American Thoracic Society

MEDICAL SECTION OF THE AMERICAN LUNG ASSOCIATION

LUNG FUNCTION TESTING: SELECTION OF REFERENCE VALUES AND INTERPRETATIVE STRATEGIES

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Contents

Introduction

Background

During the last 3 decades lung function tests have evolved from tools for physiologic study to clinical tools widely used in assessing respiratory status. In addition to their use in clinical case management, they have become a part of routine health examinations in respiratory, occupational, and sports medicine and in public health screening. It is common practice for the results of lung function tests to be interpreted in relation to reference values, and in terms of whether or not they are considered to be within the "normal" range (l-6). A wide selection of published reference values and "lower limits of normal" is available (4). Computerized equipment adds a new dimension with preselected or menus of reference values and interpretation algorithms whose origin and justification may be unclear.

To maximize the clinical value of lung function tests and to assist those managing clinical lung function testing laboratories, the American Thoracic Society (ATS) (7-12), the European Community for Coal and Steel (ECCS) (4), and the European Society for Clinical Respiratory Physiology (13) have published guidelines, focusing primarily on spirometry as the most widely used lung function test. The 1987 ATS statement in spirometry (8) outlined the steps necessary to achieve standardization: (1) equipment performance, validation, and quality control; (2) subject performance; (3) measurement procedures to determine acceptability and reproducibility; (4) reference values and interpretation. The first three have been addressed in official statements or position papers of the ATS (7-12). This statement addresses the fourth.

Focus

The charge by the ATS was to prepare a comprehensive and practical document dealing with conceptual issues and their scientific basis and providing guidelines for daily use in two areas: (1) selecting reference values and (2) interpretative strategies The statement was to address the concerns of those who generate lung function reports and those who use lung function reports to assist in clinical case management. Epidemiologic and public health issues are not addressed though epidemiologic studies provide the scientific basis for many of the concepts used in interpreting lung function results. The ATS has published standardization procedures for epidemiologic studies (14). The focus of this statement is spirometry, but reference is made to other lung function tests when pertinent. Although the statement deals primarily with adults, the conceptual issues apply to children as well. Terms and abbreviations follow the American College of Chest Physicians (ACCP)-ATS joint committee on pulmonary nomenclature recommendations (15). The next four sections deal with conceptual issues and their scientific basis; the last section deals with practical considerations and recommendations.

Sources of Variation in Lung Function Testing

Conceptual Issues Pertinent to the Interpretation of Lung Function Tests

All clinical measurements, including pulmonary function tests, are subject to (I) technical variation related to instrument, procedure, observer, subject, and their interactions; (2) biologic variation, the focus of interest of most of the nonclinical biological sciences; (3) variation caused by dysfunction or disease, the focus of clinical medicine (5). In clinical pulmonary function testing, it is important to minimize the variation *caused* by technical factors and to take biologic variation into account so that variations caused by disease can be properly interpreted. Sources of technical and biologic variation and the estimated magnitude of their effects are listed in tables 1 and 2.

Interpretation of pulmonary function tests depends upon establishing the variation of interest (the signal) and its relation to all other sources of variation (the noise) (5). Which sources of variation constitute signal and which noise will depend on the question being asked. For instance, in a physiologic study of the effects of posture on FEV,, variation caused by posture would constitute the signal and all other sources of within-individual variation, the noise. Similarly, in an epidemiologic study of the effects of an occupational exposure on a work force, variation caused by exposure will constitute the signal, and all other sources of between population variation, the noise In the clinical context, signal and noise will vary according to the clinical question. For instance, when assessing the outcome of a treatment, the signal would be the change after treatment, and the noise would be within-individual variation in the absence

TABLE 1

SOURCES OF VARIATION IN LUNG FUNCTION'

Source	Determinants
Technical	Instrument, subject, posture, observer, procedure (including number of tests), software: temperature; altitude
Biologic	
Within individual	All of the above
	Diurnal (circadian) and seasonal effects, endocrinologic effects
Between individual	All of the above
	Personal factors, including size, age, sex, physical activity, muscularity, race, and other genetic characteristics and past and present health
	Environmental factors, including tobacco smoke (personal and environmental), occupation, residence (urban or rural), air pollution (home, environmental), and socioeconomic status
Between population	All of the above
	Selection factors which determine inclusion or exclusion of certain subjects from study populations

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TABLE 2

ESTIMATES OF THE PROPORTION OF MEASURED BETWEEN-INDIVIDUAL VARIATION IN FEV, OR FVC IN ADULTS ATTRIBUTABLE TO IDENTIFIED FACTORS'

Factor		Proportion of Variation Attributable
Sex		up to 0.30
Age	0.08	
Height	0.20	up to 0.30
Weight	0.02	
Ethnic differences		0.10
Technical		0.03
Unexplained†		0.27
Total		1 .00

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† Includes all other determinants of biologic variation discussed in SOURCES OF VARIATION IN LUNG FUNCTION TESTING whether environmental (e.g., smoking, active, and passive, occupational exposures, residential pollution, socioeconomic status) or host, (e.g., genetic, allergic, past and present respiratory heafth status). The latter two are usually the focus of interest to the clinical pulmonary function laboratory.

of treatment. When lung function tests are used as an aid in diagnosis, the signal is usually the patient's results compared with the expected result for subjects without disease but similar in the personal characteristics that determine lung function such as sex, size, age, and, possibly, race (table 1).

Technical Sources of Variation

INSTRUMENTATION

Detection of instrument problems is an integral part of interpretation. Readers should consult ATS recommendations on spirometry and D_{LCO}, which give practical limits of acceptable instrument variability (7-9). Instruments and procedures used in developing of reference values and those used to evaluate patients should meet, and preferably exceed, current ATS recommendations.

PRECISION AND ACCURACY

In considering the variability of a test, a distinction must be made between precision and accuracy. Precision refers to the repeatability of the measurements, even if the values obtained are not accurate (16). Accuracy, which is not easy to establish, refers to how close the measurements made by an instrument are to the "true" value Because most instruments have better precision than accuracy, between-instrument variation usually contributes more to total measurement variability than within-instrument variation.

COMPUTER SOFTWARE AND HARDWARE

Overall, the use of computers in spirometry systems has reduced technical variability; nevertheless errors associated with computers occur. Even small differences in the techniques used to calculate flow can produce relatively large differences in derived flow measurements (17, 18). It is imperative that spirometry systems using computers be validated initially and each time changes are made in software or hardware One simple method of validating computer computations is to compare manual calculations of spirometric values with computer-calculated values. The values should be close, ± 2 to 3%, but they will not be identical. Computers can also provide immediate feedback on the success of a subject's performance and improve overall test quality. Quality control algorithms that detect coughs, late peak flows, premature termination of effort, excessive extrapolated volumes using the back extrapolation technique, and excessive variation between maneuvers can be programmed to provide immediate feedback to the technician.

SPECIAL CONSIDERATIONS FOR TESTING CHILDREN

Equipment for testing children should have an accuracy for volume of ± 50 ml to below 0.5 L. The output for the hard copy display should be scaled to the size of the signal with a variable attenuation to a minimum of 30 mm/L. There should be a visible real-time display to encourage both the child and the technician and to ensure that effort is sustained over a sufficient time Equipment, including mouthpieces and noseclips, should be adjustable and comfortable for children with heights as low as 120 cm. Children should be tested in a laboratory where personnel are familiar with clinical testing of children and where interpretations can be made by persons familiar with pulmonary function testing in children. Detailed recommendations for pediatric testing have recently been issued by the European Society of Clinical Respiratory Physiology (13).

Procedural Sources of Variation

The largest single source of within-subject variability is improper performance of the test. Therefore, interpretations of spirometry should include a statement about test quality before any other interpretation is rendered. The ATS (7–12), the ECCS (4), the California Thoracic Society (2), the Intermountain Thoracic Society (19), the European Society for Clinical Respiratory Physiology (13), and several texts (1, 3, 20–23) have all recognized the importance of procedure in reducing measurement variability. Readers should consult these references for detailed recommendations.

Biologic Sources of Variation

WITHIN-INDIVIDUAL (INTRAINDIVIDUAL) VARIATION

This section addresses short-term intraindividual variations in lung function that do not originate with instrumentation and are not related to disease, environment, the intake of drugs, smoking, or failure of the subject to inspire or expire maximally during spirometric maneuvers. The main residual sources of variation are: (I) body position, (2) head position, (3) effort dependence of maximal flows, and (4) circadian rhythms.

(*I*) ***Body position.*** Body position affects spirometric volumes, particularly FVC and VC, which are 7 to 8% lower in the supine than in the standing position and 1 to 2% lower in the sitting than in the standing position (24-27). Body position should be kept constant in comparison studies. The standing position may be particularly advantageous for obese subjects (28).

(2) ***Headposition.*** Systematic increases in maximal expiratory flows have been documented during neck hyperextension (29). These increases are believed to be related to elongation and stiffening of the trachea and range from minimal to 35% of baseline values for lung volumes above FRC (60 to 80% of VC). Corresponding changes in FEV, have not been documented. Conversely, neck flexion may decrease peak expiratory flow rate (29) and increase airway resistance (30). Avoiding hyperextension and flexion of the neck seems sufficient to eliminate this source of variability. The effect of neck position is usually less than that of body position, but it may be important for patients tested in bed.

(3) ***Effort dependency of maximal flows. The imperative*** for standardization is one reason for the recommendations that the expiratory maneuver be performed with maximal effort. Nevertheless, FEV, may be 100 to

200 ml lower when the effort is maximal compared with submaximal efforts because the airways are narrower with respect to the exhaled volume (31-34). Variable expiratory effort may thus be a confounding factor when assessing small changes in maximal flows or timed volumes such as those resulting from bronchodilator response, therapy, or aging. When a flow-volume curve is available, peak expiratory flow may be an index of maximal expiratory effort (31). In some subjects, repeated maximal efforts may trigger bronchospasm, resulting in a progressive decrease in FVC and FEV, (35). This may also account for a subject's inability to achieve the reproducibility standard recommended by the ATS. It is of interest that failure to meet these reproducibility standards may itself be a measure of less than perfect health (36, 37).

(*4*) ***Circadian rhythms*** Variations in lung function tests with a period of approximately 24 h are well documented (38–40). For maximal expiratory flows, the lowest values are usually seen in the early morning (4 to 6 A.M.), and the largest values are seen around noon (38). In healthy subjects, FEV_1 has been shown to increase by about 0.15 L in the morning and decrease by 0.05 L in the afternoon (39); for peak expiratory flow rate (PEFR), the peak-to-trough amplitude is on the order of 8% (40). Circadian variations have also been documented for airway resistance, specific airway conductance, functional residual capacity, total lung capacity, and residual volume (41-44). The mechanisms responsible for these diurnal variations in lung function have not yet been elucidated (45, 46). Much larger diurnal changes are seen in asthmatic patients who often exhibit a severe "morning dip" in pulmonary function parameters with decreases of 50% or more in PEFR (40, 41, 47, 48). As with healthy subjects, the largest values are usually seen around noon, but this pattern may be substantially shifted by the timing of treatment (49). Exaggerated circadian variations have also been observed in patients with chronic bronchitis (50, 51). Seasonal variations of respiratory function have also been recorded (49).

BETWEEN-INDIVIDUAL (INTERINDIVIDUAL) VARIABILITY: HOST FACTORS

The most important host factors responsible for interindividual variation in lung function are (*1*) sex and size, and (2) aging, which account for approximately 30, 22, and 8%, respectively, of the variation in adults (5) (table 2). Other sources of interindividual variation are (3) race and (*4*) past and present health. Approximately 27% of interindividual variation remains unexplained (5) (table 2).

(*1*) ***Size and sex. Size is*** usually measured as standing height (6, 52). Sitting height, not as easy to measure as standing height, generally explains less of the variability (53), but it may be a useful predictor in certain circumstances (cg., when dealing with a population of mixed ethnic origins, see below). Arm span measurements provide a practical substitute for standing height in subjects unable to stand or those with a skeletal deformity such as kyphoscoliosis (19, 54). Lung function is decreased at both extremes of weight (55, 56). Including measurements of chest circumference only slightly improves the prediction of lung function (57–60). Variations in airway and air-space dimensions and geometry also contribute to interindividual variation in lung function (61, 62). Accurate methods of measuring airway and air-space geometry are not widely available, and the contribution these measurements will make to increasing prediction accuracy is unknown. After correcting for body size, girls appear to have higher expiratory flows than do boys, whereas adult men have larger volumes and flows than do women (6, 63, 64).

(2) ***Aging. An*** appropriate model for lung function changes caused by aging during the adult years includes a period after adult height is attained in which there is either an increase (usual in young men) or little or no decrease in function (usual in young women), after which the function decreases at an accelerating rate with increasing age (6, 65) (see also GROWTH section below). These accelerated aging effects are typically found in longitudinal studies and not in studies based on cross-sectional data. The differences between cross-sectional and longitudinal studies are explained by both statistical issues (66-69) and cohort effects (5, 6, 52, 55, 70).

(3) Race. Race has been consistently shown to be an important determinant of lung function (20, 55, 58, 63, 64, 71–83). When compared with Caucasians of European descent, values for most other races usually show smaller static and dynamic lung volumes and lower forced expiratory flow rates but similar or higher FEV_1/FVC ratios. In some population groups diffusing capacity (transfer factor) is also lower (71). Regression equations derived from white populations using standing height as the measure of size usually overpredict values measured in black subjects by about 12% for TLC, FEV_1, and FVC and by approximately 7% for FRC and RV (20). People of mixed race usually have intermediate values. These differences persist after allowances are made for age., stature, smoking, air pollution, habitual activity, and altitude. The reason for the differences between the races is unclear. Differences may be due in part to differences in body build (58, 63, 64, 72-76). Blacks, on average, have a smaller trunk:leg ratio than do whites (77). The use of sitting height as an index of body size in prediction equations reduces but does not fully eliminate the observed differences between whites and blacks (58, 63, 64, 77) or the differences between Europeans, Indians, and Asians. Environmental differences, perhaps relating to nutrition, physical activity, community air pollution, and socioeconomic factors are also thought to contribute to these differences (78-85).

(4) ***Past andpresent health.*** Lung function at any one point in time reflects not only the present health of the individual but also the sum of all the insults and injuries the lung has sustained in the past including those from the prenatal and immediate postnatal periods (86-88).

BETWEEN-INDMDUAL (INTERINDIVIDUAL) VARIATION: ENVIRONMENTAL FACTORS

The effects of exposure to tobacco smoke, by far the most important environmental factor known to alter lung function, are well documented elsewhere (89). In this section consideration is given to other environmental factors that account for between-individual differences in lung function.

(*1*) ***Geographic factors.*** Altitudes as high as 1,500 m do not appear to cause measurable changes in lung volumes, though measurement of some flow rates may be affected by changes in air density even at these altitudes (90-92). FEV, and forced expiratory flows are slightly increased at high altitudes, mainly because of the decreased density of air (93, 94). During acute exposures to altitude there may be slight reductions in VC, TLC, and FRC, most likely because of increased thoracic fluid (95). Those residing at high altitudes probably have larger lung volumes than do residents at low altitudes. The reasons are unclear because of the confounding effects of variables such as nutrition (%, 97).

(2) ***Exposure to environmental and occupational pollution.*** Exposure to airborne irritams such as ozone, nitrogen dioxide, sulfur dioxide, and sulfuric acid may produce measurable transient changes in pulmonary function tests in controlled human exposure experiments and epidemiologic studies (98-102). Those who are exercising and sensitive subgroups of the general population have increased responses. For example, short-term exposures (minutes) to high concentrations of SO, can trigger transient bronchoconstriction in exercising asthmatics (103). Reduced lung function levels and an increased rate of decline in lung function have been associated with long-term exposures to sulfur oxides, inhalable particles, and photochemical oxidants (100).

Environmental exposure to tobacco smoke appears to affect the lung function of children (104,105) and, possibly, adults (106-108). More recent observations also show an effect on bronchial reactivity in children (109). The health effects of other indoor pollutants have not yet been conclusively established (110,111). Exposure to occupational pollutants, including dusts, chemicals, gas, etc., may induce acute and chronic changes in lung function (112-114).

(3) ***Socioeconomic status.*** Adverse effects of low socioeconomic status on lung function are well documented and detectable even in industrialized countries (85, 115, 116). Low socioeconomic status is often associated with unfavorable environmental conditions such as living in polluted urban-industrial areas, increased environmental and occupational exposures, increased indoor air pollution, increased rates of respiratory illness, and decreased access to health care. Moreover, dif-

ferences in lung function attributed to genetic factors may be partly or even largely attributable to differences in socioeconomic status (84).

GROWTH

Growth affects the relationships between indices of body size and spirometric measurements in children and adolescents. Some of the determinants of lung volumes and ventilatory flows are therefore briefly reviewed here.

(*1*) ***Relationship to height.*** The relationship of ventilatory function to height from childhood through late adolescence to adulthood is not linear. Prediction equations for children are usually based on power or exponential functions of height, both of which seem to fit the data equally well (63, 64, 117–120).

(2) ***Age-dependence.*** Growth in standing height, measured in cross-sectional or longitudinal population studies, is not in phase with lung growth during the adolescent growth spurt (120–125). Growth in chest dimensions lags behind that of the legs (60, 122, 124, 125). In boys, standing height and VC are often not maximal by 17 yr of age (123). VC continues to increase after growth in height ceases and may not be maximal until after 25 yr of age. Girls, however, seem to attain their maximal values at about 16 yr of age (120, 122, 123). In younger subjects, FVC and FEV_1 seem to track constant percentiles over time (126). Ideally, developmental rather than chronologic age should be included in prediction equations for children and adolescents, but such equations are not available or practical.

(3) ***Respiratory muscles.*** The opposing effects of increasing muscularity and obesity have been invoked to explain the observed increase in ventilator-y function that parallels increase in body mass and the decline in lung function beyond an optimal weight (55). Likewise, an increase in lung volumes and body mass when growth in height had stopped has been attributed to an increase in muscle mass and the consequent increase in respiratory muscle force (124, 127, 128). However, data on maximal inspiratory and expiratory pressures generated at different ages are inconclusive No differences were observed between respiratory pressures in adolescents and adults (129). In adolescents there is evidence of only a small increase in maximal respiratory pressure with growth of the lung and thorax (130-N). The average maximal respiratory pressures of boys are larger than those of girls (130-133). Although there is a large variability in maximal inspiratory and expiratory pressures between individuals of the same sex, respiratory force accounts for only a small portion of the differences in ventllatory function (134, 135).

(*4*) ***Elastic properties.*** From the neonatal period to old age, the thoracic cage grows stiffer (136). Lung recoil increases from birth to adulthood and then decreases with aging (136-143). The relatively constant FRC/TLC ratio (120) and the measurements of respiratory system mechanical properties (136) suggest that changes in lung and chest recoil are well balanced during growth.

(5) ***Lung volumes and ventilatory flows.*** From childhood to adulthood the FEV_1/FVC ratio and the ratio of maximal expiratory flow (derived from flow-volume curves) to the FVC are almost constant. Girls generate larger expiratory flows than do boys of the same age and stature (120, 127, 135, 144, 145). This is due in part to the fact that girls have a smaller VC for the same TLC than do boys, but it may also reflect both the smaller muscle mass and the smaller number of alveoli found in girls (146). Airway tone appears to decrease in girls but not in boys after a deep inspiration (147). Finally, in children between 2 and 12 yr of age airway resistance is less in girls than in boys (148). These observations warrant using different prediction equations for boys and girls at all ages.

Statistical Considerations in the Derivation of Prediction Equations

General Comments

Reference equations provide a context for evaluating the pulmonary function values of an individual patient or subject in comparison to the distribution of measurements in a reference population. The clinicians request for tests often contains the implicit question: Are these results below the "lower limit of normal?" This section deals with statistical aspects and limitations of this concept.

Characterizing the Distribution and Determinants of Lung Function in Reference Populations

Subjects with similar characteristics for the variables that affect lung function (sex, age, height, race) can be grouped together in a stratum or a cell. Comparing the performance of an individual subject with the values generated from a reference population requires one to know something about the data in the appropriate cell, specifically: (*1*) the number in the cell, (2) measures of central tendency such as the mean value, (3) estimates of dispersion such as variance or standard deviation (SD), and (4) information about the symmetry of the distribution. If the number of subjects in each cell is sufficient, lung function can be described by providing descriptors of the distribution such as mean and SD. Such tabulations are infrequently used for lung function because there are too many possible cells (consider all possible combinations of age and height). Regression equations are an economical and efficient alternative method to describe expected values as a function of sex, height, and age Regression techniques assume that pulmonary function varies in a symmetric fashion about the mean value in each cell and that the variance about the mean is constant from one cell to another. The closer the distribution of pulmonary function values comes to symmetry or, better still, to a Gaussian distribution within cells, the more it is possible to take advantage of the simplifications possible with Gaussian data.

Evaluating Prediction Equations

Linear regression is the most common but not the only model used to describe pulmonary function data in adults. Such equations perform less well at the edges of the data distribution and in those cells where there are few data. Estimates are likely to be misleading if they go beyond the range of the independent variables used to create the equation. Regression analyses are often simplified by restricting the range of possible values to cells (ranges of height and age) in which reasonable predictions are possible. One approach to regression analysis is to use separate simple regression equations for several different age groups (149,150). This approach may introduce conflicting estimates at the points of transition between equations.

Complex equations may provide more biologically plausible models and reduce the average differences between observed and predicted values for every cell (e.g., age and height) in comparison with simple linear equations. The improved predictions, however, usually come at the cost of increased complexity of computation.

The most commonly reported measures of how well regression equations fit the data they describe are the square of the correlation coefficient (r^2) and the standard error of the estimate (SEE). The proportion of variation in the observed data explained by the independent variables is measured by r^2. The SEE is the average SD of the data around the regression line SEE will decrease and r^2 will increase as regression methods diminish the differences between predicted and observed pulmonary function values in the reference population. When the same equations are used to describe a different population, SEE will invariably be larger, and r^2 will be smaller. In addition, since these statistics reflect average characteristics of the regression, r^2 and SEE may not reflect the ability of the equation to describe the tails of the distribution or the limits of "normal," and therefore are not sufficient criteria on which to choose the best equations to evaluate a clinical population.

Distributions and "Lower Limits of Normal"

Distributions of FEV, and FVC in population studies am usually found to be close to Gaussian in the middle age range, but not at the extremes. Distributions of flow measurements and ratio measures (eg., FEV_1/FVC) are usually not symmetric (149). Transformation or age statification of the data may help produce symmetric distributions about the mean. Ideally, publications describing reference populations should include not only the prediction equations but also a means of defining their lower limits. In the absence of explicit recommendations, a lower limit can be estimated from a regression model. For spirometry, values below the fifth percentile are taken as below the expected range (below

the "lower limit of normal"), and those above the fifth percentile are taken as within the expected range (149,150). Percentiles can be calculated directly from the data if there are sufficient measurements within each category (56, 149, 150). If individual observations have a distribution close to Gaussian, the value of the fifth percentile can be roughly estimated as: Lower limit of normal = Predicted value − 1.645 x SEE. Ideally, the SD of the residuals should be constant for all cells. This is true for some equations for adults (149). In other studies, the estimated SD for the logarithm of FVC and FEV, among preadolescent children, and for height-adjusted FVC and FEV, among adults, appears to be constant for each sex and race (56). If SD is proportional to the predicted mean value, as it may sometimes be in children (126), the fifth percentile can be estimated as a constant proportion of the predicted mean, i.e., a percent of predicted. A comparison of several prediction equations for spirometry has shown substantial agreement using the fifth percentile criterion but not using the −1.645 x SEE criterion (151).

Sources, Uses, and Selection of Reference Values

General Comments

Normal ventilatory function has come to mean the average spirometric values of a representative sample of healthy subjects drawn from the general population. Various criteria for excluding study subjects have been suggested based on (1) past and present medical history (eg., presence of respiratory symptoms such as cough, sputum production, and wheezing; presence of physician-diagnosed respiratory disease such as asthma, bronchitis, emphysema, or tuberculosis; hospitalization for lung or chest conditions; the presence of heart disease; employment exposures; and cigarette smoking); (2) physical examination; and (3) chest radiographic findings. The most important selection criteria are those based on a history of past disease and respiratory symptoms. A reference population should, ideally, be representative of the general population from which the clientele of the laboratory comes. Although a random sample of a population is ideal, one report found that once hospital patients were excluded, the method for selecting the study sample used to generate reference values had relatively little effect on either the mean value or the range of values obtained (152).

Sources *of Reference Equations*

In the 1960s, a number of reference equations were published based on data gathered in specific population groups such as laboratory personnel, workers in a particular industry, school populations, subjects attending a specific clinic, volunteers, and general industrial workers (153–157). Some are derived from population-based data gathered in epidemiologic studies carried out for other purposes; in these studies reference equations are a byproduct (56, 63, 126, 149, 150). Others are based *on* data gathered specifically for the creation of reference equations (91, 158).

Determination of the "Normal Range"

Fixed Percent of Predicted Values

The practice in many clinical laboratories has been to classify values of FVC and FEV, less than 80% of predicted as abnormal. This fixed value has no statistical basis in adults (91, 159-162). Although some studies have shown that for adults of average age and height, 80% of predicted FVC and FEV, is close to the fifth percentile, use of a fixed value will result in shorter, older subjects being more readily classified as "abnormal" (159, 162), whereas taller, younger adult subjects are more likely to be erroneously classified as "normal." The practice of using 80% of predicted as the lower limit of normal for $FEF_{25-75\%}$ or the instantaneous flows will also cause important errors since, for these flows, the lower limits of normal are closer to 50% of predicted (149, 150). The practice of using a fiied percent of predicted as a lower limit of normal may be acceptable in children (163) (see section on Distributions and Lower Limits of Normal).

FEV_1/FVC Ratio

Defining a fixed FEV_1/FVC ratio as a lower limit of normal is not recommended in adults because FEV_1/FVC is inversely related to age and height (91, 149, 150). The use of a fixed ratio will therefore result in an apparent increase in the prevalence of impairment associated with aging or with age-confounded factors such as cigarette smoking or occupational exposures. In addition, some athletes have values for FVC that are relatively larger than those for FEV,, resulting in a lower FEV_1/FVC. This may also be true of workers in some physically demanding occupations such as mining and deep-sea diving.

Percentiles as the "Lower Limit of Normal"

One statistically acceptable approach for establishing lower limits for any spirometric measure is to define the lowest 5% of the reference population as below the lower limit of normal (see section on Distributions and Lower Limits of Normal). This implies a 5% false positive misclassification, a rate generally considered acceptable.

Smoking as an Independent Variable

Subjects who smoke cigarettes usually have lower values for spirometry and forced expiratory flows even if they meet the same health criteria for "normal" as nonsmokers (164). Smoking has both biologic and technical effects on D_{LCO} (9,165). A clear choice for the most appropriate method of adjusting spirometric indices for the effect of smoking is not readily evident from published data in which any of the following have been used: smoking status (current smoker or exsmoker), amount currently smoked, duration of smoking, and pack-years of smoking. Neglecting the correlation of some of these factors (e.g., pack-years) with age can introduce errors in analyzing the effect of smoking. In one study, the lifetime loss of FEV, for the average male smoker was 7.4 ml/pack-year, and for the average female smoker it was 4.4 ml/pack-year (164). Current smoking also adds an acute deficit in FEV, of approximately 150 ml over and above the cumulative effect of lifetime smoking (164, 166).

The distribution of a smoking variable in the reference population and its relation to other health indicators will affect the regression term calculated for smoking. For example, in one study a twofold greater deficit in spirometric measurements in relation to pack-years was found in subjects with chronic cough compared with those without chronic cough (167). The mean spirometric value may not be the best index for determining lung function deficit caused by smoking since the effect on the susceptible minority tends to be overwhelmed by the unaffected majority (168). Whether the effects of smoking are similar across other independent variables such as sex and age is unknown. Some of the sex differences in smoking-associated pulmonary dysfunction may be related to differences in smoking behavior (169). The effect of smoking also increases with age (166). The effect of smoking on the developing lung is likely to be different from the effect of smoking *on* the adult lung.

Finally, the effects of smoking cessation on pulmonary function are inconsistent. Exsmokers are found to have both reversible and irreversible ventilatory decrements (164,166, 170). Most cross-sectional studies in older subjects have found older exsmokers to have values intermediate between those who continue to smoke and those who have never smoked. Young exsmokers may exhibit higher spirometric values than never smokers, probably as a result of health selection effect (134, 171). Whether the pulmonary function of ex-smokers is better or worse than that of current smokers probaby depends on the age of the subjects, how long they have smoked, and on why they abandoned smoking.

Cross-sectional and Longitudinal Predictions

Cross-sectional data are subject to a bias called "cohort" effect. A person who is 40 yr of age today is different from one who became 40 two decades ago because of a variety of host and environmental factors (6, 52). The age-related lung function deficit predicted from cross-sectional data tends to be greater than that predicted from longitudinal pulmonary function data in adults (67-70) and children (172-174). Prediction equations based on cross-sectional data are appropriate for determining the prevalence of pulmonary function impairment in defined populations. They are less well-suited to determine age-related events including the incidence or progression of impairment. Percentiles of ad-

justed lung function (similar to those used by pediatricians to assess growth) have been advocated by several investigators for assessment of both growth and decline of pulmonary function (56, 63, 126). A person would be expected to track along the same percentile as he or she ages if the loss (gain) in function was at a rate comparable to that of the reference population.

Criteria for Selection of Reference Values

Criteria for selecting reference values to be used in the clinical or in the epidemiologic context fall into three categories: methodologic, epidemiologic, and statistical (5).

(I) ***Methodologic criteria.*** If possible, reference values should be based on data obtained by trained operators using equipment and techniques that meet ATS criteria (7-12). In contrast with the use of the FVC in America, predictions of VC from Europe are usually based on inspiratory vital capacity (IVC) or slow expiratory vital capacity (EVC). The IVC and EVC are, on average, somewhat larger than FVC in healthy subjects; in subjects with airflow limitation, the differences are more pronounced (4, 175).

(2) ***Epidemiologic criteria. The*** population from which the subjects are drawn should be similar with respect to age, height, sex, and ethnic composition to the population to whom the prediction values are to be applied. Prediction equations should use age, height, sex, and, probably, ethnic group as independent variables. For most clinical uses they should be based on cross-sectional studies of lifetime nonsmokers.

(3) ***Statistical criteria.*** These are discussed in STATISTICAL CONSIDERATIONS IN THE DERIVATION OF PREDICTION EQUATIONS. Both biologic plausibility and simplicity in the model used to develop prediction equations are important issues in the selection of reference values. However, neither is as important as the choice of a reference population that (*1*) provides an appropriate comparison for the subjects to be evaluated, and (2) is based on measurements made with instruments and methods comparable to those used in the laboratory for which reference values are being selected (2, 5).

Published Reference Equations

For the convenience of readers, selected published reference equations for adult whites and blacks and scaling factors for blacks currently in use are listed in tables 3 to 9. A comprehensive listing up to 1983 was published by the ECCS (4). The results of a survey of reference equations used in North American pulmonary teaching centers is shown in table 10. Equations for children and adolescents are detailed elsewhere (13, 63, 117-119, 131, 149, 176, 177). Laboratories should use the published reference equations that most closely describe the populations tested in their laboratories. This may also be assessed empirically by comparing the results for a group of 20 to 40 local reference subjects with those provided by the intended reference equations. The local reference subjects should be appropriately selected by age, ethnic group, and sex, to match the clientele of the laboratory and should meet the selection criteria listed in section CRITERIA FOR SELECTION OF REFERENCE VALUES.

Limitations of Currently Available Equations

Reference equations now available include relatively few results for adolescents and the elderly. Even fewer equations span the ages from grade school through adulthood and, with few exceptions, they are discontinuous for children and adults (55, 178). Older subjects reflect their lifetime experiences with respect to nutrition, health status, and other factors and are therefore subject to a cohort effect. Most equations in current use are based on linear statistical models. All these aspects are subject to change. For this reason, reference equations should be reviewed regularly.

Interpretative Strategies

Conceptual Issues Concerning Normality and the Limits of Normal

The word "normal" is used in a number of ways (5, 6, 13, 179). In popular use it means ideal, conventional, or usual. It is used by statisticians to describe a specific distribution about a central tendency and by biologists in ways that vary according to their focus of interest. Anatomists, for instance, use it to describe structural variations consistent with good function; physiologists use it to describe variations that preserve the "internal milieu," and clinicians use it to describe variation within the limits of "good health" and exclusive of "disease" (5). Issues of biologic "normality" are discussed in greater detail elsewhere, and interested readers are referred to those reviews (5, 6, 179-181).

Because most laboratory tests are quantitative variables with overlap between measurements in healthy and diseased subjects, the idea of a range of values defining biologically "normal" is, in the view of its critics, misleading (5, 6, 182). For instance, in interpreting laboratory test results where there is an overlap between healthy and diseased populations, the "normal" range should theoretically change with different disease processes and with the clinical questions being asked (181). It has also been pointed out that selecting a normal range "requires careful evaluation of benefit in terms of morbidity or mortality, inconvenience, and distress caused to

TABLE 3

PREDICTED VALUES FOR FE'.', AND FVC DERIVED FROM SELECTED STUDIES OF NONSMOKING CAUCASIAN MEN'

First Author, Year (Ref)	Age Range (yr)	Number Studied	FEV_1† for Ht 1.75 m. Age 45 yr	Regression Coefficient		RSD or SEE	FVC† for Ht 1.75 m, Age 45 yr	Regression Coefficient		RSD or SEE
				Ht	Age			Ht	Age	
Morris, 1971 (224)	20-84	517	3.63	3.62	− 0.032	0.55	4.84	5.83	− 0.025	0.74
Cherniack, 1972 (225)	15-79	870	3.74	3.59	− 0.023	NR	4.52	4.76	-0.014	NR
Quanjer, 1977 (4)	21-64	189	3.59	4.05	− 0.031	0.43	4.51	6.11	− 0.032	0.56
Crapo, 1981 (91)	15-91	125	3.96‡	4.14	− 0.024	0.49	4.89‡	6.00	− 0.021	0.64
Knudson, 1983 (149)	25-84	86	3.61	6.65	− 0.029	0.62	4.64	8.44	− 0.030	0.64
Dockery, 1985 (56)	25-74	624	3.78	Equation nonlinear§		0.40	4.72	Equation nonlinear5		0.47
Roca, 1986 (226)	20-70	443	3.95	4.99	-0.021	0.44	5.15	6.78	− 0.015	0.53
Paoletti, 1986 (150)	29-64	59	3.83	4.94	-0.027	0.48	5.06	7.24	− 0.027	0.58
Miller, 1986 (158)	18-85	176	3.94	5.66	− 0.023	0.41	4.84	7.74	− 0.021	0.51

Definition of abbreviations: RSD = residual standard deviation; SEE = standard error of the estimate; NR = not reported.

* To be included studies had to (I) include man and women; (2) adequately describe the methods used; (3) analyze spirometric values in terms of age and height. Instruments of measurement were: water spirometer (56, 91. 224); dry or wedge spirometer (158, 225); pneumotachograph (4, 149. 150, 226). Equation to predict FEV_1 or FVC using this table:

Predicted FEV, or FVC = Prediiad value† for Ht 1.75 m, Age 45 + Ht Coefficient × (Ht − 1.75) • Age Coefficient × (Age − 45)

† Predicted value for Ht = 1.75 m, Age = 45.

*Studies carried out at an altitude of 1,400 m.

§ $FEV_1 = Ht'(1.541 - 4.06 \times 10^{-3}\ Age - 6.14 \times 10^{-5}\ Age^2)$; $FVC = Ht^2\ (1.75 - 1.35 \times 10^{-4}\ Age - 1.01 \times 10^{-4}\ Age^2)$.

TABLE 4

PREDICTED VALUES FOR FEV, AND FVC DERIVED FROM SELECTED STUDIES OF NONSMOKING CAUCASIAN WOMEN'

First Author, Year (Ref)	Age Range (yr)	Number Studied	FEV,† for Ht 1.65 m, Age 45 yr	Regression Coefficient Ht	Regression Coefficient Age	RSD or SEE	FVC† for Ht 1.65 m, Age 45 yr	Regression Coefficient Ht	Regression Coefficient Age	RSD or SEE
Morris, 1971 (224)	20–84	471	2.72	3.56	− 0.025	0.47	3.54	4.53	− 0.024	0.52
Cherniack, 1972 (225)	15-79	452	2.67	2.37	-0.019	NR	3.36	3.08	-0.015	NR
Quanjer, 1977 (4)	21-64	514	2.71	3.17	− 0.031	0.35	3.39	4.64	− 0.027	0.42
Crapo, 1981 (91)	15-64	126	2.92‡	3.42	− 0.026	0.33	3.54‡	4.91	-0.022	0.39
Knudson. 1983 (149)	20-87	264	2.79	3.09	− 0.020	0.39	3.36	4.27	− 0.017	0.49
Dockery, 1965 (56)	25-74	1,630	2.79	Equation nonlinear§		0.40	3.41	Equation nonlinear5		0.47
Roca, 1986 (226)	20-70	427	2.67	3.17	− 0.025	0.31	3.72	4.54	− 0.021	0.40
Paoletti, 1986 (150)	21-64	313	2.64	2.43	− 0.020	0.29	3.76	4.12	-0.015	0.39
Miller, 1986 (158)	18-62	193	2.91	2.66	− 0.025	0.33	3.59	4.14	− 0.023	0.45

* To be included studies had to (7) include men and women; (2) adequately describe the methods used; (3) analyze spimmetnc values in terms of age and height. Instruments of measurement were: water spirometer (56, 91. 224); dry or Wedge spirometer (156. 225); pneumotachograph (4, 149, 150, 226). Equation to predict FEV, or FVC using this table:

Predicted FEV, or FVC = Predicted value† for Ht 1.65 m, Age 46 + Ht Coefficient x (Ht − 1.65) + Age Coefficient x (Age − 45)

† Predicted value for Ht = 1.65 m, Age = 45 yr.
‡ Studies carried out at an altitude of 1,400 m.
§ FEV, Ht^2 = (1.332 − 4.06 × 10^{-3} Age − 6.14 × 10^{-5} Age^2); FVC = HP (1.463 − 1.36 × 10^{-4} Age − 1.01 × 10^{-4} Age^2).

TABLE 5

PREDICTED VALUES FOR FEV, AND FVC DERIVED FROM SELECTED STUDIES OF BLACK MEN AND WOMEN'

First Author, Year (Ref)	Age Mean or Range	Number Studied	FEV, for Ht and Age†	Regression Coefficients Ht	Regression Coefficients Age	RSD or SEE	FVC for Ht and Age†	Regression Coefficients Ht	Regression Coefficients Age	RSD or SEE
Men			Ht 1.75 m Age 45 yr				Ht 1.75 m Age 45 yr			
Johannaen. 1968 (227)	20-50	120	2.96‡	2.67	− 0.017	0.46	4.07‡	4.09	−	0.52
Miller, 1970 (229)	35–54	96	3.05	3.40	− 0.024	0.37	3.79	4.44	− 0.024	0.46
Oscherwitz, 1972 (61)	50.3 ± 6.6	110	2.94	2.99	− 0.031	0.64	3.76	3.70	− 0.027	0.66
Rossiter, 1974 (229)	21-70	147	3.04	4.51	− 0.027	0.52§	3.64	5.77	− 0.019	0.596
Lapp, 1974 (236)	34.9 ± 11.9	79	3.53	3.54	− 0.025	0.23	4.11	3.94	− 0.021	0.32
Cookaon, 1976 (231)	43.6 ± 15.1	141	3.12	2.20	− 0.024	0.50	3.74	3.90	− 0.017	0.65
Patrick, 1976 (232)	18–65	213	3.11	4.23	− 0.023	NR	3.72	3.51	− 0.025	NR
Women			Ht 1.65 m Age 45 yr				Ht 1.65 m Age 45 yr			
Johannaen. 1966 (227)	20-50	100	2.25‡	2.18	− 0.013	0.34	2.74‡	2.51	− 0.015	0.35
Miller, 1970 (228)	35-54	109	2.19	2.45	− 0.018	0.31	2.74	3.15	− 0.020	0.36
Cookaon, 1976 (231)	36.7 ± 11.6	102	2.35	2.40	− 0.026	0.41	2.86	3.00	-0.019	0.42
Patrick, 1976 (232)	16-65	117	2.10	1.49	− 0.014	NR	2.64	3.17	− 0.020	NR

* Instruments of measurement used were: water spirometer (227, 229, 231), a dry or bellows spirometer (226.230). and various others (81, 232). Predicted values for men and woman are calculated as shown in footnotes to tables 3 and 4.
† Predicted value for a 45-yr-old man 1.75 m tall. and a 45-yr-old woman 1.66 m tall.
‡ Corrected from ATPS to BTPS conditions, assuming a spimmeter temperature of 22° C.
§ Includes caucasian subjects.

subjects by further investigation and treatment, and the costs of making the wrong decision" (182). The "normal" range only gives information about the distribution of test results in the healthy population from which they were derived. It says nothing about the true positive rate, the false negative rate, or the predictive power of a positive test.

To draw inferences about the presence of disease from a test, one should, ideally, know the prior probability that the patient has the disease and the distributions of test values for subjects with and without the disease in question. Although this ideal is rarely met, clinicians must use their understanding of the clinical situation to put an interpretation in proper perspective

Obstructive and Restrictive Ventilatory Defects

DEFINITION OF AN OBSTRUCTIVE DEFECT

An obstructive ventilatory defect may be defmed as a disproportionate reduction of maximal airflow from the lung with respect to the maximal volume (VC) that can be displaced from the lung. It indicates airflow limitation and implies airway narrowing during expiration. The earliest change associated with flow limitation in small airways is thought to be slowing in the terminal portion of the spirogram even when the initial part of the spirogram is unaffected (1, 21-23). This slowing is reflected in a proportionally greater reduction in the instantaneous flow measured after 75% of the FVC has been exhaled (FEF_{75}) or in $FEF_{25-75\%}$ than in FEV,. Abnormalities in these midrange flow measurements during a forced exhalation are, however, not specific for small airway disease and, though suggestive, should not be used to diagnose small airway disease in individual patients (183). As airway disease becomes more advanced and/

TABLE 6

PREDICTED VALUES FOR $FEV_1/FVC\%$ DERIVED FROM SELECTED STUDIES OF CAUCASIAN AND BLACK MEN AND WOMEN'

First Author, Year (Ref)	Age Range (yr)	Number Studied	$FEV_1/FVC\%$† for Ht 1.75 m and Age 45 yr	Regression Coefficients: Ht	Regression Coefficients: Age	RSD or SEE	Number Studied	$FEV_1/FVC\%$† for Ht 1.65 m and Age 45 yr	Regression Coefficients: Ht	Regression Coefficients: Age	RSD or SEE
			Caucasian Men					Caucasian Women			
Quanjer. 1977 (4)	21-64	189		—	-0.16	5.3	514	80.2		— 0.24	6.4
Crapo, 1981 (91)	15-91	125	80.9‡	— 13.0	-0.15	4.8	126	81.9‡	— 20.2	-0.25	5.3
Knudson, 1983 (149)	25-85	86	82.0	—	-0.11	6.3	204	82.8	-18.5	-0.19	7.6
Paoletti. 1986 (150)	8-64	263	75.9	— 5.3	— 0.23	6.1	538	70.5	— 4.311	— 0.31	5.8
Miller, 1986 (158)	18-85	176	80.5	— 13.1	-0.15	5.6	193	82.3	-21.5	-0.15	6.8
			Black Men					Black Women			
Johannsen, 1968 (227)	20-50	120	75.0	—	— 0.29	8.6					
Oscherwitz, 1972 (81)	50.3 (± 6.6)	110	i7.7	4.2	— 0.32	10.2					
Rossiter, 1974 (229)	21-70	147	77.2	0.62	-0.34	7.26					
Cookson, 1976 (231)	43.6 (± 15.1)	141	81.4	—	-0.25	10.7	102	82.3		-0.38	11.7

* Table comprises studies cited in tables 3 to 5. which also reported values for $FEV_1/FVC\%$ analyzed in relation to height and age. For the instruments of measurement used, see footnotes to tables 3 to 5. Note: studies of Caucasian subjects were confined to nonsmokers: studies of black subjects included all smoking categories. Predicted values for FEV_1/FVC are calculated as shown in footnotes to tables 3 and 4. Only one study gives equations for black women.

† Predicted value for a 45-yr-old man 1.75 m tall, and a 45-yr-old woman 1.65 m tall.

‡ Studies carried out at an attitude of 1,400 m.

§ Includes Caucasian subjects.

‖ Coefficient not significant.

TABLE 7

PREDICTED VALUES FOR DIFFUSING CAPACITY (D_{LCO}) AND KCO (D_{LCO}/V_A) DERIVED FROM SELECTED STUDIES OF MEN AND WOMEN'

First Author, Year (Ref)	Age Mean ± SD or Range	Number Studied	D_{LCO}† for Ht and Age	Regression Coefficients: Ht	Regression Coefficients: Age	RSD or SEE	D_{LCO}/V_A† for Ht and Age	Regression Coefficients: Ht	Regression Coefficients: Age	RSD or SEE
Men			Ht 1.75 m, Age 45 yr				Ht 1.75 m, Age 45 yr			
Billiet, 1963 (233)	20-75	57	35.3	57.6	— 0.24	4.2	4.96		—0.04	0.92
Cotes. 1965 (20)	19-72	127	30.3	32.5	— 0.20	5.1	4.83		-0.04	0.81
Teculescu, 1970 (234)	19-67	47	32.6	33.3	— 0.30	4.2	5.17‡		—0.04	0.73
Van Ganse. 1972 (235)	25-79	70	29.3	16.4	— 0.20	3.8	5.68	—0.90	-0.03	1.07
Frans, 1975 (236)	39 ± 12	64	33.3	28.5	-0.14	4.2	NR			
Marcq, 1976 (237)	17-79	64	29.9	10.4	— 0.20	3.9	4.59		— 0.03	0.65
Satorinne, 1976 (238)	20-69	69	30.7	14.2	— 0.23	3.6	5.02	-3.53	— 0.03	0.63
Crapo. 1981 (239)	15-91	123	36.66	41.6	— 0.22	4.8	5.455		-0.03	0.84
Miller, 1983 (165)	43 ± 16	74	31.4	16.4	-0.23	4.8	4.77	— 2.24	— 0.03	0.73
Paoletti, 1985 (240)	19-64	80	37.1‖	44.1	-0.19	5.8	4.81‖	—0.12††	— 0.02	0.71
Knudson, 1987 (241)	25-64	71	38.411	35.5	-0.27	4.6	5.61‖	—2.35††	— 0.04	0.80
Roca, 1990 (242)	20-70	194	33.6	36.7	— 0.20	4.4	Equation nonstandard¶			
Women			Ht 1.65 m, Age 45 yr				Ht 1.65 m, Age 45 yr			
Billiet, 1963 (233)	20-68	41	25.2	21.9	-0.16	3.6	5.55		-0.03	0.85
Van Ganse. 1972 (235)	24-76	72	20.3	16.8	-0.16	3.6	5.61	-0.17	— 0.01	0.99
Salorinne, 1976 (238)	20-69	101	25.0	21.9	-0.12	2.8	5.27	— 3.96	-0.01	0.74
Hall, 1979 (243)	27-74	113	30.1"	28.3	-0.19	4.1	5.66"		—0.02	0.74
Crapo, 1981 (239)	17-84	122	27.45	25.6	-0.14	3.6	5.469		-0.03	0.78
Miller. 1983 (165)	43 ± 15	130	23.7	16.0	-0.11	4.0	4.62	-1.81	— 0.02	0.80
Paoletti, 1985 (240)	18-64	291	27.9‖	15.7	-0.07	4.3	4.85‖	— 2.51	-0.02	0.85
Knudson, 1987 (241)	20-86	99	28.21)	18.7	-0.15	4.5	5.37‖	—2.78††	— 0.03	0.85

* Table refers to D_{LCO} and includes prediied values from published reports in which the number of subjects studied and their age were given and in which equations for D_{LCO} were described in terms of height and age according to ATS recommendations (9). All but one study (20) refer to nonsmokers. Residual volume or FRC was measured as follows: single-breath helium dilution (165, 234, 236–242), multiple-breath helium dilution (20, 233, 243), open circuit N_2 washout (235). Predicted values for D_{LCO} and D_L/V_A are calculated as Shown in footnotes to tables 3 and 4.

† Predicted value for a 45-yr-old man 1.75 m tall, and a 45-yr-old woman 1.65 m tall.

‡ Results adjusted to 1 BTPS.

§ Measurements made at an altitude of 1,400 m.

‖ Correction for breathholding time as in the Epidemiology Standardization Project (240, 241). Note that calculated D_L is sensitive to the methods used to calculate breathhold time.

¶ Form of the equation not that recommended by the ATS.

•• Results calculated for all smoking categories and adjusted for smoking effect.

†† Coefficient not significant.

TABLE 8

PREDICTED VALUES FOR TOTAL LUNG CAPACITY (TLC) AND RESIDUAL VOLUME (RV) DERIVED FROM SELECTED STUDIES OF MEN AND WOMEN*

First Author, Year (Ref)	Age Mean or Range	Number Studied	TLC† for Ht and Age	Regression Coefficients Ht	Age	RSD or SEE	RV† for Ht and Age	Regression Coefficients Ht	Age	RSD or SEE
Men			Ht 1.75 m, Age 45 yr				Ht 1.75 m, Age 45 yr			
Goldman, 1959 (92)	44 ± 17	44	6.61	9.40	-0.015	0.65	2.04	2.70	0.017	0.39
Cotes, 1965 (20)	19-72	127	6.68	8.67	—	0.91		Not reported		
Boren, 1966 (155)	20–62	422	6.35	7.80	—	0.87	1.62	1.90	0.012	0.53
Black, 1974 (244)	1659	83	6.84	7.80	—	0.68	2.15	3.80	0.034	0.57
Crapo, 1982 (245)	15-91	123	6.72	7.95	0.003	0.79	1.67	2.16	0.021	0.37
Women			Ht 1.65 m, Age 45 yr				Ht 1.65 m. Age 45 yr			
Goldman, 1959 (92)	38 ± 16	50	5.10	7.90	- 0.008	0.53	1.78	3.20	0.009	0.37
Grimby, 1963 (246)	18–72	58	5.05	7.31	- 0.016	0.52	1.44	2.92	0.008	0.35
Black. 1974 (244)	16-59	110	5.20	6.40	—	0.62	1.76	2.30	0.021	0.46
Hall, 1979 (243)	27-74	113	5.30	7.46	- 0.013	0.51	1.80	2.80	0.016	0.31
Crapo, 1982 (245)	17-04	122	5.20	5.90	—	0.54	1.73	1.97	0.020	0.38

* Only one (245) Of these studies conforms strictly to the ATS recommendations for spirometry (8); references 20. 155. 243. 244 included all smoking categories, and in two (92. 246) smoking status was not defined. Residual volume was measured as follows: helium rebreathing (20, 92, 243.246). whole-body plethysmograph (244). single-breath helium dilution (245). and helium rebreathing on open circuit N_2 washout in one study (155). Predicted values for TLC and RV are calculated as shown in footnotes to tables 3 and 4.

† Predicted value for a 45-yr-old man 1.75 m tall. and a 45-yr-old woman 1.65 m tall.

or more proximal airways become involved, timed segments of the spirogram such as the FEV, will become reduced out of proportion to the reduction in VC.

Definition of a Restrictive Defect

A restrictive ventilatory defect is characterized physiologically by a reduction in TLC. One may infer the presence of a restrictive ventilatory defect when VC is reduced and FEV_1/FVC is normal or increased. Severe airflow limitation is another common cause of a reduced VC either because airflow is so slow the subject cannot continue to exhale long enough to complete emptying or because airways collapse Occasionally, patients will have a small VC, a normal FEVJFVC, and a normal TLC. If there is a contradiction between VC and TLC in defining restriction the classification should be based on TLC.

Bronchodilator Response

Bronchial responsiveness is an integrated physiologic mechanism involving airway epithelium, nerves, mediators, and bronchial smooth muscle. Because the within-individual difference in response to a series of different bronchodilators is variable, and as many as 20 to 30% of responsive subjects will respond to one type of agent but not to another (184), 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 (185). The correlation between bronchoconstrlction and bronchodilator responses is imperfect, and it is not possible to infer with certainty the presence of one from the other.

Data on the percent change in FVC, FEV_1, and $FEF_{25-75\%}$, after bronchodilator administration in general population studies as well as in patient populations are summarized in table 11. These studies showed a tendency for the calculated bronchodilator response to increase with decreasing baseline VC or FEV_1, whether response was considered as an absolute change or as a percent of the initial value Bronchodilator responses in patient-based studies are, not surprisingly, somewhat higher than those in general population studies (table 11).

Interpretation of change after a bronchodilator should be made in light of the clinical question. If the question is whether a patient has an increased bronchodilator response, the appropriate reference is probably one of the population-based studies. If the question is whether the patient is different from other patients or from previous visits, patient groups may provide the most appropriate reference data.

There *is* no clear consensus on what constitutes reversibility in subjects with airflow obstruction (192). In part, this is because there

TABLE 9

FACTORS FOR ADJUSTING REFERENCE VALUES FOR CAUCASIANS WITH A VIM TO THEIR BEING USED FOR BLACK AMERICANS'

FEV,	0.88†
W C	0.88†
FEV_1/FVC	0
TLC	0.88
RV	0.93‡
RV/TLC	1.05
Diffusing Capacity (transfer factor)	0.93
TI/VA (BTPS)	1.05

* Source: Rossiter and Weill with annotation (229). Although the average Caucasian admixture in studies of Black Americans varies. a reasonable average is 22% (247).

† Also apply to women younger than 55 yr of age; in older subjects, the correction may be larger (approximately 0.80; Dockery *et al.* [56]).

‡ A larger correction (approximately 0.88) was proposed by Lapp *et* al. (230).

TABLE 10

SURVEY OF SPIROMETRY REFERENCE EQUATIONS USED IN NORTH AMERICAN PULMONARY TRAINING CENTERS'

	FVC or VC		FEV,		FEV_1/FVC†	
	M	F	M	F	M	F
Morris *et* al. (224)	65	65	65	65	58	60
Crapo et al. (91)	27	27	27	27	29	29
Knudson et *al.* (149)	24	24	25	25		
Kory *et al.* (153)	7		8			
Kory *et* al. (249)		7		8		
Chemiack et *al.* (225)	3	3	4	4		
Miller *et al.* (180)	2	2	2	2	2	2
Other studies‡	11	11	6	8	11	9

* Based on a questionnaire survey of adult respiratory disease training programs in the United States and Canada. Responses from 139 of 160 institutions are summarized (248).

† Thirty-nine centers predicted FEV_1/FVC by dividing predicted FEV_1 by predicted FVC.

‡ Studies cited only once.

TABLE 11

RESPONSE TO BRONCHODILATOR: RESULTS FROM SELECTED POPULATION STUDIES

Population	Agent/Mode of Delivery	WC	FEV,	$FEF_{25-75\%}$ or FEF,	Comments
1,063 subjects 8-75 yr of age General population sample from Tucson, AZ (186)	Two inhalations of isoproterenol via metered-dose inhaler	10.7% (403 ml)	7.7% (315 ml)	20%	95th percentile for percentage change from baseline (absolute value in parentheses)
2,609 subjects; random sample of three areas in Alberta, Canada (187)	500 µg terbutaline administered via spacer		Females 9% (224 ml) Males 9% (338 ml)	—	95th percentile for percentage change from baseline in asymptomatic never smokers with FEV, > 89% predicted (absolute value in parentheses)
75 selected normal subjects (188)	Two inhalations from a Bronkometer™ metered-dose inhaler	5.1% (231 ml)	10.1% (365 ml)	48.3%	Upper 95% confidence limits (two-tailed) for percentage change from baseline
RESPONSE TO BRONCHODILATOR: RESULTS FROM SELECTED PATIENT STUDIES					
40 patients referred to pulmonary function lab (189)	Placebo	14.9% (340 ml)	12.3% (178 ml)	45.1%	Upper 95% confidence interval change after placebo inhalation. Absolute values in parentheses.
985 patients with COPD participating in the IPPB trial (190)	250 µg isoproterenol air compressor nebufiier		15%		Average increase as percent of initial FEV, (5% as percent of predicted normal FEV_1)
150 patients with airway obstruction (191)	200 µg salbutamol or 500 µg terbutaline via metered-dose inhaler	15% (330 ml)	10% (160 ml)		95% confidence interval for absolute change: absolute rather than relative change preferred measure of bronchcdilator response

is no consensus on how a bronchodilator response should be expressed. The three most common methods are: percent of the initial spirometric value, percent of the initial predicted baseline value, and absolute change Expressing the change in FEV, as a percent of predicted FEV, deserves further study as it has been reported to have advantages over current methods (193). When using the percent change from the initial values as the criterion, most authorities would require at least a 12 to 15% increase in FEV_1 from the baseline value as necessary to define a meaningful response Increments of less than 8% (or of less than 150 ml) are likely to be within measurement variability (191,192). One should interpret improvement in an individual subject only if the percent change and absolute change in FEV, or VC are clearly beyond the expected variability of the measurement during a single testing session. A patient may respond to long-term bronchodilator therapy even though a bronchodilator response is not seen in a single laboratory testing session.

The $FEF_{25-75\%}$ is a highly variable spirometric test, in part because of its dependence on FVC, which increases with expiratory time with obstruction. If FVC changes, postbronchodilator $FEF_{25-75\%}$ is not comparable with that measured prebronchodilator. Volume adjustment of $FEF_{25-75\%}$ has been used to deal with this issue (194,195). At least two studies have assessed the utility of $FEF_{25-75\%}$. The results were disappointing, with only 8% of asthmatics (195) and 7% of patients with chronic obstructive pulmonary disease (COPD) (196) identified by $FEF_{25-75\%}$ criteria alone as outside the expected range Tests such as the FEV_1/VC ratio and flow rates 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.

Current published criteria and the Workshop recommendations for determining bronchodilator response are given in table 12.

Interpretation of Lung Function Tests in Clinical Practice

Pulmonary function tests may be used to address major issues in clinical case management. These include describing dysfunction and assessing its severity, explaining it in terms of diagnosis, establishing prognosis, planning management, and assessing trends over time, including changes after treatment. pulmonary function tests may also be used to identify an abnormality in subjects without a known pulmonary disorder, as in preoperative assessments, in routine health status evaluations, and in clinical screening. Finally, pulmonary function tests are increasingly requested as part of health assessment on behalf of a third party (cg., an insurance company or a governmental agency) where the clinician is not in his or her usual patient advocacy role and the subject or patient is, consequently, wary. In each of these situations, the question asked of the puhnonary function laboratory is quite different. Ideally, interpretations of pulmonary function tests should depend on the purpose of the tests and, when performed on patients with known disease, should be oriented to answering the specific question of the clinician ordering the procedure Tests interpreted without clinical information will be limited in their clinical utility and the interpretation will usually represent only a refined description of the data obtained.

The first step in interpreting a lung function test is to evaluate the quality of the study. If there are reasons to suspect the quality of the test, avoid specific diagnostic statements. Dysfunction discovered under these circumstances should indicate only the need for more definitive testing.

TABLE 12

RECOMMENDED CRITERIA FOR RESPONSE TO A BRONCHODILATOR IN ADULTS

Organization	FVC (%)	FEV, (%)	$FEF_{25-75\%}$ (%)	Comments
American College of Chest Physicians (197)	15-25	15-25	15-25	% of baseline in at least two of three tests
Intermountain Thoracic Society (19)	15	12	45	% of baseline
ATS (current document)	12	12		% of baseline and an absolute change of 200 ml

PATTERNS OF DYSFUNCTION

Certain patterns of physiologic abnormalities can be recognized, and although they are seldom if ever pathognomonic for a specific disease entity, the types of clinical illnesses most likely to produce the observed set of physiologic disturbances can be pointed out. Regardless of the extent of testing, the most important point with regard to pattern recognition is the need to be conservative with respect to suggesting a specific diagnosis for the underlying disease process based only on pulmonary function abnormalities. Recognition of characteristic patterns of dysfunction depends a great deal the comprehensiveness of the lung function evaluation. However, even with only spirometric results, one can determine whether the pattern is compatible with obstruction with or without a reduction in VC. A reduced VC without evidence of expiratory slowing is a nonspecific finding. There was controversy among Workshop participants about using the term "restrictive" when VC is low. The majority thought it was acceptable to interpret the finding as indicating a "restrictive type of ventilatory impairment," or a "restrictive ventilatory defect" while recognizing that it does not necessarily indicate restrictive lung disease Others argued the interpretation should be descriptive only, in, simply noted as "reduced vital capacity" or "nonobstructive defect," and call for further testing, including lung volumes, to clarify its nature.

The VC, FEV,, and FEVJVC ratio are the basic parameters used to interpret spirometry. Although FVC is often used in place of VC it is preferable to use the largest VC, whether obtained on inspiration (IVC), slow expiration (EVC), or forced expiration (FVC), for clinical testing. The FVC is usually reduced more than IVC or EVC in airflow obstruction. Limiting primary interpretation of spirograms to three variables avoids the problem of simultaneously examining a multitude of measurements to see if any abnormalities are present, a procedure that will lead to an inordinate number of "abnormal" tests among the healthiest groups in a population (198, 199). Even 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 FEV,, FVC, and FEV_1/FVC ratio were examined and increased to 24% when a battery of 14 different measurements were analyzed (198).

The FEV_1/VC ratio is the most important measurement for distinguishing an obstructive impairment. Expiratory flow measurements other than the FEV_1 and FEVJVC should be considered only after determining the presence and clinical severity of obstructive impairment using the basic values mentioned above When FEV, and the FEVJVC ratio are within the expected range, abnormalities in flow occurring late in the maximal expiratory flow-volume (MEFV) curve should not be graded as to severity, and, if mentioned, interpretation of their clinical significance should be guarded. In the presence of a borderline value for FEV_1/FVC, however, they may help confirm the presence of airway obstruction. The same is true for average flows such as $FEF_{25-75\%}$. Even when used in this limited way, the wide variability of these tests in healthy subjects must be taken into account in their interpretation.

One should be cautious in interpreting obstructive dysfunction when the FEV, and VC are both above predicted even when the FEV_1/VC ratio is below the lower limit of normal since this pattern is sometimes seen in healthy subjects, including athletes. Tests other than spirometry, including lung volumes, diffusing capacity, and blood gas determinations allow amplifying statements on the overall pattern of the dysfunction observed during spirometry.

LOWER LIMITS OF "NORMAL" IN CLINICAL INTERPRETATION

Lower limits of normal are often used in clinical practice without thoughtful reflection about their inherent variability (5, 180, 181, 200–207) or their implications (5, 182). (See also sections DISTRIBUTION AND LOWER LIMITS OF NORMAL, DETERMINATION OF THE NORMAL RANGE, and CONCEPTUAL ISSUES CONCERNING NORMALITY AND THE LIMITS OF NORMAL.) Although clinical interpretation is usually straightforward when a pulmonary function result is well above or below a "lower limit of normal," this is not so when a measured value falls close to the "lower limit of normal." Predicting the presence or absence of disease requires knowledge about the distribution of dysfunction in various disease states and the prior probability of disease. For example, consider the meaning of a spirometric study that shows FEV, values and other expiratory flow rates to be just above the lower limit of normal. If the patient were a healthy male who sought medical assistance because he was disqualified for life insurance on the basis of his spirometry, it would be appropriate to interpret his spirometry as within normal limits. If, in contrast, the same data were obtained from a smoker with complaints of intermittent coughing and occasional wheezing, it would be appropriate to suggest that the study is consistent with mild obstructive dysfunction, although it could also represent a variant of normal. In both of these instances, computer printouts, or robotic physician interpretation that simplistically declare the results to be "normal" or "abnormal" on the basis of whether the observed values fall to one side or the other of a single number, could give information that does not perform a useful service to the patient. One suggestion for minimizing the problems of overly simplistic use of the lower limits of "normal" in the interpretation of lung function tests is use of terms such as 'Unusually low" rather than "abnormal" for tests close to the lower limit of normal.

ASSESSING SEVERITY

Severity scores are most appropriately derived from studies that relate pulmonary function test values to independent indices of performance such as ability to work and function in daily life, morbidity, and prognosis (208-212). For instance, in general, ability to work and to function in daily life relates to one's pulmonary function level. FVC and/or FEV,, which also relate to maximal $\dot{V}O_2$ and work effort, are used in several published systems to rate impairment (208, 209). Pulmonary function level is also associated with morbidity; those with lower function having more respiratory complaints (212). Lung function level is also associated with prognosis, including a fatal outcome from heart as well as lung disease (213, 214) even in patients who have never smoked (215). In the Framingham study, vital capacity was a major independent predictor of cardiovascular morbidity and mortality (213,214). In several occupational cohorts FEV, and FEV_1/FVC were independent predictors of all cause or respiratory disease mortality (216-218). In addition, a meta-analysis of mortality in six surveys in various U.K. working populations showed that the risk of dying of COPD was related to FEV, level. In comparison to those whose FEV, at initial examination was within 1 SD of average, those whose FEV, was more than 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 (219). A reduced FEV, also carries a 4- to S-fold excess risk of lung cancer mortality (adjusted for cigarette smoking) (220,221). Although there is good evidence that FEV, correlates with the severity of symptoms and prognosis in many circumstances (208. 211, 212, 219), the correlations do not allow one to accurately predict symptoms or prognosis for individual patients.

In clinical practice, predicted values are also used to grade severity. The severity of the spirometric abnormality is usually based on the actual or percent predicted FEV_1 in the case of obstructive disorders or on VC in nonobstructive disorders. An example of an algorithm sometimes employed for grading severity when nothing is known about the clinical question being asked is shown in table 13. It is intended only as an example and not as a standard. Its approach is based as much on clinical impression as on objective data. Although clinical experience has always played a major role in assessing severity, it can be enhanced by more exact methods, and physicians should probably view arbitrary severity scoring systems with caution.

Comments on the severity or significance of any abnormality depend on the circumstances under which a test is obtained. For example the assessment of severity of obstruction illustrated in table 13 may be relevant to COPD, but it would not be applicable to a patient with tracheal stenosis whose obstruction could be life-threatening and yet classified as only mildly reduced by this scheme

The VC has some relationship to the extent of loss of functioning lung parenchyma

TABLE 13

EXAMPLE OF CRITERIA FOR ASSESSING THE SEVERITY OF ABNORMALITIES*

A. Normal: The test is interpreted as "within normal limits" if both the VC and the FEV_1/VC ratio are in the normal range.

B. Obstructive abnormality: This is interpreted when the FEV_1/VC ratio is below the normal range. The severity of the abnormality might be graded as follows:

"May be a physiological variant"	% Pred FEV, ≥ 100
'Mild"	% Pred FEV, < 100 and ≥ 70
"Moderate"	% Pred FEV, < 70 and ≥ 60
'Moderately severe"	% Pred FEV, < 60 and ≥ 50
'Severe"	% Pred FEV, < 50 and ≥ 34
"Very severe"	% Pred FEV, < 34

C. Restrictive abnormality: This is most reliably interpreted on the basis ef TLC. If this is not available. one may interpret a reduction in the VC without a reduction of the FEV,NC ratio as a "restriction of the volume excursion of the lung." The severity of the abnormality might be graded as follows:

Based on the TLC	
"Mild"	% Pred TLC < LLN but ≥ 70
"Moderate"	% Pred TLC < 70 and ≥ 60
"Moderately severe"	% Pred TLC < 60
Based on spirometry	
"Mild"	% Pred VC < LLN but ≥ 70
"Moderate"	% Pred VC < 70 and ≥ 60
"Moderately severe"	% Pred VC < 60 and ≥ 50
Severe"	% Pred VC < 50 and ≥ 34
"Very severe"	% Pred VC < 34

Definition of abbreviation: LLN = lower limit of normal.

* This schema was contributed by Burrows and Lebowitz. It has been in use in the lung function laboratory at the Health Sciences Center in Tucson. Arizona for clinical purposes. It is intended only as an *example* of a transparent schema for assessing severity. Other schema may be acceptable as well. More work is required before any schema can be adopted as a standard. Note: All statements regarding severity should be accompanied by a disclaimer such as "as assessed by spirometry" or "physiologic assessments of seventy may differ from clinical assessments."

TABLE 14

CHANGE IN SPIROMETRIC INDICES OVER TIME

	Percent Chanaes Reauired to be Significant		
	FVC	FEV,	FEF_{25-75}
Within a day (222)			
Normal subjects	≥ 5	≥ 5	≥ 13
Patients with COPD	≥ 11	≥ 13	≥ 23
Week to week (222)			
Normal subjects	≥ 11	≥ 12	≥ 21
Patients with COPD	a20	≥ 20	≥ 30
Year to year (69)	≥ 15	≥ 15	

in many nonobstructive lung disorders. It is also of some use in assessing respiratory muscle involvement in certain neuromuscular diseases. Here again, however, the 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, and a relatively small decrement in VC may indicate the onset of a severe respiratory problem in patients with a rapidly progressive neuromuscular disease.

The FEV_1/VC ratio should not be used in isolation to determine the severity of an obstructive disorder. Both the FEV, and VC may decline with progression of disease, and an FEV_1/VC of 0.5/1.0 indicates more impairment than one of 2.0/4.0, though both yield a ratio of 50%. Systems that use FEV_1/FVC to grade the severity of obstruction must deal with the effect of total expiratory time on FVC and FEV_1/FVC (19).

CHANGES IN SPIROMETRY OVER TIME

Reliance should be placed on FEV, and VC for examining changes over time as they are the only spirometric variables that will consistently and correctly reflect the direction of the change in overall ventilatory function. Even using these simple tests, it is never easy to determine whether a change is "real" or only a result of test variability. All lung function measurements tend to be more variable when made weeks to months apart than when repeated at the same test session or even daily (222, 223). Changes should therefore be interpreted cautiously. It is more likely that a real change has occurred when there are a series of tests that show a consistent trend. As shown in table 14 significant changes, whether statistical or biologic, vary by parameter, time period, and the type of patient. For FVC and VC in healthy subjects, within-day change of 5% or more, between-weeks changes of 11 to 12% or more, and yearly change of 15% or more were generally thought by the Workshop to be clinically important.

The clinician seeing the patient can often interpret results of serial tests in a useful manner, not reproducible by any simple algorithm. For example, seemingly stable tests may prove very reassuring in a patient receiving therapy for a disease that is otherwise rapidly progressive. The same tests may be very disappointing if one is treating a disorder that is expected to improve dramatically with the therapy prescribed. Depending on the clinical situation, statistically insignificant trends in function may be very meaningful to the clinician. The greatest errors occur when one attempts 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 (69). Thus, in subjects with "normal" lung function, changes in VC or FEV, over 1 yr should probably exceed 15% (table 14) before any confidence can be given to the opinion that a meaningful year-to-year change has occurred.

Recommendations

Overall

TECHNICAL ISSUES

Although technical sources of variation in spirometry have been fully dealt with in other documents, it was considered important to reemphasize their key role, particularly in relation to the following points.

1. Laboratory directors should be constantly on guard to maintain the precision and accuracy of the measurements made in their laboratories and should be aware of the potential sources of technical variation. Quality control includes strict adherence to ATS guidelines for equipment performance and calibration.
2. Attention should be given to the spirometer temperature where the tests are performed. Temperature-related errors will be reduced when the spirometer temperature is between 17° and 40° C.
3. Computer calculations should be validated at the time equipment is purchased and after any changes are made in software or hardware.

BIOLOGIC VARIATION AND STATISTICAL ISSUES

1. Laboratory directors should be aware of the biologic Sources of within- and between-individual variation in order to optimize the application of lung function tests to a particular patient. A number of within-individual sources of variation fall within the domain and control of the laboratory, whereas between-individual sources of variation are important in selecting appropriate reference values.
2. Environmental sources of variation pertinent to a given patient are more likely to be known to the referring clinician than to

the laboratory director and should be used in evaluating the clinical pertinence of a given lung function report. Laboratory directors should request this information from clinicians.

3. Those who generate and report lung function tests should be aware of the strengths and weaknesses of the statistical techniques used to generate the prediction values used for interpretation. Laboratory directors and chest physicians should also be aware of the strengths and limitations of the statistical concepts of normality.

Selecting Reference Values

General Considerations

1. Because of unexplained differences between published reference values, no one set of reference values is likely to be applicable to all laboratories and all clientele under all circumstances. The choice of reference values should be a matter of careful consideration by laboratory directors. It should not be left to the judgment of manufacturers of automated equipment.
2. Laboratories should indicate the source of reference values on their reports.
3. Ideally, reference values should be based on data obtained using equipment and procedures that conform to current ATS recommendations. The prediction equations listed in tables 3 and 4 and published since 1981 conform to current ATS recommendations.

Epidemiologic Considerations

1. Reference values should not come from studies based on hospital patients.
2. Reference values for most clinical applications should be based on cross-sectional studies.
3. Subjects used to generate reference values should be free of respiratory symptoms and disease. It is preferable to choose reference values for men and women from the same population source.
4. Reference equations based on nonsmokers should be used for most clinical applications. The problems in making adjustments for the biologic effects of smoking lead to the recommendation that such adjustments should not be part of routine clinical interpretation. Such adjustments may, occasionally, be made to address specific questions.
5. Altitude may be important in the selection of reference values for flow rates and D_{LCO}.

Statistical Considerations

1. Prediction equations for adults should include age and height as independent variables. Usually, separate equations are used for men and women.
2. Linear equations perform adequately for adults though they may overpredict in young adults and underpredict in the elderly.
3. Prediction equations should come from studies that present lower limits of normal or present information from which such lower limits can be calculated.
4. Reference equations should, in general, not be extrapolated for ages or heights beyond those covered by the data that generated them. If, for example, one calculates a predicted FEV, for an 85-yr-old person from prediction equations based on a population younger than 65 yr of age, the report should contain a cautionary statement.
5. The choice of reference values should consider the ethnic origins of the clientele of the laboratory. Although it is preferable to use equations based on the ethnic origins of the subject being tested, this is not always possible or practical. For instance, if a laboratory only occasionally serves subjects of a particular ethnic group, it is acceptable to adjust for ethnic differences by using a scaling factor as suggested in table 9.

Lower Limits of Normal

1. Normal ranges should be based on calculated fifth percentiles. Estimates of fifth percentiles based on the SEE are acceptable for indices with distributions that are close to Gaussian.
2. Lower limits of normal are variable and, therefore, should not be considered as arbitrary limits that correctly classify all patients into normal and abnormal groups. Patient values that lie close to lower limits should be interpreted with caution.
3. The use of 80% of predicted for a lower limit of normal for adult pulmonary function parameters is not recommended. This criterion works only for average persons and for a limited number of parameters. It creates major errors when applied to $FEF_{25-75\%}$ and the instantaneous flows. Fixed percent of predicted values may be acceptable in children.
4. In adults, it is not acceptable to used a fixed FEV_1/FVC ratio as a lower limit of normal.

Other Considerations

1. It is preferable for North American laboratories to select reference value studies based on North American populations and European laboratories studies based on European populations because an important portion of the variation between population studies remains unexplained.
2. To assist in the choice of reference values, it may be useful to make an empirical assessment of how different equations relate to measurements made in 20 to 40 healthy subjects typical of the laboratory's clientele. If the distribution of these measurements is, on the whole, within the range predicted, the choice is probably suitable If this is not the case, the differences may be due to the laboratory (apparatus, technician, procedure) or it may be that the reference values are inappropriate for the laboratory's clientele. Both possibilities should be considered.

Recommendations for Interpretation

Overall Clinical Interpretation

1. Because interpretation of the lung function tests of an individual patient is best made in light of the clinical question asked of the tests, the clinician requesting the test should frame this question as precisely as possible. Likewise, the laboratory director responsible for seeing that the tests are carried out should insist that the clinical question be included in the requisition.
2. Interpreters of lung function tests should be conservative in suggesting a specific diagnosis based only on pulmonary function abnormalities.
3. Borderline "normal" values should be interpreted with caution. Such interpretations should, when possible, use clinical information in the decisions as to what is normal and what is abnormal.
4. The first step in interpretation is to evaluate and comment on the quality of the tests.
5. The number of test indices (e.g., FVC, $FEV_,$ etc.) used in interpretation should be limited to avoid an excessive number of false positive results.
6. The primary guides for spirometry interpretation should be VC (slow or forced), $FEV_,$ and FEVJVC.
7. Tests performed on children are best interpreted by those familar with pulmonary function in children.

Concerning Airway Obstruction

1. FEVJVC should be the primary guide for distinguishing obstructive from nonobstructive patterns.
2. Instantaneous and mid flows may be used to confirm the presence of airway obstruction in the presence of a borderline FEV_1/VC.
3. $FEF_{25-75\%}$ and the instantaneous flows should not be used to diagnose small airway disease in individual patients.
4. The pattern of a low FEVJVC ratio and greater than average VC and FEV, should be recognized as one that may occur in healthy individuals.
5. The severity of airway obstruction should be based on FEV, rather than FEVJVC.
6. Abnormalities in instantaneous flows and $FEF_{25-75\%}$ should not be graded as to severity when FEV, and FEVJVC are within the normal range

Concerning Bronchodilator Response

1. VC (forced or slow) and FEV, should be the primary indices used to judge bronchodilator response. Total expiratory time should be considered when using FVC to assess bronchodilator response since FVC increases in obstructed patients as expiratory time increases.
2. A 12% increase, calculated from the prebronchodilator value, *and* a 200-ml increase in either FVC or FEV, are reasonable criteria for a positive bronchodilator response in adults.
3. $FEF_{25-75\%}$ and the instantaneous flows should be considered secondarily in evaluating bronchodilator response If used, they must be volume-adjusted or the effect or changing FVC must be dealt with in the interpretation.
4. Ratios such as FEVJVC should not be used to judge bronchodilator response

5. Patients may respond to bronchodilator therapy even though a bronchodilator response is absent in a laboratory test.

CONCERNING RESTRICTION

1. The diagnosis of a restrictive lung abnormality is based on a reduced TLC. A reduced VC in the presence of a normal FEV_1/VC may be used to suggest but not diagnose the presence of restriction.
2. The severity of restriction should be based on TLC. If VC is used to infer the presence of restriction, severity may be based on VC.

This Statement was prepared by the participants of a Workshop on Lung Function Testing: Selection of Reference Values and Interpretative Strategies. The workshop participants were: MARGARET BECKLAKE, M.D., and ROBERT 0. CRAPO, M.D., Co-Chairpersons, A. SONIA Buts-r, M.D., BENJAMIN BURROWS, M.D., JACK L. CLAUSEN, M.D., ALLAN L. COATES, M.D., JOHN COTES, D.M., DOUGLAS W. DOCICERY, PH.D., REED M. GARDNER, PH.D., JOHN L. HANKINSON, PH.D., JAMES HANLEY, PH.D., ROBERT L. JOHNSON, JR., M.D., MICHAEL D. LEBOWITZ, PH.D., PAOLO PAOLETTI, M.D., RENE PESLIN, M.D., GEORGE POLGAR, M.D., PHILIP H. QUANJER, M.D., MELVYN S. TOCKMAN, M.D., SCOTT T. WEISS, M.D., M.S., MARY ELLEN B. WOHL, M.D.

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