satisfied. Criteria to define subjects as “normal” or healthy have been discussed in previous American Thoracic Society (ATS) and European Respiratory Society (ERS) statements [5, 7, 8].

Height and weight should be measured for each patient at the time of testing; technicians should not rely on stated height or weight. Height should be measured with a stadiometer, with shoes off, using standard techniques (patient standing erect with the head in the Frankfort horizontal plane) [9]. When height cannot be measured, options include using stated height or estimating height from arm span, as indicated in a previous document from this series of Task Forces and other publications [1, 10, 11].

Specific recommendations for selecting reference values to be used in any lung function laboratory have also been discussed [3]. These include the following: matching age-range, anthropometric, race/ethnic, socio-economic and environmental characteristics between subjects investigated by the laboratory and the reference population from which the prediction equations have been drawn; using similar instruments and lung function protocols in the reference population as in the laboratory; and using reference values derived by valid and biologically meaningful statistical models, taking into account the dependence of lung function with age. If possible, all parameters should be taken from the same reference source. For example, forced vital capacity (FVC), forced expiratory

volume in one second (FEV₁), and FEV₁/FVC should come from the same reference source.

The subjects being tested should be asked to identify their own race/ethnic group, and race/ethnic-specific reference equations should be used whenever possible. If such equations are not available or are unsuitable for a particular setting, a race/ethnic adjustment factor based on published data may be used for lung volumes. The use of adjustment factors is not as good as specific race/ethnic equations [12]. An example of adjustment factors is the finding that populations using standing height as the measure of size tend to overpredict values measured in Black subjects by ~12% for total lung capacity (TLC), FEV₁ and FVC, and by ~7% for functional residual capacity (FRC) and residual volume (RV) [5]. A race/ethnic adjustment factor of 0.94 is also recommended for Asian Americans based on two recent publications [13, 14]. Such adjustment factors should not be applied to the FEV₁/FVC or FEV₁/vital capacity (VC) ratios. The use of sitting height does not completely account for race/ethnic differences in pulmonary function [15]. If a race adjustment factor is used, a statement should be included in the report, along with the race adjustment value used.

Differences in the evaluation of lung function using different sets of reference equations have been documented [16, 17]. Ideally, spirometric reference values should be derived from a population similar to the individual subject using the same kind of instrument and testing procedure.

There have been recommendations to compare selected reference equations with measurements performed on a representative sample of healthy subjects tested in each laboratory. The reference equation that provides the sum of residuals (observed – predicted) computed for each adult subject, or log (observed) – log (predicted) for each subject in the paediatric age range) closest to zero will be the most appropriate for that laboratory [7]. However, for spirometry, a relatively large number of subjects (*i.e.* n=100) is necessary to be confident that a significant difference between the published reference equations and the values from the local community does not exist [18]. Therefore, the suggestion is impractical for most laboratories.

When using a set of reference equations, extrapolation beyond the size and age of investigated subjects should be avoided [7]. If a patient's age or height is outside the limits of the reference population, a statement in the interpretation should indicate that an extrapolation has been made.

Publications on reference equations should include explicit definitions of the upper and lower limits of the normal range, or provide information to allow the reader to calculate a lower range [5]. For each lung function index, values below the 5th percentile of the frequency distribution of values measured in the reference population are considered to be below the expected “normal range” [5]. If the reference data have a normal distribution, the lower 5th percentile can be estimated as the 95% confidence interval using Gaussian statistics. If the distribution is skewed, the lower limit should be estimated with a nonparametric technique, such as the 95th percentile. The practice of using 80% predicted as a fixed value for the lower limit of normal may be acceptable in children, but can

lead to important errors when interpreting lung function in adults [5]. The practice of using 0.70 as a lower limit of the FEV₁/FVC ratio results in a significant number of false-positive results in males aged >40 yrs and females >50 yrs [12], as well as in a risk of overdiagnosis of chronic obstructive pulmonary diseases (COPD) in asymptomatic elderly never-smokers [19]. This discussion has been focused on the lower limit of the reference range. Upper limits are appropriate where the variable can be either too high or too low. Such variables include TLC, RV/TLC and DL_{CO}. As equipment and techniques for lung function testing improve, advanced mathematical models to describe lung function data are implemented. Furthermore, the characteristics of the populations of “normal” subjects, with respect to nutrition, health status, environmental conditions and other factors, evolve (a phenomenon also described as “cohort effect”). Consideration should be given to the opportunity to update reference equations on a regular basis, *e.g.* every 10 yrs, taking into account the applicability of the newer reference equations and the effect on interpretation of longitudinal patient follow-up.

Manufacturers should also provide software that allows users to easily select among a panel of reference equations. They should also allow easy insertion of new equations. The reference values used should be documented on every pulmonary function report with the first author's last name (or organisation) and the date of publication.

Spirometry

The European Community for Coal and Steel (ECCS) [8, 20] and the ATS [5, 21] have both published comprehensive listings of published reference equations for spirometry. A number of additional studies on lung function reference values, dealing with a variety of ethnic/race groups and age ranges, have been published in the last 10 yrs [12, 14, 17, 22, 23].

Spirometric reference equations are usually derived from cross-sectional studies and are subject to “cohort effect”. Few authors have published longitudinal equations covering ages from childhood to the elderly [24–26], and there are few published sets of equations that cover volume and flow indices over a wide range of ages [27, 28]. Table 1 includes reference equations published from 1995 to August 2004. The table was created from known equations and a MEDLINE search using the keywords “reference equations” and “spirometry”. Its purpose is to recognise and encourage the continuing interest of worldwide researchers in deriving and using reference equations.

In the USA, ethnically appropriate National Health and Nutrition Examination Survey (NHANES) III reference equations are recommended for those aged 8–80 yrs [12]. For children aged <8 yrs, the equations of WANG *et al.* [29] are recommended. Other prediction equations may be used if there are valid reasons for the choice. In Europe, the combined reference equations published in the 1993 ERS statement [8] are often used for people aged 18–70 yrs, with a height range of 155–195 cm in males, and 145–180 cm in females, and those from QUANJER *et al.* [30] in paediatric ages. Currently, the current authors do not recommend any specific set of equations for use in Europe, but suggests the need for a new

Europe-wide study to derive updated reference equations for lung function.

Lung volumes

Lung volumes are related to body size, and standing height is the most important correlating variable. In children and adolescents, lung growth appears to lag behind the increase in standing height during the growth spurt, and there is a shift in relationship between lung volume and height during adolescence [31, 32]. The height growth rate in young males aged between 12.5 and 18 yrs peaks ~1 yr before the growth rate of weight and FVC, and ~1.5 yrs before the growth rate of maximum flow at 50% FVC. In young females, growth rates of all spirometric indices decrease over the same age range. Using simple allometric relationships between stature and lung volumes, volume predictions are too high in the youngest age group and too low in the oldest adolescents.

Furthermore, for the same standing height, young males have greater lung function values than young females, and Whites have greater values than Blacks. Lung function increases linearly with age until the adolescent growth spurt at aged ~10 yrs in females and 12 yrs in males. The pulmonary function *versus* height relationship shifts with age during adolescence. Thus, a single equation or the pulmonary function–height growth chart alone does not completely describe growth during the complex adolescent period. Nevertheless, race- and sex-specific growth curves of pulmonary function *versus* height make it easy to display and evaluate repeated measures of pulmonary function for an individual child [29].

Details of reference populations and regression equations for children and adolescents are summarised by QUANJER *et al.* [30]. Lung volume reference equations have been frequently derived from relatively small populations (<200 children) over a 6–12-yr age range when growth and developmental changes are extremely rapid. Relatively few studies have taken puberty or age into account.

A comprehensive listing of published reference equations for lung volumes was published in 1983 by the ECCS [20] and updated in 1993 [8]. A set of equations was created by combining the equations in this list with the intent to use the combined equations for adults aged 18–70 yrs with a height range of 155–195 cm in males, and 145–180 cm in females.

A report on an ATS workshop on lung volume measurements [7] reviewed published reference values in infants, pre-school children, children, adolescents and adults, and gave recommendations for selecting reference values, expression of results, measuring ancillary variables and designing future studies. Most reference equations for children are derived from Caucasian populations.

Differences due to ethnicity are not well defined [33–36]. These differences may be explained, in part, by differences in trunk length relative to standing height, but there are also differences in fat-free mass, chest dimensions and strength of respiratory muscles. Until better information is available, correction factors for Black and Asian children could be the same as those recommended for adults [7]. Reference values for RV, VC and TLC are, on average, 12% lower in Blacks than in Whites [35];

TABLE 1 Outcomes of a MEDLINE search using the keywords "reference equations" and "spirometry"

Author	Year	Country/area/nature of study	Journal
KOTANIEMI	2004	Finland; adults	<i>Int J Circumpolar Health</i> 2004; 63: 129–139
SUBBARAO	2004	Canada; comparison of references	<i>Pediatr Pulmonol</i> 2004; 37: 515–522
FALASCHETTI	2004	England; prediction equations from the Health Survey	<i>Eur Respir J</i> 2004; 23: 456–463
BOTSIS	2003	Greece; neural networks for the prediction of spirometric reference values in the elderly	<i>Med Inform Internet Med</i> 2003; 28: 299–309
BEN SAAD	2003	Tunisia; vital capacity and peak expiratory flow rates in the elderly	<i>Rev Mal Respir</i> 2003; 20: 521–530 (French)
MUSTAJBEGOVIC	2003	Croatia; comparison with European reference values	<i>Croat Med J</i> 2003; 44: 614–617
PEREZ-PADILLA	2003	Mexico; comparison with Mexican American children	<i>Pediatr Pulmonol</i> 2003; 35: 177–183
TORRES	2003	Brazil; height and arm span in children	<i>Pediatr Pulmonol</i> 2003; 36: 202–208
GOLSHAN	2003	Iran	<i>Eur Respir J</i> ; 22: 529–534
MOHAMED	2002	Italy	<i>Lung</i> 2002; 180: 149–159
BOSKABADY	2002	Iran	<i>Respiration</i> 2002; 69: 320–326
HAVRYK	2002	Himalayan Sherpas	<i>Respir Physiol Neurobiol</i> 2002; 132: 223
DEJSOMRITRUTAI	2002	Thailand	<i>Respirology</i> 2002; 7: 123–127
LANGHAMMER	2001	Norway	<i>Eur Respir J</i> 2001; 18: 770–779
MILIVOJEVIC-POLEKSIC	2001	Pacific Island	<i>Respirology</i> 2001; 6: 247–253
MARION	2001	USA; American Indian	<i>Chest</i> 2001; 120: 489–495
KIVASTIK	2001	Estonia; school children	<i>Clin Physiol</i> 2001; 21: 490–497
MANZKE	2001	Germany; children aged 6–16 yrs from "hospital normals"	<i>Eur J Pediatr</i> 2001; 160: 300–306
PEREZ-PADILLA	2001	Mexico; Mexican workers	<i>Salud Publica Mex</i> 2001; 43: 113–121 (Spanish)
PISTELLI	2000	Italy	<i>Am J Respir Crit Care Med</i> 2000; 161: 899–905
VIJAYAN	2000	India; South Indian children	<i>Indian J Chest Dis Allied Sci</i> 2000; 42: 147–156
BALTOPOULOS	2000	Greece; Greek elderly	<i>Lung</i> 2000; 178: 201–212
IP	2000	Chinese children and adolescents in Hong Kong	<i>Am J Respir Crit Care Med</i> 2000; 162: 424–429
DEJSOMRITRUTAI	2000	Thailand	<i>J Med Assoc Thai</i> 2000; 83: 457–466
QUADRELLI	1999	Italy	<i>Respir Med</i> 1999; 93: 523–535
MORATO RODRIGUEZ	1999	Spain; children of Basque Autonomic Community	<i>An Esp Pediatr</i> 1999; 51: 17–21 (Spanish)
CRAPO	1999	Comparison of Mongolians/Caucasians	<i>Eur Respir J</i> 1999; 13: 606–609
HANKINSON	1999	USA population sample, aged 8–80 yrs (NHANES III)	<i>Am J Respir Crit Care Med</i> 1999; 159: 179–187
BAUR	1999	Germany; comparison of lung function reference values	<i>Int Arch Occup Environ Health</i> 1999; 72: 69–83
MCDONNELL	1998	USA; older adults	<i>Respir Med</i> 1998; 92: 914–921
MARTIN	1998	Canada; Quebec	<i>Rev Mal Respir</i> 1998; 15: 781–788 (French)
CASTELLSAGUE	1998	ECRHS; European populations	<i>Respir Med</i> 1998; 92: 401–407
ROCA	1998	ECRHS; validation	<i>Eur Respir J</i> 1998; 11: 1354–1362
PAN	1997	China; Taiwan	<i>Chin J Physiol</i> 1997; 40: 165–174
RAJKAPPOR	1997	India; school children	<i>Indian J Chest Dis Allied Sci</i> 1997; 39: 97–105
LUTTMANN	1997	Germany; 7–18-yr-old probands	<i>Pneumologie</i> 1997; 51: 47–54 (German)
CHIN	1997	Singapore; nonsmoking adults	<i>Respirology</i> 1997; 2: 143–149
OYARZUN	1996	Chile	<i>Rev Med Chil</i> 1996; 124: 1365–1367 (Spanish)
GUTIERREZ	1996	Chilean population >5 yrs old	<i>Rev Med Chil</i> 1996; 124: 1295–1306 (Spanish)
ENRIGHT	1996	USA; elderly Blacks	<i>Chest</i> 1996; 110: 1416–1424
DIEZ-HERRANZ	1996	Comparison reference values recommended by the pneumology Spanish and European societies	<i>Arch Bronconeumol</i> 1996; 32: 459–462 (Spanish)
LOUW	1996	South African males (normative values)	<i>S Afr Med J</i> 1996; 86: 814–819
PARMA	1996	Male Italians aged 7–18 yrs	<i>Eur J Epidemiol</i> 1996; 12: 263–277
GIRI	1996	Bhutan	<i>J Assoc Physicians India</i> 1996; 44: 320–322
BRANDLI	1996	Adult Swiss population	<i>Thorax</i> 1996; 51: 277–283
SHARP	1996	Japanese-American males aged 71–90 yrs	<i>Am J Respir Crit Care Med</i> 1996; 153: 805–811
QUINTERO	1996	Healthy Nicaraguan male workers	<i>Am J Ind Med</i> 1996; 29: 41–48
ENRIGHT	1995	USA; healthy Minnesota 65–85-yr-old males and females	<i>Chest</i> 1995; 108: 663–669
SIROTKOVIC	1995	Croatia; school children from Dalmatia	<i>Monaldi Arch Chest Dis</i> 1995; 50: 258–263

TABLE 1 (Continued)

Author	Year	Country/area/nature of study	Journal
GORE	1995	Healthy adult lifetime nonsmokers in Australia	<i>Eur Respir J</i> 1995; 8: 773–782
QUANJER	1995	White European children and adolescents	<i>Pediatr Pulmonol</i> 1995; 19: 135–142
DUFETEL	1995	Togo; Senegalese Black children and adolescents	<i>Rev Mal Respir</i> 1995; 12: 135–143 (French)
FULTON	1995	USA; MVV in African American adolescent females	<i>Pediatr Pulmonol</i> 1995; 20: 225–233

NHANES: National Health and Nutrition Examination Survey; ECRHS: European Community Respiratory Health Survey; MVV: maximum voluntary ventilation.

TABLE 2 Outcomes of a MEDLINE search under the keywords “reference equations” and “lung volumes”

Author	Year	Country/area/nature of study	Journal
TORRES	2003	Brazil; height and arm span in children	<i>Pediatr Pulmonol</i> 2003; 36: 202–208
VERMA	2003	India; dimensional statistics for estimation of lung volumes in children and adolescents	<i>Anthropol Anz</i> 2003; 61: 79–84
NEVE	2002	France; puberty and thoracic volume index	<i>Eur Respir J</i> 2002; 20: 1292–1298
ZHENG	2002	China; survey on clinical application	<i>Zhonghua Jie He He Hu Xi Za Zhi</i> 2002; 25: 69–73 (Chinese)
MANZKE	2001	Germany; children aged 6–16 yrs from “hospital normals”	<i>Eur J Pediatr</i> 2001; 160: 300–306
COTES	2001	UK workers; body mass index	<i>Thorax</i> 2001; 56: 839–844
IP	2000	Chinese children and adolescents in Hong Kong	<i>Am J Respir Crit Care Med</i> 2000; 162: 424–429
NEDER	1999	Brazil	<i>Braz J Med Biol Res</i> 1999; 32: 729–737
BAUR	1999	Germany; comparison of lung function reference values	<i>Int Arch Occup Environ Health</i> 1999; 72: 69–83
CORDERO	1999	Latin population of Spanish descent	<i>Respiration</i> 1999; 66: 242–250
ROCA	1998	Spain	<i>Respir Med</i> 1998; 92: 454–460
CORZO-ALVAREZ	1998	Nonsmoking healthy males in Maracaibo, Venezuela	<i>Invest Clin</i> 1998; 39: 3–17 (Spanish)
MAHAJAN	1997	Healthy females of Haryana	<i>Indian J Chest Dis Allied Sci</i> 1997; 39: 163–171
CHIN	1997	Singapore; nonsmoking adults	<i>Respirology</i> 1997; 2: 143–149
McCOY	1995	USA; normal infants	<i>Pediatr Pulmonol</i> 1995; 19: 282–290
ROSENTHAL	1993	UK; body plethysmographic gas volumes in prepubertal and pubertal school children in London	<i>Thorax</i> 1993; 48: 803–808

this difference may be smaller in elderly persons than in young adults [36]. Reference values for absolute lung volumes for adults of Asian ethnicity are generally considered to be lower than for Whites, but the magnitude of the differences is not well defined, and the difference may be less in Asians raised on “Western” diets during childhood [37]. According to the ATS 1991 document [5], no race correction is used for TLC or RV in Hispanic or Native American subjects in North America. For African American, Asian American and East Indian subjects, race corrections of 0.88 for TLC, FRC, and 0.93 for RV, are used. Race corrections should not be used for RV/TLC.

Table 2 reports studies on reference equations published from 1993 to August 2004, and equations derived from a MEDLINE search under the keywords “reference equations” and “lung volumes”. Its purpose is to recognise and encourage the continuing interest of worldwide researchers in deriving and using reference equations, although less numerous than for spirometry.

In practice, many USA and European laboratories use the reference equations for TLC, FRC and RV recommended by the 1995 ATS/ERS workshop [7] or by the ECCS [8, 20].

Diffusing capacity for carbon monoxide

Selecting reference values for DL_{CO} is more problematic than selecting reference values for spirometry because inter-laboratory differences are much larger for DL_{CO} [38, 39]. Some of these differences can be attributed to the method of calculating DL_{CO} and adjusting for haemoglobin concentration, carboxyhaemoglobin concentration and altitude. Laboratory directors should thoughtfully select reference values that match the numbers produced in their laboratories. Optimally, it would require individual laboratories to measure DL_{CO} in a sample of healthy subjects and compare the results with several reference equations. At the very least, laboratory directors should be alert to frequent interpretations that do not match the clinical situation. Such mismatches may signal inappropriate reference values or problems with the DL_{CO} measurement.

Predicted values of alveolar volume (V_A) inspired volume (V_I), DL_{CO} and transfer coefficient of the lung for carbon monoxide (K_{CO}) should be derived from the same source. As DL_{CO} and K_{CO} may be variably affected by factors previously described in this series of Task Force reports [4], a statement should be included describing which parameters might have been used to adjust the predicted values (e.g. V_A , haemoglobin and carboxyhaemoglobin concentrations, and altitude).

Table 3 shows studies on reference equations, published from 1995 to August 2004, and some derived from a MEDLINE search under the keywords "reference equations" and "diffusing capacity" or "diffusion". Its purpose is to recognise and encourage the continuing interest of worldwide researchers in deriving and using reference equations, although less numerous than for spirometry.

A single "summary" prediction equation was proposed by the ERS [38] and suggested by the ATS [39]. At present, however, a single equation set for DL_{CO} cannot be recommended because of the relatively high inter-laboratory variability. Commonly used equations appear to be those from the 1993 ERS document [38] and those of CRAPO and MORRIS [40]. In Europe, equations from COTES *et al.* [41], PAOLETTI *et al.* [42], and ROCA *et al.* [43] are also used.

Table 4 provides a summary of the reference values that are used for general issues, spirometry, lung volumes and diffusing capacity.

TYPES OF VENTILATORY DEFECTS

General issues

PFT interpretations should be clear, concise and informative. A mere statement of which values are normal or low is not helpful. Ideally, the principles of clinical decision making should be applied to the interpretation of the results of PFTs [44], where the post-test probability of disease is estimated

after taking into consideration the pre-test probability of disease, the quality of the test results, the downside of a false-positive and false-negative interpretation, and, finally, the test results themselves and how they compare with reference values. This is often not possible because many, if not most, tests are interpreted in the absence of any clinical information. To improve this situation, it may be useful, whenever possible, to ask the physicians who are responsible for ordering tests to state the clinical question to be answered and, before testing, ask patients why they were sent for testing. Similarly, recording respiratory symptoms, such as cough, phlegm, wheezing and dyspnoea, as well as smoking status, and recent bronchodilator use could be helpful in this regard.

The interpretation will be most meaningful if the interpreter can address relevant clinical diagnoses, the chest radiograph appearance, the most recent haemoglobin value, and any suspicion of neuromuscular disease or upper airway obstruction (UAO).

Obstructive abnormalities

An obstructive ventilatory defect is a disproportionate reduction of maximal airflow from the lung in relation to the maximal volume (*i.e.* VC) that can be displaced from the lung [45–47]. It implies airway narrowing during exhalation, defined by a reduced FEV_1/VC ratio below the 5th percentile of the predicted value. A typical example is shown in figure 1a.

The earliest change associated with airflow obstruction in small airways is thought to be a slowing in the terminal portion of the spirogram, even when the initial part of the spirogram is barely affected [45–47]. This slowing of expiratory flow is most obviously reflected in a concave shape on the flow–volume curve. Quantitatively, it is reflected in a proportionally greater reduction in the instantaneous flow measured after 75% of the FVC has been exhaled (FEF75%) or

TABLE 3 Outcome of a MEDLINE search under the keywords "reference equations" and "diffusing capacity" or "diffusion"

Author	Year	Country/area/nature of study	Journal
NEVE	2002	France; puberty and thoracic volume index	<i>Eur Respir J</i> 2002; 20: 1292–1298
ZHENG	2002	China; survey on clinical application	<i>Zhonghua Jie He He Hu Xi Za Zhi</i> 2002; 25: 69–73 (Chinese)
ZANEN	2001	The Netherlands; alveolar membrane diffusion capacity and pulmonary capillary blood volume	<i>Eur Respir J</i> 2001; 18: 764–769
COTES	2001	UK workers; body mass index	<i>Thorax</i> 2001; 56: 839–844
HUGHES	2001	UK; in defence of K_{CO} (T_L/V_A)	<i>Eur Respir J</i> 2001; 17: 168–174
JOHNSON	2000	USA; correction for V_A for both DL_{CO} and K_{CO}	<i>Respir Med</i> 2000; 94: 28–37
NEDER	1999	Brazil	<i>Braz J Med Biol Res</i> 1999; 32: 729–737
BAUR	1999	Germany; comparison of lung function reference values	<i>Int Arch Occup Environ Health</i> 1999; 72: 69–83
MARTIN	1998	Canada/Québec	<i>Rev Mal Respir</i> 1998; 15: 781–788 (French)
MAHAJAN	1997	India; healthy females of Haryana	<i>Indian J Chest Dis Allied Sci</i> 1997; 39: 163–171
CHIN	1997	Singapore; nonsmoking adults	<i>Respirology</i> 1997; 2: 143–149
GUENARD	1996	France; elderly subjects	<i>Eur Respir J</i> 1996; 9: 2573–2577
COLLARD	1996	Belgium; obstructive sleep apnoea and obesity	<i>Chest</i> 1996; 110: 1189–1193
CHINN	1996	UK workers; standardised for alveolar volume	<i>Eur Respir J</i> 1996; 9: 1269–1277
STAM	1996	The Netherlands; at reduced alveolar volumes in children	<i>Pediatr Pulmonol</i> 1996; 21: 84–89

K_{CO} : transfer coefficient of the lung for carbon monoxide; T_L : transfer factor of the lung; V_A : alveolar volume; DL_{CO} : carbon monoxide diffusing capacity.

TABLE 4 Summary of the usage of reference values

Item	Reference values
General	<p>Predicted values should be obtained from studies of "normal" or "healthy" subjects with the same anthropometric (e.g. sex, age and height) and ethnic characteristics of the patient being tested</p> <p>Height and weight should be measured for each patient at the time of testing</p> <p>If possible, all parameters should be taken from the same reference source</p> <p>When comparing selected reference equations with measurements performed on a sample of healthy subjects in a laboratory, it is suggested to choose the reference equation that provides the sum of residuals (observed – predicted computed for each adult subject, or log (observed) – log (predicted) for each subject in the paediatric age range) closest to zero</p> <p>When using a set of reference equations, extrapolation beyond the size and age of the investigated subjects should be avoided</p> <p>For each lung function index, values below the 5th percentile of the frequency distribution of values measured in the reference population are considered as below the expected "normal range"</p>
Spirometry	<p>In the USA, ethnically appropriate NHANES III reference equations published in 1999 for those aged 8–80 yrs, and the equations of WANG <i>et al.</i> [29] for children aged <8 yrs are recommended</p> <p>In Europe, the ECCS combined reference equations published in 1993 [8] are often used for 18–70-yr-old people, and those from QUANJER <i>et al.</i> [30] for paediatric ages</p> <p>Currently, a specific set of equations is not recommendable for use in Europe. A new Europe-wide study to derive updated reference equations for lung function is needed</p> <p>Table 1 includes reference equations published from 1995 to August 2004</p>
Lung volumes	<p>No specific set of equations is generally recommendable</p> <p>In practice, many USA and European laboratories use the reference equations for TLC, FRC and RV recommended by the 1995 ATS/ERS workshop [7] or by the ECCS in 1993 [8]</p> <p>Table 2 reports studies on reference equations published from 1993 to August 2004</p>
Diffusing capacity	<p>No specific set of equations is generally recommendable</p> <p>Commonly used equations appear to be those by the ECCS in 1993 [38] and those of CRAPO and MORRIS [40]. In Europe, equations from COTES <i>et al.</i> [41], PAOLETTI <i>et al.</i> [42] and ROCA <i>et al.</i> [43] are also used</p> <p>Table 3 shows studies on reference equations published from 1995 to August 2004</p>

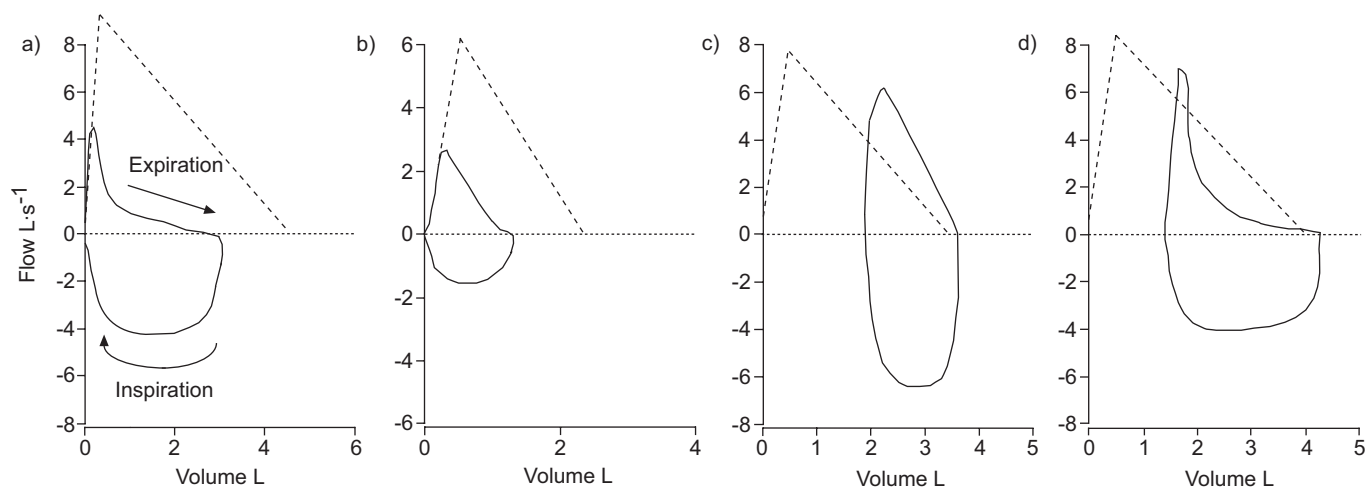


FIGURE 1. a, b) Examples of obstructive pulmonary defects with a low (a; forced expiratory volume in one second (FEV₁) 38%; FEV₁/vital capacity (VC) 46%; peak expiratory flow (PEF) 48%; total lung capacity (TLC) 101%) or normal (b; FEV₁ 57%; FEV₁/VC 73%; PEF 43%; TLC 96%) ratio of FEV₁/VC. In both cases, TLC is normal, and flows are less than expected over the entire volume range. c) Example of a typical restrictive defect (FEV₁ 66%; FEV₁/VC 80%; PEF 79%; TLC 82%). The TLC is low, and flow is higher than expected at a given lung volume. d) Example of a typical mixed defect characterised by a low TLC and a low FEV₁/VC ratio (FEV₁ 64%; FEV₁/VC 64%; PEF 82%; TLC 72%). - - -: predicted flow–volume curves; —: observed inspiratory and expiratory flow–volume curves (as indicated in a).

in mean expiratory flow between 25% and 75% of FVC than in FEV₁. However, abnormalities in these mid-range flow measurements during a forced exhalation are not specific for small airway disease in individual patients [48].

As airway disease becomes more advanced and/or more central airways become involved, timed segments of the spirogram such as the FEV₁ will, in general, be reduced out of proportion to the reduction in VC.

Special attention must be paid when FEV₁ and FVC are concomitantly decreased and the FEV₁/FVC ratio is normal or almost normal. This pattern most frequently reflects failure of the patient to inhale or exhale completely. It may also occur when the flow is so slow that the subject cannot exhale long enough to empty the lungs to RV. In this circumstance, the flow–volume curve should appear concave toward the end of the manoeuvre. TLC will be normal and FEF₇₅ will be low. Measurement of slow VC (inspiratory or expiratory) may then give a more correct estimate of the FEV₁/VC ratio. Another possible cause of this pattern is patchy collapse of small airways early on during exhalation [8, 49–52]. Under these conditions, TLC may be normal, but RV is ordinarily increased. A typical example is shown in figure 1b. When this pattern is observed in a patient performing a maximal, sustained effort, it may be useful to repeat spirometry after treatment with an inhaled bronchodilator. Significant improvement in the FEV₁, FVC or both would suggest the presence of reversible airflow obstruction.

Apart from this unusual circumstance, measurement of lung volumes is not mandatory to identify an obstructive defect. It may, however, help to disclose underlying disease and its functional consequences. For example, an increase in TLC, RV or the RV/TLC ratio above the upper limits of natural variability may suggest the presence of emphysema, bronchial asthma or other obstructive diseases [47], as well as the degree of lung hyperinflation.

Airflow resistance is rarely used to identify airflow obstruction in clinical practice. It is more sensitive for detecting narrowing of extrathoracic or large central intrathoracic airways than of more peripheral intrathoracic airways [47]. It may be useful in patients who are unable to perform a maximal forced expiratory manoeuvre.

Restrictive abnormalities

A restrictive ventilatory defect is characterised by a reduction in TLC below the 5th percentile of the predicted value, and a normal FEV₁/VC. A typical example is shown in figure 1c. The presence of a restrictive ventilatory defect may be suspected when VC is reduced, the FEV₁/VC is increased (>85–90%) and the flow–volume curve shows a convex pattern. Once again, the pattern of a reduced VC and a normal or even slightly increased FEV₁/VC is often caused by submaximal inspiratory or expiratory efforts and/or patchy peripheral airflow obstruction, and a reduced VC by itself does not prove a restrictive ventilatory defect. It is associated with a low TLC no more than half the time [53, 54].

Pneumothorax and noncommunicating bullae are special cases characterised by a normal FEV₁/VC and TLC measured in a body plethysmograph, but low FEV₁ and VC values. In these conditions, TLC assessed by gas dilution techniques will be low.

A low TLC from a single-breath test (such as VA from the DL_{CO} test) should not be interpreted as demonstrating restriction, since such measurements systematically underestimate TLC [55]. The degree of underestimation increases as airflow obstruction worsens. In the presence of severe airflow obstruction, TLC can be underestimated by as much as 3 L, greatly increasing the risk of misclassification of the type of

PFT abnormality [55, 56]. A method of adjusting the single-breath VA for the effect of airway obstruction has been published, but needs further validation [57].

Mixed abnormalities

A mixed ventilatory defect is characterised by the coexistence of obstruction and restriction, and is defined physiologically when both FEV₁/VC and TLC are below the 5th percentiles of their relevant predicted values. Since VC may be equally reduced in both obstruction and restriction, the presence of a restrictive component in an obstructed patient cannot be inferred from simple measurements of FEV₁ and VC. A typical example is presented in figure 1d. If FEV₁/VC is low and the largest measured VC (pre- or post-bronchodilator VC or V_I in the DL_{CO} test) is below its lower limits of normal (LLN), and measurement of TLC by body plethysmography was not carried out, one can state that the VC was also reduced, probably due to hyperinflation, but that a superimposed restriction of lung volumes cannot be ruled out [58]. Conversely, when FEV₁/VC is low and VC is normal, a superimposed restriction of lung volumes can be ruled out [53, 54].

Table 5 shows a summary of the types of ventilatory defects and their diagnoses.

COMMENTS ON INTERPRETATION AND PATTERNS OF DYSFUNCTION

The definition of an obstructive pulmonary defect given in the present document is consistent with the 1991 ATS statement on interpretation [5], but contrasts with the definitions suggested by both Global Initiative for Chronic Obstructive Lung Disease (GOLD) [59] and ATS/ERS guidelines on COPD [60], in that FEV₁ is referred to VC rather than just FVC and the cut-off value of this ratio is set at the 5th percentile of the normal distribution rather than at a fixed value of 0.7. This committee feels that the advantage of using VC in place of FVC is that the ratio of FEV₁ to VC is capable of accurately identifying more obstructive patterns than its ratio to FVC, because FVC is more dependent on flow and volume histories [61]. In contrast with a fixed value of 0.7, the use of the 5th percentile does not lead to an overestimation of the ventilatory defect in older people with no history of exposure to noxious particles or gases [62].

The assumption that a decrease in major spirometric parameters, such as FEV₁, VC, FEV₁/VC and TLC, below their relevant 5th percentiles is consistent with a pulmonary defect is a useful simple approach in clinical practice. Problems arise, however, when some or all of these variables lie near their upper limits of normal or LLN. In these cases, a literal interpretation of the functional pattern is too simplistic and could fail to properly describe the functional status.

The current authors suggest that additional studies should be done in these circumstances if they are indicated by the clinical problem being addressed. Such tests could include bronchodilator response, DL_{CO}, gas-exchange evaluation, measurement of respiratory muscle strength or exercise testing.

Caution is also recommended when TLC is at the LLN range and coexists with a disease expected to lead to lung restriction. A typical example is lung resection. The expected restrictive defect would be difficult to prove on the simple basis of TLC as

TABLE 5 Types of ventilatory defects and their diagnoses

Abnormality	Diagnosis
Obstruction	<p>FEV₁/VC <5th percentile of predicted</p> <p>A decrease in flow at low lung volume is not specific for small airways disease in individual patients</p> <p>A concomitant decrease in FEV₁ and VC is most commonly caused by poor effort, but may rarely reflect airflow obstruction.</p> <p>Confirmation of airway obstruction requires measurement of lung volumes</p> <p>Measurement of absolute lung volumes may assist in the diagnosis of emphysema, bronchial asthma and chronic bronchitis. It may also be useful in assessing lung hyperinflation</p> <p>Measurements of airflow resistance may be helpful in patients who are unable to perform spirometric manoeuvres</p>
Restriction	<p>TLC <5th percentile of predicted</p> <p>A reduced VC does not prove a restrictive pulmonary defect. It may be suggestive of lung restriction when FEV₁/VC is normal or increased</p> <p>A low TLC from a single-breath test should not be used as evidence of restriction</p>
Mixed defect	FEV ₁ /VC and TLC <5th percentile of predicted

FEV₁: forced expiratory volume in one second; VC: vital capacity; TLC: total lung capacity.

per cent of predicted if the latter remains above the 5th percentile of predicted as a result of subsequent lung growth or of a large TLC before surgery. Similar care must be taken in cases where diseases with opposing effects on TLC coexist, such as interstitial lung disease (ILD) and emphysema.

While patterns of physiological abnormalities can be recognised, they are seldom pathognomonic for a specific disease entity. The types of clinical illness most likely to produce an observed set of physiological disturbances can be pointed out. Regardless of the extent of testing, it is important to be conservative in suggesting a specific diagnosis for an underlying disease process based only on pulmonary function abnormalities.

The VC, FEV₁, FEV₁/VC ratio and TLC are the basic parameters used to properly interpret lung function (fig. 2). Although FVC is often used in place of VC, it is preferable to use the largest available VC, whether obtained on inspiration (IVC), slow expiration (SVC) or forced expiration (*i.e.* FVC). The FVC is usually reduced more than IVC or SVC in airflow obstruction [61]. The FEV₆ (FVC₆) may be substituted for VC if the appropriate LLN for the FEV₁/FEV₆ is used (from the NHANES III equations) [12, 63]. Limiting primary interpretation of spirometry to VC, FEV₁ and FEV₁/VC avoids the problem of simultaneously examining a multitude of measurements to see if any abnormalities are present, a procedure leading to an inordinate number of “abnormal” tests, even among the healthiest groups in a population [64, 65]. When the rate of abnormality for any single test is only 5%, the frequency of at least one abnormal test was shown to be 10% in 251 healthy subjects when the FEV₁, FVC and FEV₁/FVC ratio were examined and increased to 24%, and a battery of 14 different spirometric measurements were analysed [23]. It should be noted, however, that additional parameters, such as the peak expiratory flow (PEF) and maximum inspiratory flows, may assist in diagnosis of the extrathoracic airways obstruction.

The most important parameter for identifying an obstructive impairment in patients is the FEV₁/VC ratio. In patients with

respiratory diseases, a low FEV₁/VC, even when FEV₁ is within the normal range, predicts morbidity and mortality [66]. For healthy subjects, the meaning of a low FEV₁/FVC ratio accompanied by an FEV₁ within the normal range is unclear. This pattern is probably due to “dysanaptic” or unequal

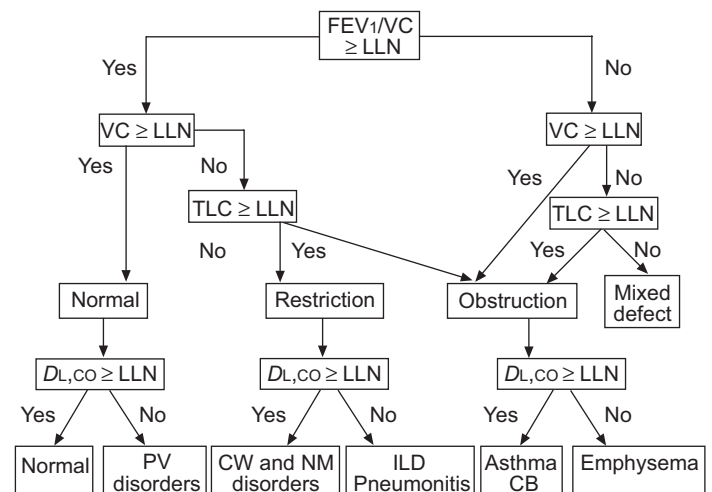


FIGURE 2. A simplified algorithm that may be used to assess lung function in clinical practice. It presents classic patterns for various pulmonary disorders. As in any such diagram, patients may or may not present with the classic patterns, depending on their illnesses, severity and lung function prior to the disease onset (e.g. did they start with a vital capacity (VC) close to the upper or lower limits of normal (LLN)). The decisions about how far to follow this diagram are clinical, and will vary depending on the questions being asked and the clinical information available at the time of testing. The forced expiratory volume in one second (FEV₁)/VC ratio and VC should be considered first. Total lung capacity (TLC) is necessary to confirm or exclude the presence of a restrictive defect when VC is below the LLN. The algorithm also includes diffusing capacity for carbon monoxide (DL_{CO}) measurement with the predicted value adjusted for haemoglobin. In the mixed defect group, the DL_{CO} patterns are the same as those for restriction and obstruction. This flow chart is not suitable for assessing the severity of UAO. PV: pulmonary vascular; CW: chest wall; NM: neuromuscular; ILD: interstitial lung diseases; CB: chronic bronchitis.

growth of the airways and lung parenchyma [67] (referred to in a previous ATS document as a possible physiological variant when FEV₁ was $\geq 100\%$ pred [5]). Whether this pattern represents airflow obstruction will depend on the prior probability of obstructive disease and possibly on the results of additional tests, such as bronchodilator response, DL_{CO}, gas-exchange evaluation, and measurement of muscle strength or exercise testing. Expiratory flow measurements other than the FEV₁ and FEV₁/VC should be considered only after determining the presence and clinical severity of obstructive impairment using the basic values mentioned previously. When the FEV₁ and FEV₁/VC are within the expected range, the clinical significance of abnormalities in flow occurring late in the maximal expiratory flow–volume curve is limited. In the presence of a borderline value of FEV₁/VC, however, these tests may suggest the presence of airway obstruction. The same is true for average flows, such as mid-expiratory flow (MEF_{25–75%}), especially in children with cystic fibrosis [68, 69]. Even with this limited use, the wide variability of these tests in healthy subjects must be taken into account in their interpretation.

The maximal voluntary ventilation (MVV) is not generally included in the set of lung function parameters necessary for diagnosis or follow-up of the pulmonary abnormalities because of its good correlation with FEV₁[70]. However, it may be of some help in clinical practice. For example, a disproportionate decrease in MVV relative to FEV₁ has been reported in neuromuscular disorders [71, 72] and UAO [73]. In addition, it is also used in estimating breathing reserve during maximal exercise [74], although its application may be of limited value in mild-to-moderate COPD [75, 76]. For these purposes, the current authors suggest that MVV should be measured rather than estimated by multiplying FEV₁ by a constant value, as is often done in practice.

SEVERITY CLASSIFICATION

A method of categorising the severity of lung function impairment based on the FEV₁ % pred is given in table 6. It is similar to several previous documents, including GOLD [59], ATS 1986 [77], ATS 1991 [5], and the American Medical Association (AMA) [78]. The number of categories and the exact cut-off points are arbitrary.

Severity scores are most appropriately derived from studies that relate pulmonary function test values to independent indexes of performance, such as ability to work and function in

daily life, morbidity and prognosis [79–82]. In general, the ability to work and function in daily life is related to pulmonary function, and pulmonary function is used to rate impairment in several published systems [77–79, 83]. Pulmonary function level is also associated with morbidity, and those with lower function having more respiratory complaints [82].

Lung function level is also associated with prognosis, including a fatal outcome from heart as well as lung disease [84, 85], even in patients who have never smoked [86]. In the Framingham study, VC was a major independent predictor of cardiovascular morbidity and mortality [84, 85]. In several occupational cohorts, FEV₁ and FEV₁/FVC were independent predictors of all-cause or respiratory disease mortality [87–89]. In addition, a meta-analysis of mortality in six surveys in various UK working populations showed that the risk of dying from COPD was related to the FEV₁ level. In comparison to those whose FEV₁ at an initial examination was within 1 SD of average, those whose FEV₁ was >2 SD below average were 12-times more likely to die of COPD, over 10 times more likely to die of non-neoplastic respiratory disease, and more than twice as likely to die of vascular disease over a 20-yr follow-up period [90]. Although there is good evidence that FEV₁ correlates with the severity of symptoms and prognosis in many circumstances [79, 82, 90], the correlations do not allow one to accurately predict symptoms or prognosis for individual patients.

Also, the DL_{CO} was an important predictor of mortality either in the general population [91] or in patients after pulmonary resection [92].

Though the FEV₁ % pred is generally used to grade severity in patients with obstructive, restrictive and mixed pulmonary defects, it has little applicability to patients with UAO, such as tracheal stenosis, where obstruction could be life-threatening and yet be classified as mildly reduced by this scheme. In addition, there is little data documenting the performance of other functional indexes, such as FRC in airflow obstruction or TLC in lung restriction as indices to categorise severity of impairment.

VC is reduced in relation to the extent of loss of functioning lung parenchyma in many nonobstructive lung disorders. It is also of some use in assessing respiratory muscle involvement in certain neuromuscular diseases. Once again, VC may be only slightly impaired in diffuse interstitial diseases of sufficient severity to lead to marked loss of diffusing capacity and severe blood gas abnormalities [63]. The onset of a severe respiratory problem in patients with a rapidly progressive neuromuscular disease may be associated with only a small decrement in VC [47, 93].

FEV₁ and FVC may sometimes fail to properly identify the severity of ventilatory defects, especially at the very severe stage for multiple reasons. Among them are the volume history effects of the deep breath preceding the forced expiratory manoeuvre on the bronchial tone and, thus, calibre [94–98], and the inability of these parameters to detect whether tidal breathing is flow limited or not [99–102]. The FEV₁/VC ratio should not be used to determine the severity of an obstructive disorder, until new research data are available. Both the FEV₁

TABLE 6 Severity of any spirometric abnormality based on the forced expiratory volume in one second (FEV₁)

Degree of severity	FEV ₁ % pred
Mild	$>70\%$
Moderate	60–69
Moderately severe	50–59
Severe	35–49
Very severe	<35

% pred: % predicted.

and VC may decline with the progression of disease, and an FEV₁/VC of 0.5/1.0 indicates more impairment than one of 2.0/4.0, although the ratio of both is 50%. While the FEV₁/VC ratio should not routinely be used to determine the severity of an obstructive disorder, it may be of value when persons having genetically large lungs develop obstructive disease. In these cases, the FEV₁/VC ratio may be very low (60%), when the FEV₁ alone is within the mild category of obstruction (*i.e.* >70% pred).

Recent studies have stressed the importance of additional measurements in assessing the severity of the disease. For example, when airflow obstruction becomes severe, FRC, RV, TLC and RV/TLC tend to increase as a result of decreased lung elastic recoil and/or dynamic mechanisms [47, 103, 104]. The degree of hyperinflation parallels the severity of airway obstruction [58]. On one hand, lung hyperinflation is of benefit because it modulates airflow obstruction, but, on the other hand, it causes dyspnoea because of the increased elastic load on inspiratory muscles [47]. In a recent investigation, resting lung hyperinflation, measured as inspiratory capacity (IC)/TLC, was an independent predictor of respiratory and all-cause mortality in COPD patients [105]. In addition, in either severe obstructive or restrictive diseases, tidal expiratory flow often impinges on maximum flow [98, 99, 102]. This condition, denoted as expiratory flow limitation during tidal breathing (EFL), is relatively easy to measure in practice by comparing tidal and forced expiratory flow–volume loops. Its clinical importance is that it contributes to increased dyspnoea [100], puts the inspiratory muscles at a mechanical disadvantage [43] and causes cardiovascular side-effects [106]. Although there is currently not sufficient evidence to recommend the routine use of measurements of hyperinflation or EFL to score the severity of lung function impairment, they may be helpful in patients with disproportionate differences between spirometric impairment and dyspnoea.

Finally, the reported increase in RV in obstruction is deemed to be a marker of airway closure [47, 103]. Although its clinical relevance remains uncertain, especially with regard to assessment of severity, RV may be useful in special conditions, including predicting the likelihood of lung function improvement after lung volume-reduction surgery [104].

Table 7 shows the summary of the considerations for severity classification.

TABLE 7 Summary of the considerations for severity classification

The severity of pulmonary function abnormalities is based on FEV₁ % pred. This does not apply to upper airway obstruction. In addition, it might not be suitable for comparing different pulmonary diseases or conditions. FEV₁ may sometimes fail to properly identify the severity of a defect, especially at the very severe stages of the diseases. FEV₁ % pred correlates poorly with symptoms and may not, by itself, accurately predict clinical severity or prognosis for individual patients. Lung hyperinflation and the presence of expiratory flow limitation during tidal breathing may be useful in categorising the severity of lung function impairment.

FEV₁: forced expiratory volume in one second; % pred: % predicted.

BRONCHODILATOR RESPONSE

Bronchial responsiveness to bronchodilator medications is an integrated physiological response involving airway epithelium, nerves, mediators and bronchial smooth muscle. Since the within-individual difference in response to a bronchodilator is variable, the assumption that a single test of bronchodilator response is adequate to assess both the underlying airway responsiveness and the potential for therapeutic benefits of bronchodilator therapy is overly simplistic [107]. Therefore, the current authors feel that the response to a bronchodilator agent can be tested either after a single dose of a bronchodilator agent in the PFT laboratory or after a clinical trial conducted over 2–8 weeks.

The correlation between bronchoconstriction and bronchodilator response is imperfect, and it is not possible to infer with certainty the presence of one from the other.

There is no consensus about the drug, dose or mode of administering a bronchodilator in the laboratory. However, when a metered dose inhaler is used, the following procedures are suggested in order to minimise differences within and between laboratories. Short-acting β_2 -agonists, such as salbutamol, are recommended. Four separate doses of 100 μ g should be used when given by metered dose inhaler using a spacer. Tests should be repeated after a 15-min delay. If a bronchodilator test is performed to assess the potential therapeutic benefits of a specific drug, it should be administered in the same dose and by the same route as used in clinical practice, and the delay between administration and repeat spirometric measurements should reflect the reported time of onset for that drug.

The first step in interpreting any bronchodilator test is to determine if any change greater than random variation has occurred. The per cent change in FVC and FEV₁ after bronchodilator administration in general population studies [108–110] and patient populations [101, 111–113] are summarised in table 5. Studies show a tendency for the calculated bronchodilator response to increase with decreasing baseline VC or FEV₁, regardless of whether the response was considered as an absolute change or as a percent of the initial value. Bronchodilator responses in patient-based studies are therefore, somewhat higher than those in general population studies.

There is no clear consensus about what constitutes reversibility in subjects with airflow obstruction [111, 114]. In part, this is because there is no consensus on how a bronchodilator response should be expressed, the variables to be used, and, finally, the kind, dose and inhalation mode of bronchodilator agent. The three most common methods of expressing bronchodilator response are per cent of the initial spirometric value, per cent of the predicted value, and absolute change.

Expressing the change in FEV₁ and/or FVC as a per cent of predicted values has been reported to have advantages over per cent change from baseline [115]. When using per cent change from baseline as the criterion, most authorities require a 12–15% increase in FEV₁ and/or FVC as necessary to define a meaningful response. Increments of <8% (or <150 mL) are likely to be within measurement variability [107, 115]. The current authors recommend using the per cent change from

TABLE 8 Selected studies of bronchodilator response

Population	Agent/mode of delivery	FVC	FEV ₁	MEF _{25–75%} or MEF _{50%}	Comments
Selected population studies					
1,063 subjects 8–75 yrs of age; general population [108]	IP 2 puffs <i>via</i> MDI	10.7% (0.40 L)	7.7% (0.31 L)	20%	95th percentile for per cent change from baseline
2,609 subjects; random sample of 3 areas in Alberta, Canada [109]	TB 500 µg <i>via</i> spacer		Males 9% (0.34 L); females 9% (0.22 L)		95th percentile for per cent change from baseline in asymptomatic never-smokers with FEV ₁ >80% pred
75 selected normal subjects [110]	Two puffs <i>via</i> MDI	5.1% (0.23 L)	10.1% (0.36 L)	48.3%	Upper 95% CL (two-tailed) for per cent change from baseline
Selected patient studies					
40 patients referred to PFT laboratory [112]	Placebo	14.9% (0.34 L)	12.3% (0.18 L)	45.1%	Upper 95% CI change after placebo
985 COPD patients in the IPPB trial [111]	IP 250 µg <i>via</i> air nebuliser		15%		Per cent change from baseline
150 patients with airway obstruction [113]	SB 200 µg or TB 500 µg <i>via</i> MDI	15% (0.33 L)	10% (0.16 L)		95% CI for absolute change
78 patients with COPD/asthma [101]	SB 200 µg <i>via</i> MDI	14% (0.51 L)	15% (0.25 L)		95% CL per cent change of baseline

FVC: forced vital capacity; FEV₁: forced expiratory volume in one second; MEF_{25–75%}: mean flow between 25% and 75% of FVC; MEF_{50%}: flow at 50% of FVC; IP: isoproterenol; MDI: metered dose inhaler; TB: terbutaline; CL: confidence limits; SB: salbutamol; CI: confidence interval. Other variables as in table 6.

baseline and absolute changes in FEV₁ and/or FVC in an individual subject to identify a positive bronchodilator response. Values >12% and 200 mL compared with baseline during a single testing session suggest a “significant” bronchodilatation. If the change in FEV₁ is not significant, a decrease in lung hyperinflation may indicate a significant response. The lack of a response to bronchodilator testing in a laboratory test does not preclude a clinical response to bronchodilator therapy.

The MEF_{25–75%} is a highly variable spirometric test, in part because it depends on FVC, which increases with expiratory time in obstructed subjects. If FVC changes, post-bronchodilator MEF_{25–75%} is not comparable with that measured before the bronchodilator. Volume adjustment of MEF_{25–75%} has been proposed to solve this problem [116, 117]. At least two studies have assessed the utility of MEF_{25–75%}. The results were disappointing; only 8% of asthmatics [117] and 7% of patients with COPD were identified as outside the expected range by MEF_{25–75%} criteria alone. Tests such as the FEV₁/VC ratio and instantaneous flows measured at some fraction of the VC may also be misleading in assessing bronchodilator response if expiratory time changes are not considered and if flows are not measured at the same volume below TLC.

If the change is above the threshold of natural variability, then the next step is to determine if this change is clinically important. This aspect of the interpretation is harder to define and depends on the reasons for undertaking the test. For instance, even if asthmatics tend to show a larger increase in flow and volume after inhaling a dilator agent than COPD patients, the response to a bronchodilator has never been

shown to be capable of clearly separating the two classes of patients [101, 109, 111, 114]. In addition, it must be also acknowledged that responses well below the significant thresholds may be associated with symptom improvement and patient’s performance [118]. The possible reasons are discussed as follows.

Quite often, responses to bronchodilator therapy are unpredictably underestimated by FEV₁ and/or FVC in comparison to airway resistance or flow measured during forced expiratory manoeuvres initiated from a volume below TLC (partial expiratory flow–volume manoeuvres) in both healthy subjects and patients with chronic airflow obstruction [8, 101, 102, 119–122]. These findings are probably due to the fact that deep inhalations tend to reduce airway calibre, especially after a bronchodilator [101, 120]. In patients with airflow obstruction, the increase in expiratory flow after bronchodilation is often associated with a decrease in FRC or an increase in IC of similar extent at rest and during exercise [101, 123]. The improvement of the lung function parameters in the tidal breathing range and not following a deep breath may explain the decrease in shortness of breath after inhaling a bronchodilator, despite no or minimal changes in FEV₁ and/or FVC. Short-term intra-individual variabilities for partial flows and IC have been reported [101]. Therefore, the lack of increase of FEV₁ and/or FVC after a bronchodilator is not a good reason for precluding a 2–8-week clinical trial with bronchoactive medication.

An isolated increase in FVC (>12% of control and >200 mL) not due to increased expiratory time after salbutamol is a sign of bronchodilation [124]. This may, in part, be related to the

TABLE 9 Summary of the procedures relating to bronchodilator response

Procedures suggested to minimise differences within and between laboratories
Assess lung function at baseline
Administer salbutamol in four separate doses of 100 µg through a spacer
Re-assess lung function after 15 min. If you want to assess the potential benefits of a different bronchodilator, use the same dose and the same route as used in clinical practice. The wait time may be increased for some bronchodilators
An increase in FEV ₁ and/or FVC ≥12% of control and ≥200 mL constitutes a positive bronchodilator response
In the absence of a significant increase in FEV ₁ and/or FVC, an improvement in lung function parameters within the tidal breathing range, such as increased partial flows and decrease of lung hyperinflation, may explain a decrease in dyspnoea
The lack of a bronchodilator response in the laboratory does not preclude a clinical response to bronchodilator therapy

FEV₁: forced expiratory volume in one second; FVC: forced vital capacity.

fact that deep inhalations tend to reduce airway calibre and/or airway wall stiffness, especially after a bronchodilator [101, 120].

Table 9 shows a summary of the suggested procedures for laboratories relating to bronchodilator response.

UPPER AIRWAY OBSTRUCTION

Central airway obstruction and UAO may occur in the extrathoracic (pharynx, larynx, and extrathoracic portion of the trachea) and intrathoracic airways (intrathoracic trachea and main bronchi). This condition does not usually lead to a decrease in FEV₁ and/or VC, but PEF can be severely affected. Therefore, an increased ratio of FEV₁ divided by PEF (mL·L⁻¹·min⁻¹) can alert the clinician to the need for an inspiratory and expiratory flow–volume loop [125]. A value >8 suggests UAO may be present [126]. Poor initial effort can also affect this ratio.

At least three maximal and repeatable forced inspiratory and forced expiratory flow–volume curves are necessary to

evaluate for UAO. It is critical that the patient's inspiratory and expiratory efforts are near maximal and the technician should confirm this in the quality notes. When patient effort is good, the pattern of a repeatable plateau of forced inspiratory flow, with or without a forced expiratory plateau, suggests a variable, extrathoracic, UAO (fig. 3). Conversely, the pattern of a repeatable plateau of forced expiratory flow, along with the lack of a forced inspiratory plateau suggests a variable, intrathoracic, UAO. The pattern of a repeatable plateau at a similar flow in both forced inspiratory and expiratory flows suggests a fixed UAO (fig. 3).

In general, maximum inspiratory flow is largely decreased with an extrathoracic airway obstruction, because the pressure surrounding the airways (which is almost equal to atmospheric) cannot oppose the negative intraluminal pressure generated with the inspiratory effort. In contrast, it is little affected by an intrathoracic airway obstruction, for the pressure surrounding the intrathoracic airways (which is close to pleural pressure) strongly opposes the negative intraluminal pressure on inspiration, thus limiting the effects of the obstruction on flow. With unilateral main bronchus obstruction, a rare event, maximum inspiratory flow tends to be higher at the beginning than towards the end of the forced inspiration because of a delay in gas filling (fig. 4).

Maximum expiratory flow at high lung volume (especially peak flow) is generally decreased in both intrathoracic and extrathoracic lesions [126–129]. In contrast, maximum flows may be normal in the presence of a variable lesion, such as vocal cord paralysis. Flow oscillations (saw-tooth pattern) may be occasionally observed on the either inspiratory or expiratory phase, and probably represent a mechanical instability of the airway wall.

The effects of anatomical or functional lesions on maximum flows depend on the site of the obstruction, kind of lesion (variable or fixed) and the extent of anatomical obstruction [61, 127, 130]. Typical cases of extra- and intrathoracic UAOs are reported in figures 3 and 4. The absence of classic spirometric patterns for central airway obstruction does not accurately predict the absence of central airway pathology. As a result, clinicians need to maintain a high degree of suspicion for this

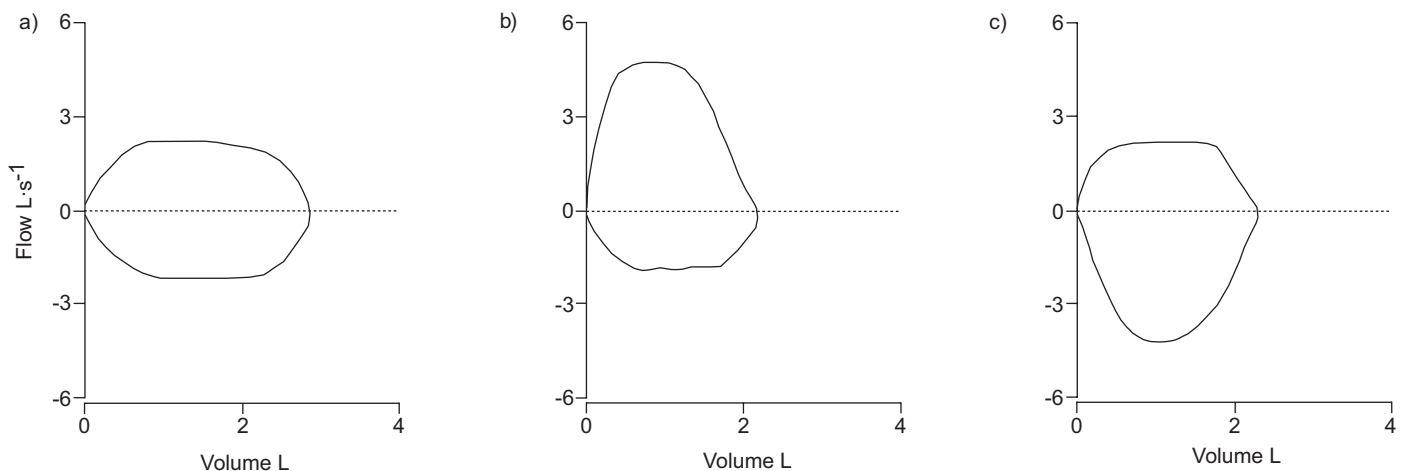


FIGURE 3. Idealised examples of a) fixed, b) variable extrathoracic, and c) variable intrathoracic upper airway obstruction.

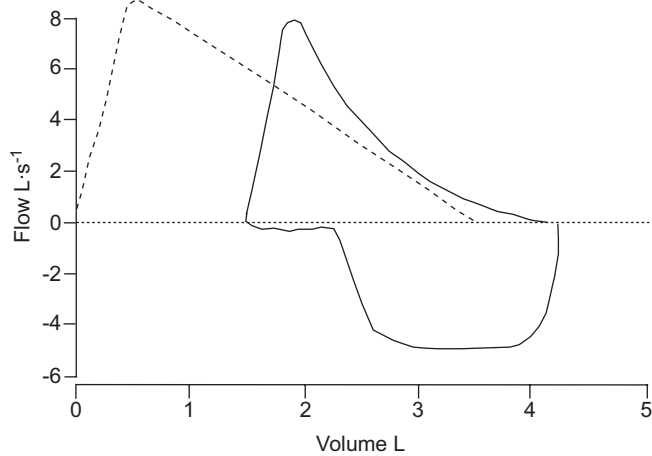


FIGURE 4. Example of unilateral main bronchus obstruction due to a valve-like mechanism occluding the main left stem during inspiration as a result of a surgical scar. There is a delay in gas filling towards the end of the forced inspiration as evidence of the variable unilateral main bronchus obstruction (forced expiratory volume in one second (FEV₁): 76%; FEV₁/vital capacity: 70%; peak expiratory flow: 93%; total lung capacity: 80%). ----: predicted flow–volume loop; —: recorded maximum inspiratory and expiratory flow–volume loops.

problem, and refer suspected cases for visual inspection of the airways. The current Task Force authors feel that, although maximum inspiratory and expiratory flow–volume loops are of great help to alert clinicians to the possibility of UAO, endoscopic and radiological techniques are the next step to confirm the dysfunction.

The parameters presented in table 10 may help to distinguish intrathoracic from extrathoracic airway obstructions.

Table 11 gives a summary of the relevant issues concerning upper airway obstruction.

INTERPRETATION OF CHANGE IN LUNG FUNCTION

Evaluation of an individual’s change in lung function following an intervention or over time is often more clinically valuable than a single comparison with external reference (predicted) values. It is not easy to determine whether a measured change reflects a true change in pulmonary status or is only a result of test variability. All lung function

TABLE 10	Lung function parameters capable of differentiating extrathoracic from intrathoracic obstruction		
	Extrathoracic obstruction		Intrathoracic obstruction
	Fixed	Variable	
PEF	Decreased	Normal or decreased	Decreased
MIF ₅₀	Decreased	Decreased	Normal or decreased
MIF ₅₀ /MEF ₅₀	~1	<1	>1

PEF: peak expiratory flow; MIF₅₀: maximum inspiratory flow at 50% of forced vital capacity (FVC); MEF₅₀: maximum expiratory flow at 50% of FVC.

TABLE 11	Summary of the issues concerning upper airway obstruction
	Special attention should be paid by the technicians to obtain maximal and repeatable PEFs and forced inspiratory manoeuvres if there is a clinical or spirometric reason to suspect upper airway obstruction
	Be aware of how to distinguish intrathoracic from extrathoracic upper airway obstruction (table 10)
	Confirm the presence of upper airway obstruction with imaging and/or endoscopic techniques
	PEF: peak expiratory flow.

measurements tend to be more variable when made weeks to months apart than when repeated at the same test session or even daily [25, 131]. The short-term repeatability of tracked parameters should be measured using biological controls. This is especially important for the DL_{CO} [132, 133], since small errors in measurements of inspiratory flows or exhaled gas concentrations translate into large DL_{CO} errors. The variability of lung volume measurements has recently been reviewed [134].

The optimal method of expressing the short-term variability (measurement noise) is to calculate the coefficient of repeatability (CR) instead of the more popular coefficient of variation [135]. Change measured for an individual patient that falls outside the CR for a given parameter may be considered significant. The CR may be expressed as an absolute value (such as 0.33 L for FEV₁ or 5 units for DL_{CO}) [136] or as a percentage of the mean value (such as 11% for FEV₁) [137].

It is more likely that a real change has occurred when more than two measurements are performed over time. As shown in table 12, significant changes, whether statistical or biological, vary by parameter, time period and the type of patient. When

TABLE 12	Reported significant changes in forced vital capacity (FVC), forced expiratory volume in one second (FEV ₁), mid-expiratory flow (MEF _{25–75%}) and carbon monoxide diffusing capacity (DL _{CO}) over time			
	FVC	FEV ₁	MEF _{25–75%}	DL _{CO}
Within a day				
Normal subjects	≥5	≥5	≥13	
COPD patients	≥11	≥13	≥23	>7%
Week to week				
Normal subjects	≥11	≥12	≥21	>6 units
COPD patients	≥20	≥20	≥30	>4 units
Year to year	≥15	≥15		>10%

The variables are the same as in tables 6 and 8. Results for spirometry are rounded to the nearest integer [25, 128]. The within-day DL_{CO} variability is from a study of diurnal variation in healthy nonsmokers [133]. The week-to-week coefficient of repeatability (CR) is given for DL_{CO} in units of mL·min⁻¹·mmHg⁻¹, as calculated from CRs originally stated in units of mmol·min⁻¹·kPa⁻¹ [138]. The year-to-year variability of healthy adults is given using a 95% confidence interval [139]. CRs from repeatability testing performed in your own laboratory should be substituted for the values in this table. COPD: chronic obstructive pulmonary disease.

there are only two tests available to evaluate change, the large variability necessitates relatively large changes to be confident that a significant change has in fact occurred. Thus, in subjects with relatively “normal” lung function, year-to-year changes in FEV₁ over 1 yr should exceed 15% before confidence can be given to the opinion that a clinically meaningful change has occurred [5].

For tracking change, FEV₁ has the advantage of being the most repeatable lung function parameter and one that measures changes in both obstructive and restrictive types of lung disease. Two-point, short-term changes of >12% and >0.2 L in the FEV₁ are usually statistically significant, and may be clinically important. Changes slightly less than these may, perhaps, be equally significant, depending on the reproducibility of the pre- and post-bronchodilator results. Other parameters such as VC, IC, TLC and DL,CO may also be tracked in patients with ILD or severe COPD [138, 140–142]. Tests like VC and FVC may be relevant to COPD because they may increase when FEV₁ does not, and changes in DL,CO, in the absence of change in spirometry variables, may be clinically important. Again, when too many indices of lung function are tracked simultaneously, the risk of false-positive indications of change increases.

The clinician seeing the patient can often interpret results of serial tests in a useful manner, which is not reproducible by any simple algorithm. Depending on the clinical situation, statistically insignificant trends in lung function may be meaningful to the clinician. For example, seemingly stable test results may provide reassurance in a patient receiving therapy for a disease that is otherwise rapidly progressive. The same test may be very disappointing if one is treating a disorder that is expected to improve dramatically with the therapy prescribed. Conversely, a statistically significant change may be of no clinical importance to the patient. The largest errors occur in attempting to interpret serial changes in subjects without disease, because test variability will usually far exceed the true annual decline, and reliable rates of change for an individual subject cannot be calculated without prolonged follow-up [143].

Test variability can be reduced when lung function standards and guidelines are followed strictly. Simple plots (*i.e.* trending) of lung function with time can provide additional information to help differentiate true change in lung function from noise. Measuring decline in lung function as a means of identifying individuals (such as smokers) who are losing function at excessive rates has been proposed. However, establishing an accelerated rate of loss in an individual is very difficult, and requires many measurements over several years with meticulous quality control of the measurements.

Table 13 shows a summary of the considerations involved in interpreting lung function changes.

DL,CO INTERPRETATION

The lower 5th percentile of the reference population should be used as LLN for DL,CO and KCO (if the latter is used). Table 14 presents a scheme to grade the severity of reductions in DL,CO.

The pathophysiological importance of this test has been recently reviewed [144, 145].

TABLE 13 Summary of the considerations for the interpretation of change in lung function

Be aware of possible significant changes in lung function parameters over time (table 12)
Multiple measurements over time are more likely to signal a real change in lung function than two measurements
When too many indices of lung function are tracked simultaneously, the risk of false-positive indications of change increases
Clinical interpretation of serial tests should not be based solely on the coefficient of repeatability, but also on the clinical findings

TABLE 14 Degree of severity of decrease in diffusing capacity for carbon monoxide (DL,CO)

Degree of severity	DL,CO % pred
Mild	>60% and <LLN
Moderate	40–60%
Severe	<40

% pred: % predicted; LLN: lower limits of normal.

Interpreting the DL,CO, in conjunction with spirometry and lung volumes assessment, may assist in diagnosing the underlying disease (fig. 2). For instance, normal spirometry and lung volumes associated with decreased DL,CO may suggest anaemia, pulmonary vascular disorders, early ILD or early emphysema. In the presence of restriction, a normal DL,CO may be consistent with chest wall or neuromuscular disorders, whereas a decrease suggests ILDs. In the presence of airflow obstruction, a decreased DL,CO suggests emphysema [146], but airway obstruction and a low DL,CO are also seen in lymphangiomyomatosis [147]. Patients with ILD, sarcoidosis and pulmonary fibrosis usually have a low DL,CO [135–137, 140]. A low DL,CO is also seen in patients with chronic pulmonary embolism, primary pulmonary hypertension [148], and other pulmonary vascular diseases. These patients may or may not also have restriction of lung volumes [149].

A high DL,CO is associated with asthma [150], obesity [151] and intrapulmonary haemorrhage [152].

Adjustments of DL,CO for changes in haemoglobin and carboxyhaemoglobin are important, especially in situations where patients are being monitored for possible drug toxicity, and where haemoglobin is subject to large shifts (*e.g.* chemotherapy for cancer).

Adjusting DL,CO for lung volume using DL,CO/VA or DL,CO/TLC is controversial [153, 154]. Conceptually, a loss of DL,CO that is much less than a loss of volume (low DL,CO but high DL,CO/VA) might suggest an extraparenchymal abnormality, such as a pneumonectomy or chest wall restriction, whereas a loss of DL,CO that is much greater than a loss of volume (low DL,CO and low DL,CO/VA) might suggest parenchymal abnormalities. The relationship between DL,CO and lung volume, however, is not linear and markedly less than 1:1, so

TABLE 15 Summary of the considerations for diffusing capacity for carbon monoxide (DL_{CO}) interpretation

Refer to a scheme to grade the severity of reductions in DL_{CO} (table 14)

Interpreting DL_{CO} in conjunction with spirometry and lung volumes may assist in diagnosing the underlying disease (fig. 2)

Adjustments of DL_{CO} for changes in haemoglobin and carboxyhaemoglobin are important

The relationship between DL_{CO} and lung volume is not linear, so DL_{CO}/VA or DL_{CO}/TLC do not provide an appropriate way to normalise DL_{CO} for lung volume

Nonlinear adjustments may be considered, but their clinical utility must be established before they can be recommended

VA: alveolar volume; TLC: total lung capacity.

these simple ratios as traditionally reported do not provide an appropriate way to normalise DL_{CO} for lung volume [154–159]. Nonlinear adjustments may be considered, but their clinical utility must be established before they can be recommended. Meanwhile, it is advisable to keep examining DL_{CO}/VA and VA separately [153], in so far as it may provide information on disease pathophysiology that cannot be obtained from their product, the DL_{CO} .

Table 15 shows a summary on the considerations for DL_{CO} interpretation.

ABBREVIATIONS

Table 16 contains a list of abbreviations and their meanings, which will be used in this series of Task Force reports.

TABLE 16 List of abbreviations and meanings

ATPD	Ambient temperature, ambient pressure, and dry
ATPS	Ambient temperature and pressure saturated with water vapour
BTPS	Body temperature (<i>i.e.</i> 37°C), ambient pressure, saturated with water vapour
C	Centigrade
CFC	Chlorofluorocarbons
Cm	Centimetres
COHb	Carboxyhaemoglobin
DL_{CO}	Diffusing capacity for the lungs measured using carbon monoxide, also known as transfer factor
DL_{CO}/VA	Diffusing capacity for carbon monoxide per unit of alveolar volume, also known as K_{CO}
DM	Membrane-diffusing capacity
DT	Dwell time of flow >90% of PEF
EFL	Expiratory flow limitation
ERV	Expiratory reserve volume
EV	Back extrapolated volume
EVC	Expiratory vital capacity
FA_X	Fraction of gas X in the alveolar gas
$FA_{X,t}$	Alveolar fraction of gas X at time t
FEF_{25–75%}	Mean forced expiratory flow between 25% and 75% of FVC
FEF_{X%}	Instantaneous forced expiratory flow when X% of the FVC has been expired
FEV₁	Forced expiratory volume in one second
FEV_t	Forced expiratory volume in t seconds

TABLE 16 (Continued)

FE_X	Fraction of expired gas X
FIF_{X%}	Instantaneous forced inspiratory flow at the point where X% of the FVC has been expired
FI_X	Fraction of inspired gas X
FIVC	Forced inspiratory vital capacity
FRC	Functional residual capacity
FVC	Forced vital capacity
H₂O	Water
Hb	Haemoglobin
Hg	Mercury
Hz	Hertz; cycles per second
IC	Inspiratory capacity
IRV	Inspiratory reserve volume
IVC	Inspiratory vital capacity
K_{CO}	Transfer coefficient of the lung (<i>i.e.</i> DL_{CO}/VA)
Kg	Kilograms
kPa	Kilopascals
L	Litres
L·min⁻¹	Litres per minute
L·s⁻¹	Litres per second
Lb	Pounds weight
MEF_{X%}	Maximal instantaneous forced expiratory flow where X% of the FVC has been expired
MFVL	Maximum flow–volume loop
mg	Milligrams
MIF	Maximal inspiratory flow
mL	Millilitres
mm	Millimetres
MMEF	Maximum mid-expiratory flow
ms	Milliseconds
MVV	Maximum voluntary ventilation
PA_{O_2}	Alveolar oxygen partial pressure
PB	Barometric pressure
PEF	Peak expiratory flow
PH_2O	Water vapour partial pressure
PI_{O_2}	Inspired oxygen partial pressure
θ (theta)	Specific uptake of CO by the blood
RT	Rise time from 10% to 90% of PEF
RV	Residual volume
S	Seconds
STPD	Standard temperature (273 K, 0°C), pressure (101.3 kPa, 760 mmHg) and dry
TB	Tuberculosis
TGV (or V_{TG})	Thoracic gas volume
t_I	Time taken for inspiration
TLC	Total lung capacity
Tr	Tracer gas
t_{tot}	Total time of respiratory cycle
TV (or V_T)	Tidal volume
VA	Alveolar volume
VA_{eff}	Effective alveolar volume
VC	Vital capacity
V_c	Pulmonary capillary blood volume
V_D	Dead space volume
V_I	Inspired volume
V_S	Volume of the expired sample gas
μg	Micrograms

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