Pulmonary Function Testing

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Objectives:

1. To understand the importance of test performance quality, normal range of values, and clinical context on interpretation of pulmonary function tests.
2. To recognize the distinct role of lung mechanics tests (particularly spirometry and lung volumes) and gas exchange tests in the evaluation of pulmonary impairment.
3. To develop a fuller understanding of the significance of the shape and pattern of the flow-volume loop and volume-time curves.
4. To recognize the pulmonary function test result patterns of abnormality found in various diseases.
5. To recognize the role of bronchoprovocation testing in excluding the diagnosis of asthma.

Key words: bronchoprovocation; diffusing capacity; lung volumes; spirometry; upper airway obstruction

Indications/Uses of Pulmonary Function Tests

When a physician orders pulmonary function tests (PFTs), there is an implicit question of diagnosis, quantification of impairment, or both. Indications include the following: (1) evaluation of a pulmonary complaint or sign; in this diagnostic role, the PFTs will indicate whether or not impairment is present and characterize it as obstructive or restrictive; (2) quantification of impairment in known disease; this may be part of the initial evaluation to quantify degree of severity, in follow-up to identify the need for initiation of treatment (*eg*, sarcoidosis), or to evaluate the response to therapy; (3) preoperative assessment to estimate risk for postoperative complications (nonthoracic surgery) or tolerance for lung resection (sometimes referred to as operability of the patient, in contrast to resectability of the tumor); and (4) disability evaluation.

Types of PFTs

Although the physiologic purpose of the lung is to maintain the normality of the arterial pH, P_{CO_2}, and P_{O_2} under varying conditions of oxygen consumption and carbon dioxide production, this goal is very dependent on the lung's behavior as a mechanical object. Physiologic tests of lung function can be separated into those that evaluate the lung as a mechanical object (volumes, flows, bronchodilator response, airway hyperreactivity [bronchoprovocation], compliance, resistance, maximal respiratory pressures, work of breathing) and those that focus on the gas exchange role of the lung (Pa_{O_2}, alveolar-arterial oxygen pressure difference [$P(A\text{-}a)O_2$], P_{CO_2}, physiologic dead space ventilation [V_D/V_T], diffusing capacity). Although lung disease tends to affect both the mechanical and gas exchanging functions of the lung, the degree of impairment can be discordant. For example, the combined use of spirometry and diffusing capacity will best characterize the degree of impairment in the initial evaluation of a patient with emphysema or interstitial lung disease.

General Approach to Interpretation

How are PFTs and BP measurements similar? Both are basic daily tools used to assess the severity of common diseases; we frequently take these tools for granted and assume the results are accurate. Yet, PFTs require significant patient effort and cooperation and must be conducted by personnel who can elicit such cooperation and recognize optimal test performance. A closer look at the "black box" will allow the technologist who performs the test, and the physician who interprets the results, to get the most out of the session.

When you sit down to interpret your patient's test, follow this series of conceptual steps:

- Is the test interpretable? The "garbage in, garbage out" principle requires that you scrutinize the graphic and numeric data of the each test component and assess the quality of the test performance. If you go directly to the single-page summary sheet, you may not recognize an unreliable test.
- Are the results normal? This requires accurate predictions of normal or reference values and recognition of the lower and upper limits of normal.
- What are the pattern and severity of abnormality? This involves categorizing the pattern as

obstructive vs restrictive, and rating as mild, moderate, or severe.

- What does this mean for this patient? PFT findings are usually nonspecific, so the final interpretation must take the clinical context into consideration. This is particularly important when results are at the borderline between normal and abnormal values.

Spirometry

This refers to the tests that can be measured with a volume-displacement spirometer, with volume as the measured variable and flow rates obtained by dividing volume into timed segments. It is now more common for flow to be the primary measurement, with integration of flow over time to obtain volume. Spirometry usually includes the measurement of the forced vital capacity (FVC); the slow vital capacity (SVC), often referred to simply as the vital capacity (VC); and the subdivisions of SVC, inspiratory capacity (IC) and expiratory reserve volume (ERV). Since other lung volumes (functional residual capacity [FRC], residual volume [RV], and total lung capacity [TLC]) require additional equipment, they are not measured directly in spirometric testing.

Basic spirometry testing, which measures the FVC, FEV_1 (volume exhaled in the first second of the FVC) and the FEV_1/FVC ratio, is readily available, inexpensive, and highly reproducible.

The FVC: Technique

The FVC begins with deep inspiration filling the lung as completely as possible (to TLC), followed by full exhalation with maximal effort to achieve the highest flow rates, with full exhalation down to RV, and then a rapid inhalation back up to TLC. This effort can be shown graphically as a flow-volume loop (FVL) or volume-time curve (V-t curve), both representing the same FVC maneuver (Fig 1).

Acceptability and Reproducibility Criteria

Examination of these curves is important to determine when an individual FVC measurement or trial has met the American Thoracic Society's (ATS) acceptability criteria for adequate effort (Table 1).[1] Full effort requires maximal force and duration, both of which are important.

Ideally, the FVL and V-t curve are printed for your review; both are helpful in recognizing a well-performed FVC (Fig 1). The FVL graphs flow vs volume, resulting in relative expansion of the graphic data for the first second, whereas the V-t curve gives equal spacing for each second, and the events marking the end of the test are easier to see. However, many office-based devices only print the FVL, which is the more useful of the two. Coughing is more easily recognized on the FVL because the rapid transients of flow cause large up and down spikes of flow.

The ATS criteria for spirometry apply acceptability criteria to individual FVC efforts (Table 1). ATS standards have been met when three acceptable efforts have been obtained, with the best and second best meeting reproducibility criteria (Table 2).[1]

Early maximal effort is important to avoid inaccurate measurement of the FEV_1. Submaximal effort is recognized graphically by a slow rise to the

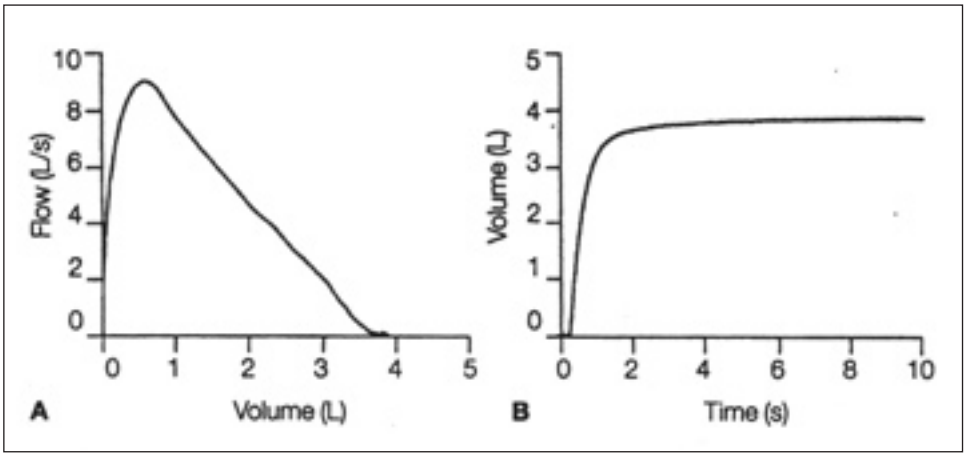

Figure 1. In a normal FVL, good early effort is shown by the rapid upstroke to a slightly rounded "sharp" peak flow (A). Good duration of effort is illustrated by the upward concavity at the end of exhalation, indicating slowing of airflow near RV. Patients with obstructive lung disease have deeper, upward concavity throughout exhalation on the FVL. Good duration of effort is seen on the volume-time curve by the plateau of volume change over time (B). (From J Respir Dis. 1999; 20:809-922; graphics modified from Am J Respir Crit Care Med 1995; 152: 1107-1136.)

peak flow, or by a rounding and broadening of the normal shape at the peak flow. Submaximal early effort is expressed quantitatively as extrapolated volume, often printed in the numerical section of the report (Figs 2 and 3).

Final Report Data

On the final report, the FEV_1 and FVC reported should be the largest values from any acceptable trial, not necessarily from the same maneuver. The "best test" curve should come from the trial with the largest sum of FVC + FEV_1. Other flow parameters come from this same curve. Generally, acceptable efforts are also reproducible. An exception is FVC trials that start exhalation at varying volumes below TLC but effort is maximal after that point, resulting in a normal-appearing FVL. The submaximal effort is recognized in this circumstance by the lack of reproducibility of otherwise acceptable efforts.

The 1994 ATS criteria for acceptable effort are less stringent than the 1987 guidelines. It turned out that many cooperative patients with severe lung disease could not produce FVC efforts meeting the stringent 1987 criteria, yet produced clinically useful studies.

A suboptimal test can be reported at the discretion of the interpreting physician, who recognizes which components were less reliable and keeps the clinical context in mind.[2] Once a test has been reviewed for quality, the next step is to decide if individual test parameters are abnormal. Depending on the overall pattern and the clinical situation, the interpreting physician may discount a single abnormal parameter.

Conversely, several borderline values may be interpreted as significant if the overall pattern is consistent with an expected disease. For example, borderline low flow rates and diffusing capacity with borderline elevated lung volumes are suggestive of emphysema.

Table 1 — *ATS Acceptability Criteria for FVC**

- Smooth continuous curve (free from artifacts, such as cough in the first second)
- Good Start of Test
  - Extrapolated volume < 5 % of FVC or 150 mL, whichever is larger (see Fig 2)
  - Time to peak flow ("rise time") < 120 ms (optional)
  - Note:. FEV_1 can be overmeasured or undermeasured with submaximal effort (see Fig 3)
- Good End of Test
  - Reaches plateau of 1 s (no further volume exhaled despite continued expiratory effort)

    —*OR*—
  - "Reasonable" duration of effort
    → minimum of 6 s
    → "optimal" 10 s
    → "exhalations longer than 15 s will rarely change clinical decisions"

* Modified from Am J Respir Crit Care Med 1995; 152:1107-1136.

Lung Volume Measurements

Definitions

A lung volume is called a "volume" if it cannot be broken down into smaller subcomponents (Fig 4):

- RV
- ERV
- Tidal volume (V_T)
- Inspiratory reserve volume (IRV)

Lung "volumes" that are made up of the addition of other lung "volumes" are referred to as "capacities":

- FRC = RV + ERV
- Inspiratory capacity (IC) = V_T + IRV
- VC = ERV + IC
- TLC = RV + ERV + V_T + IRV, or VC + RV, or FRC + IC

Directly and Indirectly Measured Lung Volumes

A source of confusion is that not all volumes are measured directly, so that errors in measurement can be carried over when an incorrect value is used in calculating other volumes or capacities.

Table 2—*ATS Acceptability and Reproducibility Criteria for FVC**

- After three acceptable maneuvers (Table 1), if the largest FEV_1 and FVC values are within 200 mL of each other, the session is completed
- If not, continue spirometry until criteria are met; OR a total of eight trials have been done; OR the patient cannot or should not continue testing
- Final Report
  - FEV_1 and FVC reported as the largest values from any acceptable trial
  - "Best Test" curve from trial with largest sum FVC + FEV_1
  - Other flow parameters from best test curve

* Modified from Am J Respir Crit Care Med 1995; 152:1107-1136.

FRC is measured directly because it is a reproducible lung volume in the relaxed, tidally breathing subject (Fig 4). It represents the resting or relaxation lung volume, a result of the balance between the inward force of the lung, outward force of the chest wall, and inactive inspiratory and expiratory muscles. This measurement is combined with a separately performed SVC maneuver, from which IC and ERV are also measured. Combinations of the data from these two separate measurements are used to obtain the other lung volumes in this manner:

- RV = FRC – ERV
- TLC = FRC + IC, or RV + VC

Viewed in this manner, RV and TLC are not directly measured. Their accuracy depends on accurate measurements of the volumes or capacities from which they are obtained. Pitfalls in the measurement of SVC and its subcomponents are demonstrated in Figure 5.

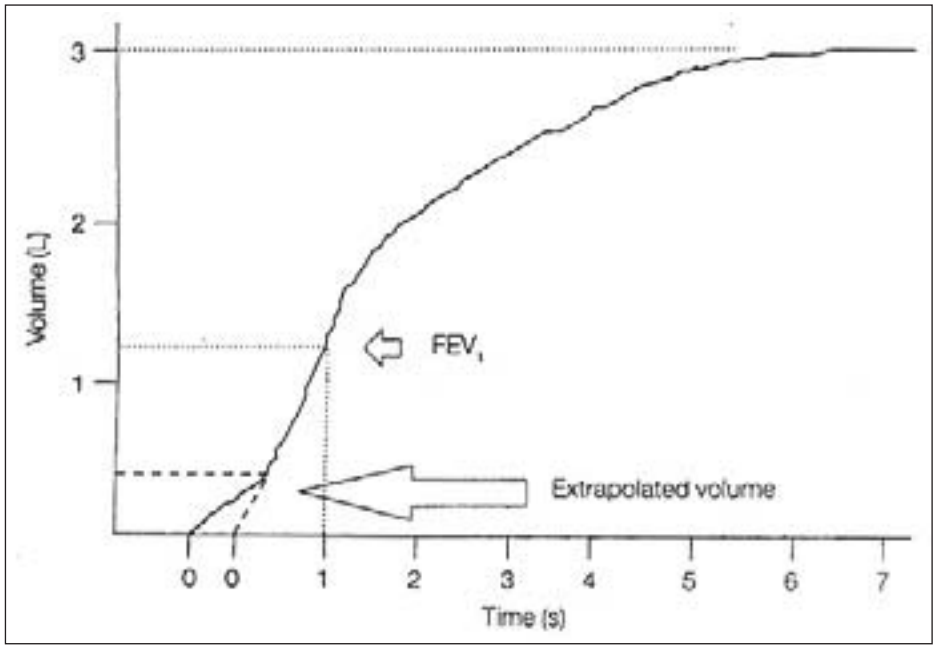

Figure 2. Back extrapolation. The volume-time curve can be inspected for a slow start and corrected for a submaximal initiation of exhalation. A line is drawn tangential to the steepest slope (the peak flow), and the patient's actual curve is corrected to a theoretical one that would be achieved with maximal effort. Where this extrapolated curve intersects the x axis is the adjusted time zero (start of FEV_1). The extrapolated volume quantitatively describes the volume of the actual curve that was replaced with extrapolated data. Measurements from curves with extrapolated volumes < 5% of the FVC or 150 mL (whichever is larger) are acceptable. (From J Respir Dis 1999; 20:809-822.)

	Trial 1	Trial 2	Trial 3
FEV_1	1.89 (62%)	1.94 (65%)	2.12 (71%)
FVC	3.57 (95%)	3.68 (98%)	3.08 (82%)
FEV_1:FVC	.53	.53	.69
Extrapolated volume	.05	.09	.19
Expiratory time (s)	13.6	15.4	5

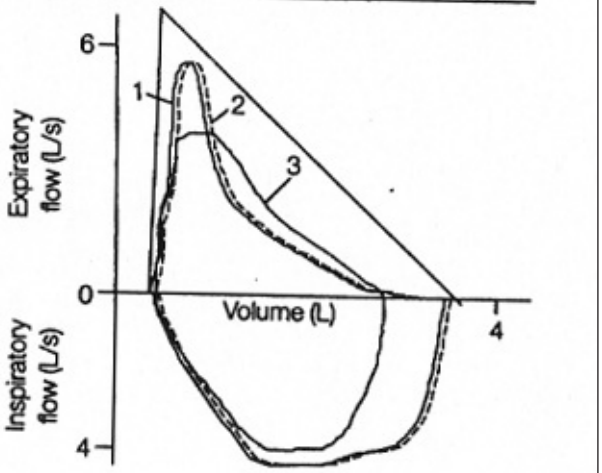

Figure 3. Two of the three FVLs meet the criteria developed by the ATS. Trials 1 and 2 are acceptable; they are concave upward near end-expiration, showing the normal slowing of expiratory flow as RV is reached. Trial 3 is unacceptable: the back extrapolation is too large and the peak flow is widened, indicating poor early effort. The expiratory time of 5 s and the downward concavity at end-expiration show premature termination of effort. Although the highest FEV_1 is in trial 3, it should not be reported because it comes from an unacceptable effort. This patient has moderate obstructive dysfunction (see Table 4). (From J Respir Dis 1999; 20:809-822.)

Measurement Techniques: Plethysmography, Gas Dilution, and Radiographic Planimetry

In normal subjects, the same values for FRC and TLC will be obtained whether measured by gas dilution (He dilution or N_2 washout), plethysmography, or planimetry (geometric) measurement from a chest posteroanterior and lateral radiograph. Gas dilution and wash-out techniques will underestimate FRC (and therefore RV and TLC) in patients who have severe inequality of the distribution of ventilation, such as those with severe airways disease. Areas of lung with a long time constant (directly proportional to resistance and compliance) fill and empty slowly and so will not be "seen" by the wash-in and wash-out techniques. Bullae are an extreme example of this poorly communicating lung. Conversely, plethysmographic techniques measure all intrathoracic gas, whether it communicates with the airways or not.

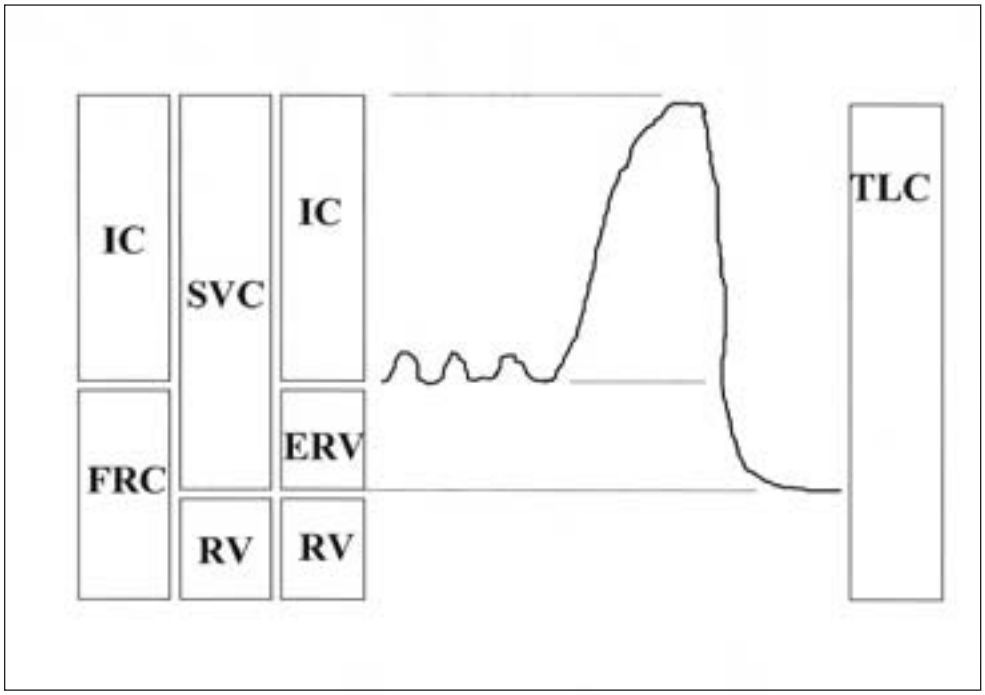

Figure 4. The static lung volumes.

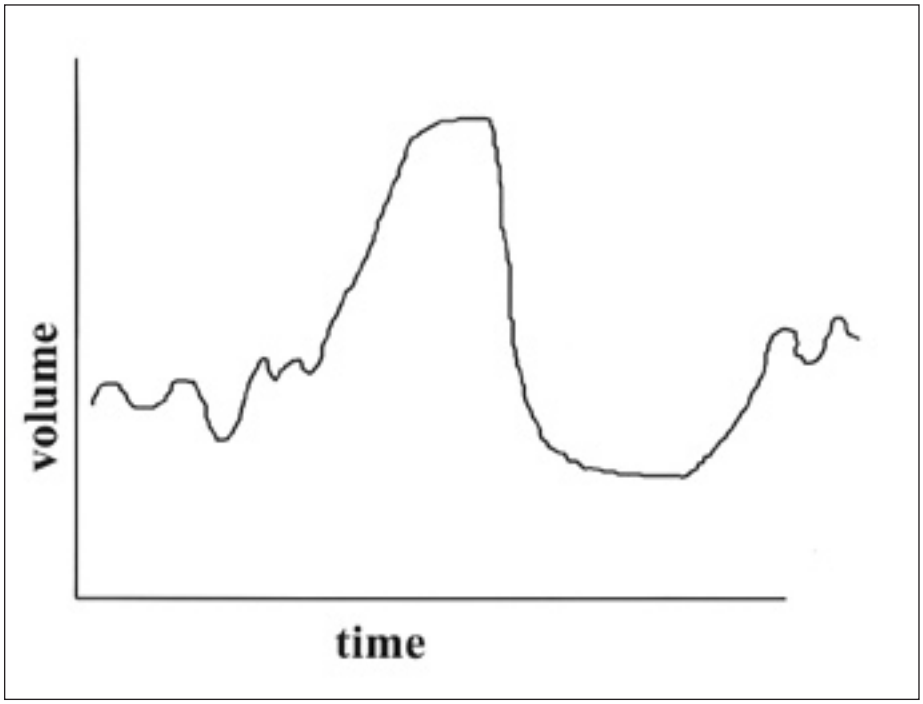

Figure 5. SVC maneuver. The SVC portion was well performed as demonstrated by the slowing of flow near full lung inflation, and near full exhalation. However, the lack of a stable end-expiratory baseline during tidal breathing will result in incorrect values for ERV and IC, the subcomponents of SVC. This will also result in incorrect values for TLC and RV, when derived from arithmetic use of FRC, IC, and ERV.

Plethysmographic techniques have become the gold standard for measurement of lung volumes. Recent data indicate that FRC (and therefore RV and TLC) can be inaccurately "overmeasured" in patients with severe airflow limitation. Plethysmographic technique assumes that mouth and alveolar pressures are equal while the subject pants against a closed shutter. This is based on the simple concept that if there is no flow between two points, pressure has to be the same at these two points. With a closed shutter at the mouthpiece, alveolar and mouth pressure should be the same. However, severe airflow limitation results in slow to-and-fro flow during panting, such that alveolar pressure is above mouth pressure (as in intrinsic positive end-expiratory pressure), resulting in a falsely high measurement of FRC, or thoracic gas volume (TGV), as it is commonly called in plethysmography. Fortunately, this small error is in the direction that enhances the ability to recognize the underlying disease (patients with airflow obstruction demonstrate hyperinflation). Most still consider plethysmographic measurements to be the most accurate technique for lung volume measurements.

Another approach to lung volume measurements in the body box is to measure the TGV with a closed shutter, followed immediately by a complete inhalation maneuver (IC) up to TLC. This can improve accuracy of the TLC measurement by adding each TGV measurement to its directly coupled IC measurement.

Predicting Normal Values

This is a difficult problem in the interpretation of PFTs.[1,2] Unlike blood pH, which has a narrow range of normal, PFT parameters vary greatly in normal people. Predicting PFTs is like determining the shape of a normal nose, another body part. It depends on height, age, sex, and racial and ethnic background. Weight and body mass index are also a factor, particularly at extremes, but most reference equations do not include this parameter, since its role is more minor.

In addition, test parameters in patients with mild disease overlap the values found in normal individuals. This creates uncertainty when values are near the low or high range of normal. The most reasonable approach is to consider the clinical context when interpreting the test, express the uncertainty in the report, and perhaps order additional tests (such as bronchoprovocation for borderline obstructive cases) or start empiric therapy and look for changes on subsequent PFTs.

Percent Predicted as Normal Range

The time-honored approach has been to consider a fixed percentage above and below a predicted value to be the normal range. This is 80% to 120% of predicted for FVC and FEV_1, although a wider range is found for most other parameters (Table 3). This has been criticized as having no sound statistical basis, merely representing the range of these values in middle-aged individuals of typical height.[2]

95% Confidence Interval as Normal Range

A sounder statistical approach, although not available for all parameters, is the 95% confidence interval, the range of values in which 95% of healthy people fall. This method also has its problems; for some reference equations, it identifies a normal range by subtracting or adding a fixed number (the confidence interval) to the predicted value of all people. This can create a very wide range of normal in a shorter, older person and a very narrow range in a taller, younger person. I use the percent and confidence interval approaches when interpreting the overall pattern of the study, recognizing that normal values are most difficult to predict in older, shorter people.

Ethnic and Racial Differences in Normal Values

The most widely used prediction equations come from white populations of northern European ancestry. Studies of other groups find lower

Table 3—*Normal Predicted Ranges of Selected Pulmonary Function Variables, as a Percent of Predicted**

Parameter	Normal Range, % Predicted
FEV_1	80-120
FVC	80-120
FEV_1/FVC	± 0.05 of predicted ratio
FEF_{25-75}	> 65% of predicted or FEF_{25-75}/ FVC > 0.66
TLC	80-120
FRC	75-120
RV	75-120
D_{LCO}	75-120

* Upper and lower limits are approximate; 95% confidence intervals for these variables should also be considered for interpretation.

predicted values when they are obtained using standing height.[2] Blacks are the other group that has been most widely studied. When using prediction equations from a white population, the following adjustments can be made for patients of African ancestry: FEV_1, FVC, and TLC, 12% lower; FRC and RV, 7% lower; FEV_1/FVC, no change; diffusing capacity of the lung for carbon monoxide (D_{LCO}), 2 mL/min/mm Hg or 7% lower.[2] The major factor is longer legs and shorter torsos in blacks vs whites of a given height, but socioeconomic factors and body mass index are also factors.[3] Those of mixed racial ancestry have intermediate values.

National Health and Nutrition Examination Survey III Spirometric Reference Equations

In a given laboratory, a single reference equation can be used with an adjustment factor as described above (*eg*, a coefficient of 0.88 × predicted Caucasian FVC or FEV_1 for an African-American). An alternative is to use different equations for different populations. An example is the more up-to-date spirometric reference values from the National Health and Nutrition Examination Survey (NHANES III)[4] that were published in 1999. This study has the virtue of size and diversity of the study population. It provides different reference equations for male and female individuals who are Caucasian, African-American, and Mexican-American. The study suggests that differences were partially due to body build. Mexican-Americans were shorter than Caucasians of the same age, and African-Americans had a smaller trunk:leg ratio on average.

Age and PFT Values

The lung grows throughout childhood and PFT parameters increase in parallel, reaching a peak in late adolescence or in the third decade of life. Female subjects attain peak PFT values earlier than male subjects, but these are numerically smaller even when adjusted for height. After the peak, most test values decline steadily with age. The exception is RV, which increases with aging. As RV increases and VC decreases, TLC remains relatively constant. The FEV_1/FVC ratio declines with age, being highest in young children and decreasing through adolescence and beyond.

Recognizing Obstructive vs Restrictive Patterns

Obstructive Pattern

If FVC and/or FEV_1 is below normal, the distinction between obstruction and restriction is based on the FEV_1/FVC ratio. A reduced ratio is the hallmark of the obstructive pattern. The precise threshold for calling a ratio low is unclear. The National Institutes of Health/World Health Organization GOLD Guidelines for COPD management recommends use of a ratio below 0.70 for the diagnosis of COPD, citing the simplicity of this approach and the lack of an internationally-accepted set of reference equations.[5] The second National Asthma Education Program Guidelines[6] sponsored by the National Institutes of Health recommended the use of 0.65 as the lower limit of normal for FEV_1/FVC. The ATS guidelines for interpretation of PFTs discourages the use of a fixed FEV_1/FVC ratio to define the lower limit of normal. The lower limit of normal that can be estimated from most reference equations is about 0.08 to 0.10 below the predicted value. For example, from the NHANES III dataset,[4] a 15-year-old Caucasian boy has a predicted FEV_1/FVC of 0.85 and a lower limit of normal of 0.75; a 70-year-old Caucasian man has a predicted FEV_1/FVC of 0.73 and a lower limit of normal of 0.64. Recognizing the uncertainties of the predicted values, and the overlap of mild disease with the lower range of normal, I generally consider a ratio that is at least 0.05 below the expected ratio to suggest obstructive dysfunction in the context of a patient with suggestive clinical features (pretest probability is high), especially when FEV_1 is in the low range of normal. Currently, that approach is in the realm of the art of interpretation. Others prefer to read the PFT in a more strict statistical fashion, acknowledging that some patients with mild obstructive or restrictive lung disease have "normal" PFT findings. Use of the term "borderline" in PFT interpretation is an acceptable and honest option.

The FVC may be less than the SVC in patients with obstructive dysfunction because the forced maneuver causes dynamic compression of the airways and premature closure of airways during expiration. For this reason, some areas of western Europe use the Tiffeneau Index (FEV_1/inspiratory VC) as the preferred marker for airflow obstruction.

Caution is needed when a reduced FEV_1/FVC ratio is found in a patient with an FEV_1 in the normal

range. In this situation, particularly when the FEV_1 is above 100%, the low ratio may be a normal variant. It is a paradox of PFTs that the lung volume measurements are most helpful in the borderline abnormal cases. In this situation, the presence of hyperinflation helps identify the obstructive pattern, or a low TLC confirms restriction when the FEV_1/FVC is not clearly outside the normal range.

FEV_6 As a Surrogate for FVC To Define Airflow Obstruction

Serial measurements of FVC require repeated forceful exhalations to RV. This can be difficult for the patient and time-consuming for the technologist. The ATS guidelines have suggested that 6 s is a minimum criterion for acceptable exhalation du-

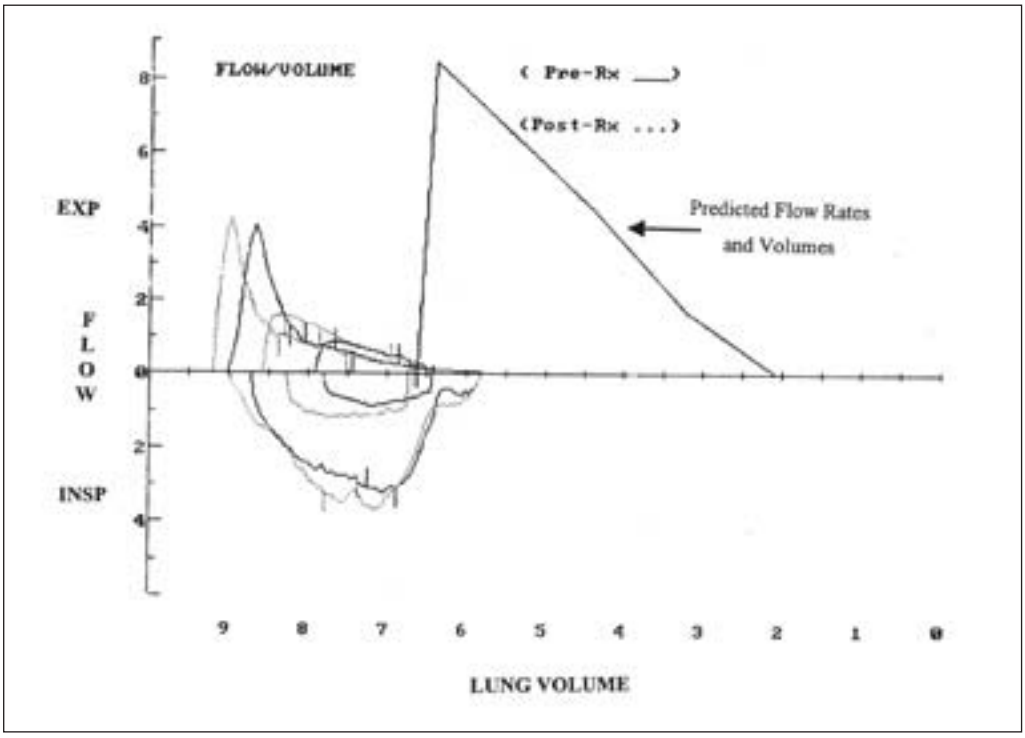

Figure 6. Severe obstructive dysfunction and hyperinflation of FRC and TLC, and air trapping (elevated RV) is shown in this FVL, which was placed at absolute lung volumes using data from lung volume measurements obtained during the same testing session.

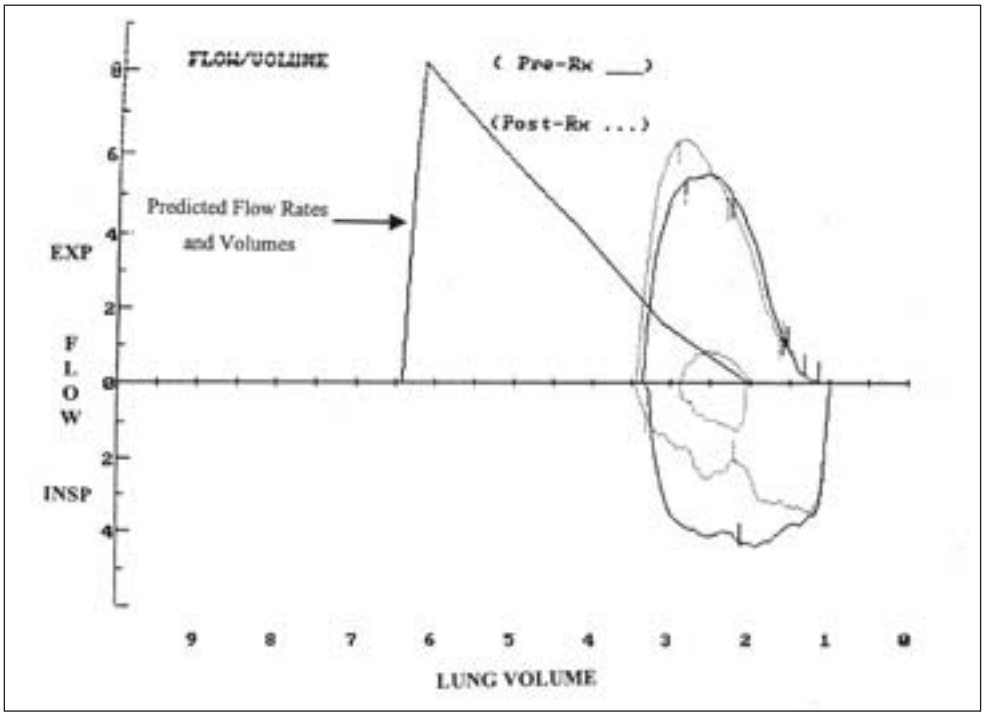

Figure 7. Restrictive dysfunction is shown in this FVL, which was placed at absolute lung volumes using data from lung volume measurements obtained during the same testing session.

ration. The NHANES III reference equations[4] have provided predicted values for the forced expiratory volume in 6 s (FEV_6) and FEV_1/FEV_6 in addition to FVC and FEV_1/FVC. One study has found the sensitivity of FEV_1/FEV_6 for diagnosing airway obstruction defined by FEV_1/FVC was 95.0% and the specificity was 97.4%.[7] When interpretations differed, the measured values were near the lower limits of the reference range.

Restrictive Pattern

A normal or elevated FEV_1 /FVC ratio with a low FEV_1 or FVC suggests "restriction," although full lung volumes (TLC, RV, FRC, SVC, IC, and ERV) are needed to confirm true restrictive dysfunction.[2] In patients who have underlying obstructive lung disease, spirometry can show "pseudorestriction," which is often recognized by hyperinflation on lung volume testing or bronchodilator responsiveness of the "restriction."

Graphic Evaluation of FVL at Absolute Lung Volumes

PFT systems that measure spirometry and lung volumes often combine the data on a single graphical image. This has the advantage of allowing the user to recognize airflow obstruction (scooped FVL) and hyperinflation (shifted to the left) at a glance (Fig 6). Restriction is recognized as a normal-shaped but smaller loop shifted to the right (lower lung volumes) (Fig 7). Often a restrictive loop will look like a tall-masted ship, with a short bow-stern length (reduced VC) but relatively high mast (flow rates are high in relation to the VC). In restriction, flow rates may be absolutely low in relation to the predicted values, yet they are high in relation to the FVC. This can be seen in the elevated FEV_1/FVC or forced expiratory flow at 50% of FVC ($FEF_{50\%}$)/FVC ratio (normal, 0.8 to 1.2), or forced expiratory flow at 75% of FVC ($FEF_{75\%}$/FVC (normal, 0.25 to 0.50). In addition, when the FVL is placed on the graphic at absolute lung volume, one sees that flow is high for that absolute lung volume (Fig 7).

Rating of Severity

Once the pattern of abnormalities is defined (obstruction vs restriction), the severity is rated. A commonly used system is from the ATS statement on reference values and interpretative strategies (Table 4).[2] Severity in an obstructive pattern is determined by the FEV_1; in restrictive patterns, by TLC; and in presumed "restrictive" patterns (when full lung volume measurements were not obtained), based on the FVC. I use both the FVC and TLC to rate the severity of restriction.

An easy way to remember the cutoff points is that severe is less than half of predicted, very severe is a third of predicted or less, and mild is above 70% (but an abnormal pattern). Moderate (60 to 69%) and moderately severe (50 to 59%) fill in the deciles between mild and severe. Our experience with lung volume reduction surgery for emphysema has zoomed our focus in the low range and I now refer to those < 25% as very, very severe. When FEV_1/FVC is low but the FEV_1 is in the normal range, it may be a normal variant, particularly when the FEV_1 is > 100%. The clinical presentation plays a large role in distinguishing normal from minimally abnormal in this circumstance.

In addition, the diffusing capacity has an important role in assessing severity in both emphysema and interstitial lung disease, and contributes independent information from the mechanics measurements (flows and volumes).

Table 4—*Rating of Severity of PFTs**

Rating	Obstruction: % Predicted FEV_1	Restriction: % Predicted TLC	Presumed Restriction (Without Measurement of TLC): % Predicted FVC
Possible Normal Variant	≥ 100		
Mild	70-99	70-lower limit of normal	70-lower limit of normal
Moderate	60-69	60-69	60-69
Moderately Severe	50-59	< 60	50-59
Severe	34-49		34-49
Very Severe	< 34		< 34

*The rating of severity is determined after the pattern is determined to be obstructive or restrictive. A low FEV_1/FVC ratio with an FEV_1above 100% is likely to be a normal variant; between 80% and 100% it may be mild or normal variant depending on the clinical situation. (Modified from Am Rev Respir Dis 1991; 144:1202-1218.)

The GOLD Guidelines for COPD[5] introduced a combined clinical-physiologic severity rating system for educational purposes that differs from the system described above. In this system, at-risk patients (stage 0) have cough and sputum but spirometry is normal. Mild (stage I) is applied when $FEV_1/FVC < 0.70$ but $FEV_1 \geq 80\%$ of predicted. Moderate is used for FEV_1 values from as low as 30% to as high as 79% of predicted, although there is a divide into Stage IIA (50 to 79% of predicted) and IIB (30 to 49% of predicted). Severe is reserved for COPD patients with an $FEV_1 < 30\%$ of predicted, respiratory failure ($Pa_{O_2} < 60$ mm Hg or $Pa_{CO_2} > 50$ mm Hg), or cor pulmonale.

Bronchodilator Response

ATS and European Respiratory Society Criteria for Bronchodilator Response

These organizations consider a significant intrasession bronchodilator response to be an increase from baseline FEV_1 or FVC > 12% *and* 200 mL.[2,8] These criteria reflect that the upper limit of normal bronchodilator response is about 8%, and that a 12% change without a 200-mL increase could be "noise" in a patient with a very low prebronchodilator FEV_1 or FVC. Testing should be done with a bronchodilator with a rapid onset of action (typically albuterol), usually with a metered-dose inhaler and a spacer device. Bronchodilators should be stopped for a time consistent with their duration of action when bronchodilator responsiveness is being assessed.

Alternate Tests of Bronchodilator Response

Failure to demonstrate intrasession, acute bronchodilator response by these criteria does not indicate their lack of clinical utility. Pre- and postbronchodilator lung volume testing may demonstrate a decrease in dynamic hyperinflation and trapped air (reduced FRC, RV, and TLC) such that significant improvement in flow at the same lung volume may be observed, despite an unchanged FEV_1 and FVC. This comparison of flow at the same lung volumes is referred to as isovolume flow (*iso* means same).

A less well-accepted test of bronchodilator responsiveness is improvement in flow at low lung volumes (*eg*, forced expiratory flow from 25 to 75% of the VC [$FEF_{25-75\%}$], referred to as midexpiratory flow in the past). Since the midflow section is always defined by the VC in which it resides, comparisons pre- and postbronchodilator need to be adjusted to reflect flow through the same range of volumes ($isoFEF_{25-75\%}$), rather than from an unadjusted $FEF_{25-75\%}$. I accept an improvement in $isoFEF_{25-75\%}$ of ≥ 35% as suggestive of bronchodilator responsiveness when taken from a study with excellent reproducibility (Fig 8).

Lastly, patients who show no intrasession bronchodilation may demonstrate improved flow between testing sessions separated by a few weeks if they are placed on a bronchodilator regimen in the interval.

Bronchodilator testing may be useful for the following reasons: along with other clinical data, it helps distinguish asthma from COPD, helps assess compliance or poor inhaler technique when the patient demonstrates in-laboratory bronchodilation despite continuing to take the medication for the testing session, and prognosis. Failure to demonstrate laboratory bronchodilator response should not prevent the use of these medications in a patient who reports subjective benefit.

Diffusing Capacity

Technique

The subject exhales to RV and then rapidly inhales a gas mixture containing a minute amount of CO. After a 10-s breath-hold at TLC, the patient rapidly exhales and the exhaled gas is analyzed to measure the amount of CO transferred into the capillary blood during the maneuver.

Concepts

The single-breath D_{LCO} measures the capacity of the lung to transfer gas, using the test gas carbon monoxide. Known as the transfer factor (T_{LCO}) in Europe, the units are mL/min/mm Hg, so it can be thought of as the flow rate (mL/min) of CO gas per mm Hg of CO pressure gradient from alveolus to capillary blood.

In general, the transfer of different gases from alveolus to capillary can be thought of as perfusion-limited, diffusion-limited, or a combination. Acetylene is so insoluble in blood that as soon as some diffuses into the capillary, no more gas can transfer until that volume of capillary blood has passed into the pulmonary venule and additional

blood arrives without acetylene present. Acetylene's uptake is perfusion-limited, so its transfer is a good measure of cardiac output.

CO is so avidly bound to hemoglobin that little back-pressure develops in the capillary to slow its transfer from alveolus to blood as a given volume of capillary blood makes its transit through the capillary bed. Consequently, its transfer is not dependent on cardiac output. It is dependent on the volume of the capillary bed and the hemoglobin concentration, as they increase the available mass of hemoglobin, which is the site of CO binding. The transfer of CO also depends on the properties of the alveolar-capillary interstitium (surface area and thickness). CO is diffusion-limited rather than perfusion-limited, and is ideal for assessing the lung's capacity to transfer gas. In addition, since little back-pressure of CO develops in the capillaries as a result of its transfer, the driving pressure for CO transfer can be measured from alveolar CO concentration alone without the measurement of blood CO (except in the tobacco user).

The transfer of O_2 is affected by both perfusion and diffusion, and the venous back-pressure opposing diffusion must be known in order to measure its transfer rate. These characteristics make CO a superior gas to O_2 for measuring the lung's capacity for transferring gas, and is also more sensitive than O_2 measurements for detecting mild impairment.

Disease Processes Causing Abnormalities of Diffusing Capacity

Diffusing capacity is decreased in conditions that disrupt the alveolar-capillary surface for gas transfer. This can occur due to loss of surface area (pulmonary resection, pulmonary fibrosis, emphysema, pneumonia); reduced lung capillary volume

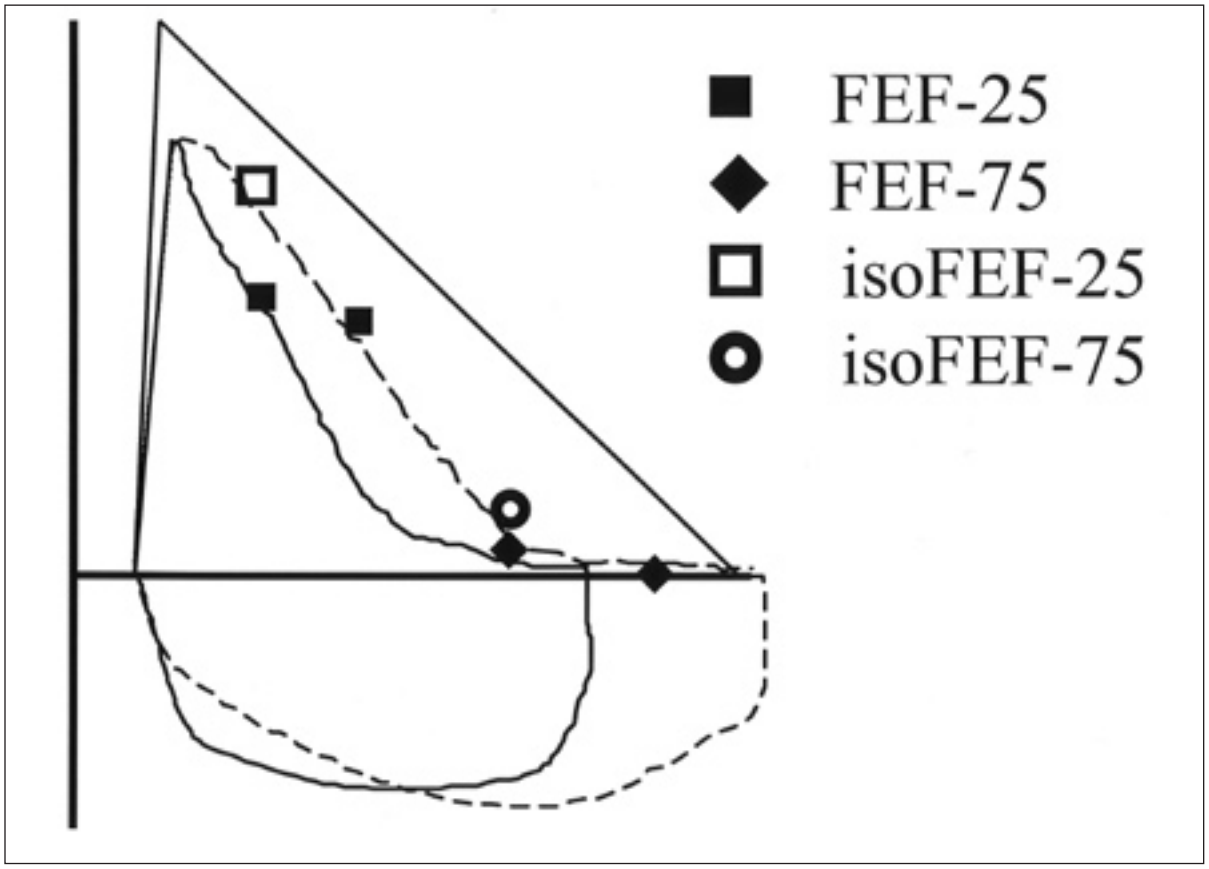

Figure 8. FVL before (solid line) and after (dotted line) bronchodilator. The instantaneous flows at 25% and 75% of the vital capacity (FEF_{25} and FEF_{75}) and the flows between these two points, the forced expiratory flow from 25 to 75% of the vital capacity (FEF_{25-75}), known as the maximum midexpiratory flow in the past, is defined from the FVC in which it occurs. When comparing the flow before and after bronchodilator, one wishes to know if flow has improved at the same lung volume predrug and postdrug. The isovolume flow (for example, $isoFEF_{25-75}$) references the postbronchodilator flow segment to the same lung volume before the drug to allow this comparison. In this example, the isovolume flows show improvement in flow rates, whereas the flow rates defined in the usual way appear to have decreased because of the large FVC response to bronchodilator.

(pulmonary vascular disease including vasculitis, pulmonary thromboembolism, and primary pulmonary hypertension; and also in emphysema and interstitial lung disease); or increased diffusion distance (pulmonary alveolar proteinosis, *Pneumocystis carinii* pneumonia).

It is increased by conditions that lead to recruitment of the pulmonary vascular bed and increase in the capillary blood volume (exercise, mild congestive heart failure, left-to-right shunt, asthma), or by an increased amount of hemoglobin, which binds CO (pulmonary hemorrhage, erythrocytosis).

Isolated Reduction in Diffusing Capacity

It is a well-established clinical pearl that isolated reduction in diffusing capacity (with normal flow rates and diffusing capacity) suggests disease in the pulmonary vascular compartment (primary or thromboembolic pulmonary hypertension, or pulmonary vasculitis) or early/mild interstitial lung disease. Recent data indicate that we should also consider emphysema in this setting. Patients may have normal or near-normal FEV_1, FVC, and FEV_1/FVC associated with more marked abnormalities of diffusing capacity, and CT or pathologic evidence of emphysema.[9] In contrast to the low diffusing capacity seen in emphysema, asthmatics tend to have high-normal or frankly elevated diffusing capacity.[10] The increased diffusing capacity is related to physiologic and technical factors. The major factor is most likely increased capillary blood volume (and therefore hemoglobin to take up CO) when the asthmatic takes a forced inspiratory VC against high airways resistance before performing the DLCO breath-hold.

Hemoglobin and Carboxyhemoglobin Adjustments of Measured DLCO

Be wary of DLCO values that are reported without adjustment for hemoglobin. Patients with anemia have a lower measured DLCO, and patients with erythrocytosis have an elevated DLCO. You should report the measured DLCO and "adjusted" or "corrected" DLCO, but interpretation and trending should be based on the adjusted measurement. The absolute adjustment, and the adjustment per g/dL of hemoglobin deviation from normal (14.6 g/dL for men and 13.4 for women), increases with increasing anemia. A hemoglobin concentration of 12 requires an 8% adjustment in the measured value; a hemoglobin of 10, an 18% adjustment; and a hemoglobin of 7, a 45% adjustment.[11]

Patients are instructed not to use tobacco before their PFTs to minimize the effect of capillary CO in reducing CO transfer from the alveoli, and a lower measured DLCO. Although the ATS statement considers it optional, we adjust for this back-pressure by routinely measuring the carboxyhemoglobin (COHb) on a cooximeter if we obtain an arterial blood gas, or from the venous sample obtained for the hemoglobin adjustment. The adjustment is only 1% of the measured DLCO per %COHb. In our urban practice, we find that nonsmokers typically measure between 1% and 2% COHb from metabolic and environmental sources, so the adjustment is not essential. However, a smoker who does not comply with instructions to abstain from tobacco use prior to the test may have a COHb of 5 to 10%, a source of error for which we prefer to correct.

Diffusing Capacity Per Unit Lung Volume

There is a common misconception regarding the use of the volume adjustment for DLCO based on the observation that DLCO measurements will be reduced when measured below true TLC.[11] Consequently, some clinicians have incorrectly inferred that a low DLCO with a normal DLCO per unit lung volume (DLCO/VA) rules out an intrinsic lung problem. Indeed, this is consistent with an extrapulmonary cause of restriction, such as chest wall, pleural, or neuromuscular diseases. However, a normal DLCO/VA does not rule out interstitial lung disease. Conversely, a *low* DLCO/VA does suggest parenchymal lung disease (*eg*, interstitial lung disease, emphysema, or pulmonary vascular disease).

It is more useful to think of the DLCO/VA as a ratio that tells you whether there is proportionate defect in mechanics and gas exchange (normal DLCO/VA) or proportionately greater abnormality in gas exchange (low DLCO/VA) (Fig 9).[12] Patients with interstitial lung disease or other lung parenchymal disorders can have normal or low DLCO/VA; patients with extrapulmonary restriction can have normal or high DLCO/VA.

Diffusing Capacity in Interstitial Lung Diseases

The most sensitive tests for demonstrating abnormalities in early or mild interstitial lung disease

is DLCO and P(A-a)O_2 during exercise, both of which may be abnormal when flow rates, lung volumes, and blood gases at rest are normal. Although DLCO and DLCO/VA tend to be lower in idiopathic pulmonary fibrosis compared with other interstitial lung diseases, the pattern of abnormalities on PFTs does not have sufficient specificity to be helpful in the differential diagnosis of interstitial lung disease. Serial PFTs are important for treatment decisions for patients with interstitial lung diseases. The role of DLCO for serial assessment is better established for idiopathic pulmonary fibrosis than sarcoidosis. It has been suggested that a significant change in DLCO is ≥ 15% or ≥ 3 mL/min/mm Hg, and for TLC or VC ≥ 10% (or ≥ 200 mL).[13]

Restriction and Its Variants

True Restrictive Disorders

These conditions include the intraparenchymal disorders (interstitial and infiltrative lung disease, diffuse alveolar disease) and chest wall restriction (pleural, skeletal). These have the classic findings of reduced TLC, FRC, RV, and VC, and normal to high FEV_1/FVC ratio.

Obesity

Obesity causes a pattern that is similar to mild restriction. With reduced chest wall and abdominal compliance, FRC, TLC, and VC are mildly reduced or in the low-normal range.[14] FRC is more consistently reduced in obese patients than is TLC or VC. Abdominal compression of the lower lung leads to early airway closure (low ERV and high RV) with reduced flow at low lung volumes (low $FEF_{50\%}$ and $FEF_{75\%}$) and midexpiratory flow ($FEF_{25-75\%}$).[15] This contrasts with true restrictive disorders in which a reduced VC results from a low IC rather than a low ERV. In addition, a low RV is typical of true restrictive disorders.

Neuromuscular Disease

These patients generally have a normal lung and chest wall, but weakness of the inspiratory muscles (mainly the diaphragm) and the expiratory muscles (mainly the abdominal muscles) limit the deviation from the resting lung volume (FRC). Consequently, the SVC is reduced by reduction in both IC and ERV. The reduced IC, with a normal FRC, results in a reduced TLC (and hence is "restrictive"). The reduced ERV, with a normal FRC, results in an increased RV. This elevation of RV distinguishes the

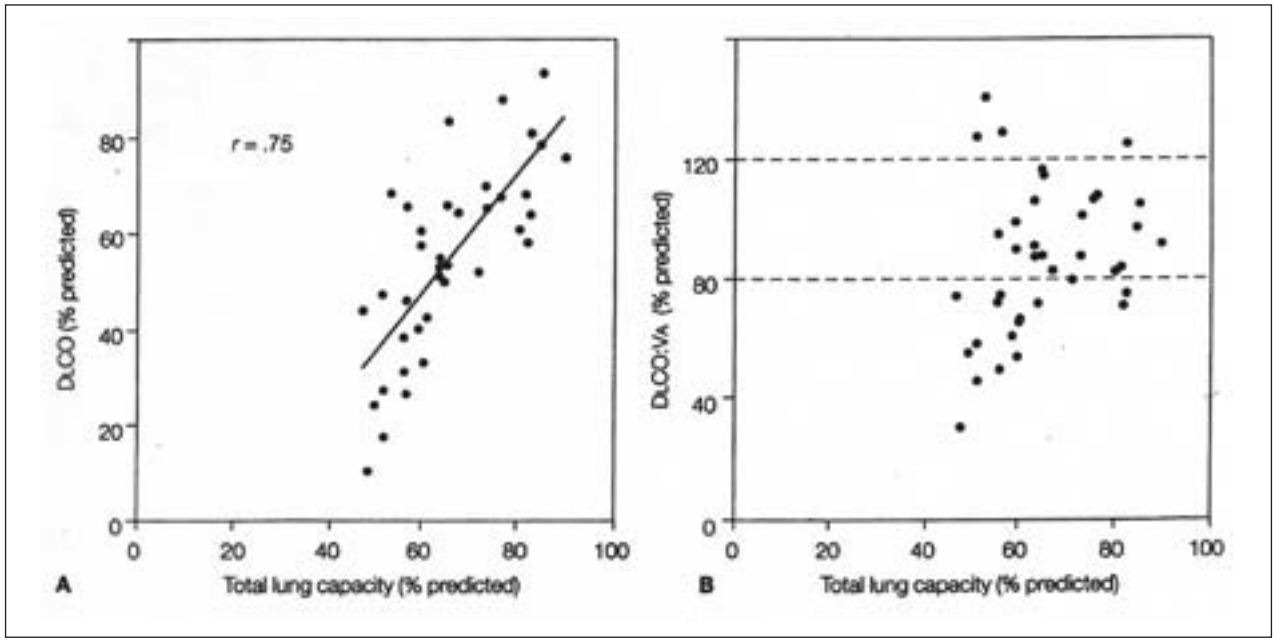

Figure 9. As interstitial lung disease worsens, diffusing capacity (DLCO) and lung volumes decrease proportionately (r=0.75, p=0.01) (A). However, individuals vary considerably with respect to the relative effect on gas exchange (DLCO) and lung mechanics. Half the patients have a DLCO per unit lung volume (DLCO/VA) > 80% predicted (normal range), indicating that the DLCO was reduced in proportion to the reduction in lung volumes (B). The other half have a low DLCO/VA, indicating a greater abnormality of gas exchange than lung mechanics.(From J Respir Dis 1999; 20:809-822; modified from Chest 1989; 96:1036-1042.)

"restriction" of neuromuscular disease from true restrictive disorders. If hypoxemia is present, it is due to hypoventilation, so $Paco_2$ is elevated. The normal $P(A\text{-}a)O_2$ (alveolar-arterial oxygen gradient) identifies the mechanism of hypoxemia to be pure hypoventilation and extrapulmonary in origin (outside of the lung parenchyma and airways).

With progression of muscle weakness, impaired cough and sigh mechanisms may lead to subsegmental or even lobar atelectasis. PFTs may show reduction in all lung volumes, including FRC and RV, when these complications supervene. At this point, the $P(A\text{-}a)O_2$ is widened, since atelectasis is a pulmonary complication causing shunt as the mechanism of hypoxemia.

Maximum Respiratory Pressures: The most specific tests to identify neuromuscular weakness as the cause of restriction are the maximal inspiratory pressure (MIP) and maximal expiratory pressure (MEP). The MIP is also known as the negative inspiratory force or inspiratory pressure maximum (PImax). The MEP is also known as the expiratory pressure maximum (PEmax). The MIP tests inspiratory muscle strength by measuring the lowest pressure that the patient can generate when trying to inhale from a blocked mouthpiece connected to a manometer. The most negative pressure is obtained when the test is performed at RV since the diaphragm is at its longest precontraction length, the optimal position for force generation. Conversely, the MEP is measured as an expiratory effort after inhaling to TLC.

Although simple tests, they are very effort dependent (patient and tester). A small leak is introduced to eliminate glottic and buccal occlusion and inadvertent measure of mouth pressures rather than intrathoracic pressures. Due to a learning curve, five trials are needed. The reported value should be the largest value that is reproducible; the best two efforts should match within 5%. The lower limit of normal is about 50% of predicted, and significant changes on follow-up are > 25%.

Although the MIP and MEP are the more specific and sensitive tests for muscle weakness, I often will follow VC in my neuromuscular disease patients because VC measurement is simpler for them to perform. VC is a good predictor of the development of hypercapnic respiratory failure and the need for ventilatory support (noninvasive or invasive).

Spirometric Clues To Distinguish True Restriction, Obesity, and Asthma: Subcomponents of VC (IC and ERV)

Patients with obesity or asthma may have spirometric findings that may be confused with those associated with true restrictive disorders. The FVL may be lacking the upward concavity characteristically seen in obstructive patterns. FVC may be borderline low-normal with a normal or elevated FEV_1/FVC ratio.

The utility of the subcomponents of the SVC, the IC and ERV, have been underappreciated. Both IC and ERV can be seen as the forced ERV and forced IC in an FVL that has also recorded the tidal breathing loop (Fig 10).[4] The forced or slow IC/ERV ratio helps distinguish true restriction from the "pseudorestriction" of obesity and asthma.

Clues to distinguish a pseudorestrictive pattern in asthma from true restriction and from the pseu-

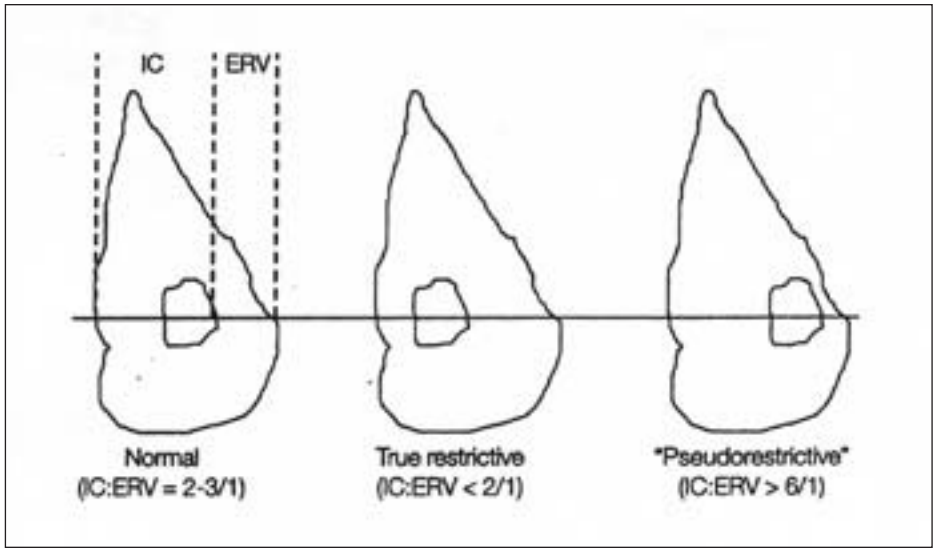

Figure 10. FVL patterns in the normal patient, true restrictive disorders, and "pseudo-restriction" due to obesity or asthma. The location of the tidal breathing loop within the maximal FVL, and the IC/ERV ratio, help differentiate these patterns. (From J Respir Dis 1999; 20:809-822.)

dorestriction of obesity include the following:

- Significant improvement of FEV_1 or FVC on pre- and postbronchodilator spirometry
- Elevated FRC and TLC (RV can be low or high in obesity)
- Improved "restriction" with asthma therapy
- Very low ERV, forced ERV
- Positive bronchoprovocation test
- Both obesity and asthma can cause elevated D_{LCO} and D_{LCO}/VA

Causes of restrictive spirometry in asthma are not entirely clear. Suggestions have been complete airway occlusions due to mucus plugging. The atelectasis causes a "restrictive" pattern as seen in lung resection (less lung is present). Another explanation relates to patients in whom premature airway closure predominates, such that FVC is reduced as much as flow rates (FEV_1), resulting in a normal FEV_1/FVC ratio.

A spirometric diagnosis of "restriction" was found to have a sensitivity of 93% but a specificity of only 82%. In this study,[16] true restriction and obstruction were defined by clinical and plethysmographic criteria. Spirometry was called "restrictive" if FVC was low and the FEV_1/FVC ratio was >70%. They noted that 10% of pure obstructive defects had "restrictive" spirometry. This finding supports the ATS recommendation that an interpretation of restriction from spirometry requires confirmation by full lung volume measurements using gas dilution or plethysmographic methods.

Pseudo-Pseudorestriction

Patients with obstructive lung disease who do not complete the expiratory effort on the FVC have undermeasurement of the FVC. This may result in a below-normal FEV_1 and FVC with a normal ratio ("pseudonormalization" of the ratio). This may be mistaken for restriction. However, the short expiratory time, lack of an expiratory plateau, hyperinflation on lung volume measurements, and scooped-out FVL indicate that the true disorder is obstructive.

Mixed Obstructive and Restrictive Patterns

Diffuse interstitial or infiltrative lung disease typically causes restrictive patterns with normal or high FEV_1/FVC and reduced lung volumes (TLC, FRC, RV). Obstructive ventilatory defects are seen relatively commonly in sarcoidosis, somewhat less so in rheumatoid lung disease, and occasionally in advanced idiopathic pulmonary fibrosis. This may be due to granulomatous airways disease (*eg*, sarcoidosis), bronchiolitis (*eg*, rheumatoid lung disease), or airway distortion from severe parenchymal fibrosis, or cystic spaces with honeycombing, in any advanced interstitial lung disease.

Bronchiectasis causes reduced expiratory flow rates as a result of total obliteration of some airways and increased collapsibility of dilated, patent airways. However, reduced TLC (restriction) is present due to fibrosis of parenchyma in the bronchiectatic lung segments.

Patients with some diffuse infiltrative/interstitial diseases typically present with airflow obstruction and increased lung volumes. Eosinophilic granuloma and lymphangioleiomyomatosis are the two main examples.

Although bronchiolitis is an "airway" disease, proliferative bronchiolitis, such as bronchiolitis obliterans organizing pneumonia , usually has a restrictive pattern. Mixed patterns can be seen, but this is usually in smokers. In contrast, constrictive bronchiolititis, such as transplant-associated bronchiolitis and diffuse panbronchiolitis, usually has an obstructive pattern with hyperinflation.

Upper Airway Obstructive Patterns

Although uncommon, a high index of suspicion must be maintained for the FVL patterns seen in upper airway obstruction (UAO). The mechanisms of UAO include extrinsic compression (such as goiter or mediastinal masses), intrinsic structural narrowing (such as tracheal stenosis or tumor), or functional disorders of airway tone (such as vocal cord dysfunction syndrome or functional stridor) from the hypopharynx to the tracheal bifurcation at the main carina. This pattern is referred to as upper airway obstruction in contrast to the obstructive dysfunction of asthma and COPD, located in lower airways, both large and small.

The FVL Pattern in UAO

These disorders causing UAO have a flow-volume pattern distinguishable from the pattern seen in asthma or COPD, with their characteristic "scooped-upward" concavity. UAO causes a dis-

tinct flattening of the inspiratory or expiratory limb of the FVL, or both.

Fixed UAO: When the obstruction is "fixed," both inspiratory and expiratory limbs have a plateau-like flattening (Fig 11). Neck position can affect the observed pattern and severity of UAO with thyroid enlargement (Fig 12).

Variable Extrathoracic UAO: Other upper airway lesions are "variable" in severity as transmural pressures across the airway vary from inspiration to expiration. When the obstruction is above the suprasternal notch, these variable lesions have flattened inspiratory limbs and the patient has inspiratory stridor because negative intraluminal pressure during inspiration compresses the airway, accentuating the narrowing (Figs 13 and 14).

Variable Intrathoracic UAO: When the UAO is within the thoracic cavity (below the suprasternal notch), the obstruction worsens on expiration because of compressive transmural forces causing a plateau-like flattening distinct from asthma or COPD; however, expiratory wheezing is heard in all of these intrathoracic obstructive diseases, whether upper or lower airways are involved (Figs 15 and 16).

Flutter Waves on FVL

High frequency "flutter" waves are sometimes superimposed on normal FVLs and in patients with UAO patterns. This was first reported in patients with obstructive sleep apnea, and initially was thought to be specific to that condition. Subsequently, it was also identified in patients with neuromuscular disease, and more recently in some normal individuals. The fluttering is likely due to vibration of redundant or hypotonic tissues in the upper airway, or caused by a jet of flow downstream of a narrowed section of airway. The presence of these flutter waves is suggestive of but not diagnostic for UAO.

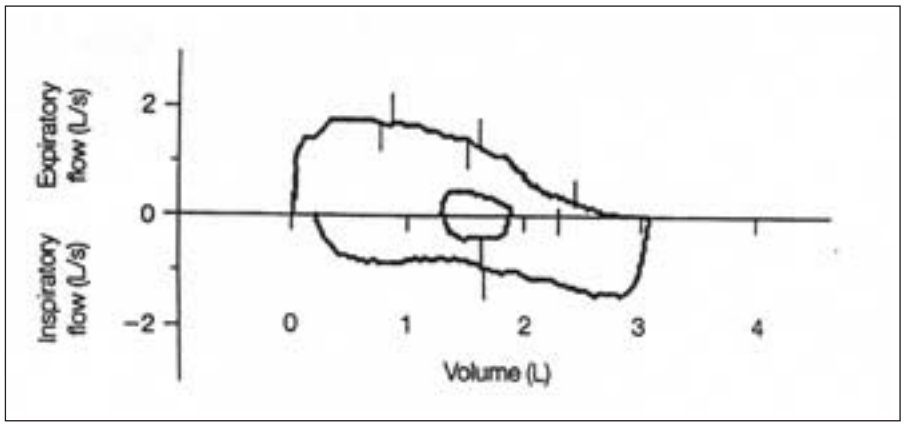

Figure 11. Fixed UAO, caused by tracheal stenosis, is demonstrated on this FVL. Although this stenosis was at the suprasternal notch, fixed obstructions of the upper airway will look the same whether they are intrathoracic or extrathoracic. (From J Respir Dis 1999; 20:809-822.)

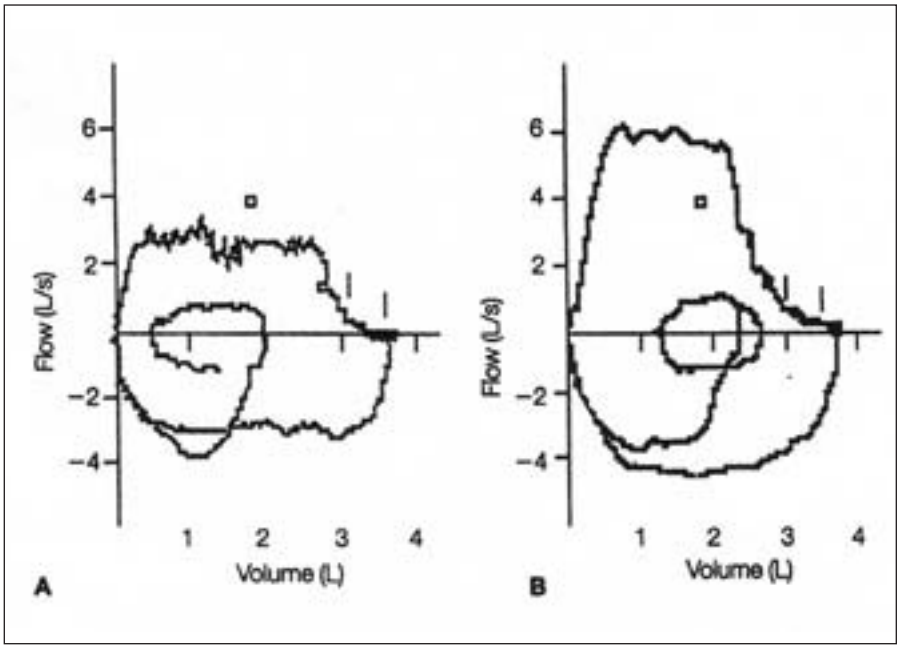

Figure 12. Fixed UAO pattern with a plateau of both inspiration and expiration caused by a thyroid mass. Neck flexion worsens UAO as the thyroid slides into the root of the neck/upper thorax ("thyroid cork" effect) (A). Neck extension reduces the degree of airflow obstruction (B). Thyroid masses without retrosternal extension may show a pure extrathoracic UAO pattern (inspiratory only). (From J Respir Dis 1999; 20:809-822.)

Numeric Indexes of UAO

Some measurements are helpful in identifying UAO. These include an $FEF_{50\%}$/forced inspiratory flow at 50% of FVC ratio > 1 in extrathoracic UAO (normally the midinspiratory flow is higher than the midexpiratory flow), and a peak expiratory flow rate/FEV_1 ratio < 8 in intrathoracic UAO and fixed UAO. However, assessing the overall shape of the FVL is currently the best way to identify these disorders.

Diseases causing UAO patterns are uncommon, and many suggestive loops will be due to poor effort, or sometimes represent a normal variant. The peak flow and early expiratory flows, as well as inspiratory flows, are the most effort-dependent part of the FVL. Several features help to distinguish effort-related rounding or flattening in these regions from pathologic causes. Poor effort results in lack of reproducibility of the results, whereas true abnormalities are reproducible.

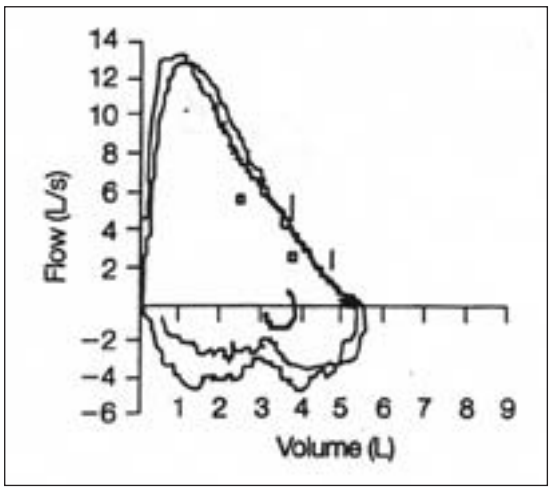

Figure 13. Variable extrathoracic UAO caused by vocal cord dysfunction syndrome is evident on this FVL. The inspiratory limb of the loop shows flattening and flow rates much below the expiratory limb. This functional disorder of vocal cord adduction is also known as functional stridor, factitious asthma, and laryngeal dyskinesia. Some patients have concomitant asthma, but when vocal cord dysfunction is an asthma mimic, only inspiratory stridor is present. The FVL or laryngoscopy establishes the diagnosis. (From J Respir Dis 1999; 20:809-822.)

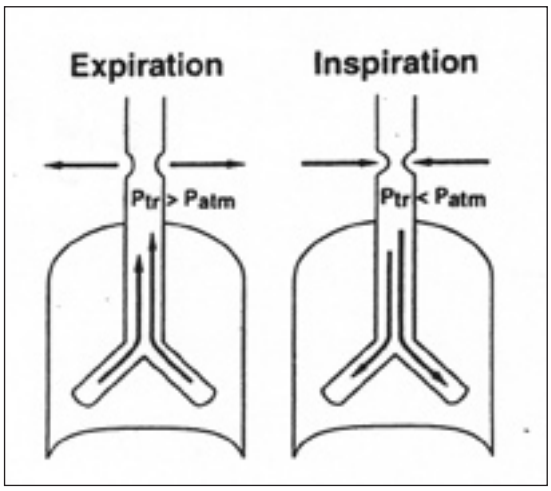

Figure 14. Variable extrathoracic UAO. During expiration, the transmural pressure gradient acting across the tracheal wall distends the airway, lessening the obstruction to airflow. On inspiration, the transmural gradient causes critical narrowing and a flow plateau develops. (From Clin Chest Med. 1994; 15: 35-53; adapted from Am J Med 1976; 61:85.)

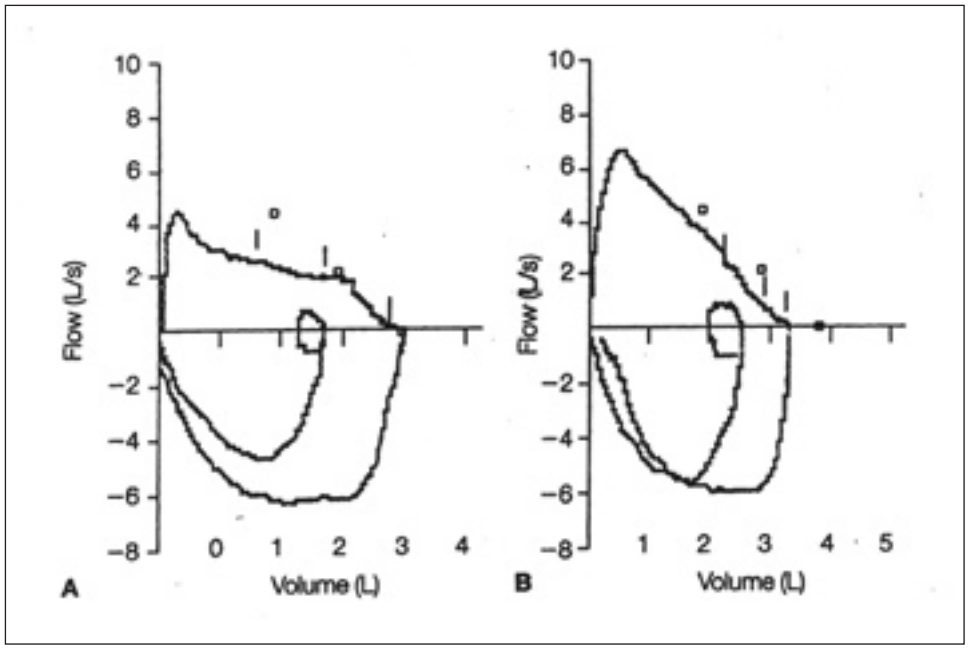

Figure 15. Variable intrathoracic UAO in this FVL was caused by a rare granular cell tumor of the distal trachea (A). Since the patient presented with wheezing, asthma was suspected. The plateau and abrupt concave-down shoulder at the right end are typical and contrast with the scooped upward concavity typical of COPD or asthma. The small "squeak" of a peak flow before the plateau is sometimes seen and does not rule out UAO if a plateau of flow is present. A normal FVL is shown after tumor resection (B). (From J Respir Dis 1999; 20:809-822.)

I also find that the maximum voluntary ventilation (MVV) is useful in this circumstance. The patient is instructed to breathe in and out as rapidly as he or she can for 12 s. The result is reported in L/min by multiplying by 5. If the MVV is close to $FEV_1 \times 40$ (the expected relationship to this expiratory parameter), then one can presume that inspiratory flow is normal, and flattening on the inspiratory limb of the FVL was effort-related. If the MVV is lower than $FEV_1 \times 40$, both the FVL and MVV may have been suboptimally performed, or the patient has a true UAO.

Normal Variant Mimic of UAO

Some young normal subjects have a "shoulder," or downward concavity, in the upper third of the expiratory limb that simulates true intrathoracic UAO. These may be distinguished in most cases because the flow-volume envelope exceeds or is close to the predicted loop in absolute flows, not reduced as in pathologic conditions (Fig 17).

Bronchoprovocation

FEV_1 and peak expiratory flow rate are good measures of asthma severity, and measure the degree of airflow obstruction. A related but distinct aspect of asthma is the degree of twitchiness of the airways. This tendency to bronchoconstriction can be assessed for specific antigens, although it is more common to assess nonspecific hyperresponsiveness in the laboratory with pharmacologic agents (methacholine or histamine), exercise (exercise-induced bronchospasm), or cold, dry air inhalation (which is often combined with exercise). Although these techniques are complementary in yield, the pharmacologic agent methacholine is most frequently used.

Methacholine Challenge Testing

Clinically, this test is most commonly used to diagnose asthma in patients who have had normal results of routine PFT studies, yet have symptoms that may be due to asthma. When symptoms are typical, an empiric course of treatment for asthma is a reasonable alternative. Cough-variant asthma frequently presents as monosymptomatic cough without wheeze, and normal routine PFT results.

Patients inhale concentrations of methacholine, doubling from 0.05 mg/mL up to 25 mg/mL, with measurement of FEV_1 after each concentration. The

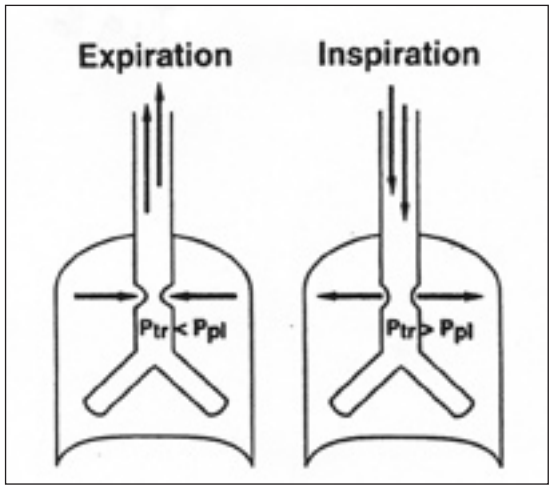

Figure 16. Variable intrathoracic UAO. The transmural pressure gradient during expiration results in compression of the intrathoracic trachea, as it does in the lower airways in asthma and COPD. This narrowing in the trachea results in a flow ceiling (plateau) during expiration. During inspiration, the gradient across the tracheal wall distends the airway and flow limitation at this site does not occur. (From Clin Chest Med 1994; 15:35-53; adapted from Am J Med 1976; 61:85.)

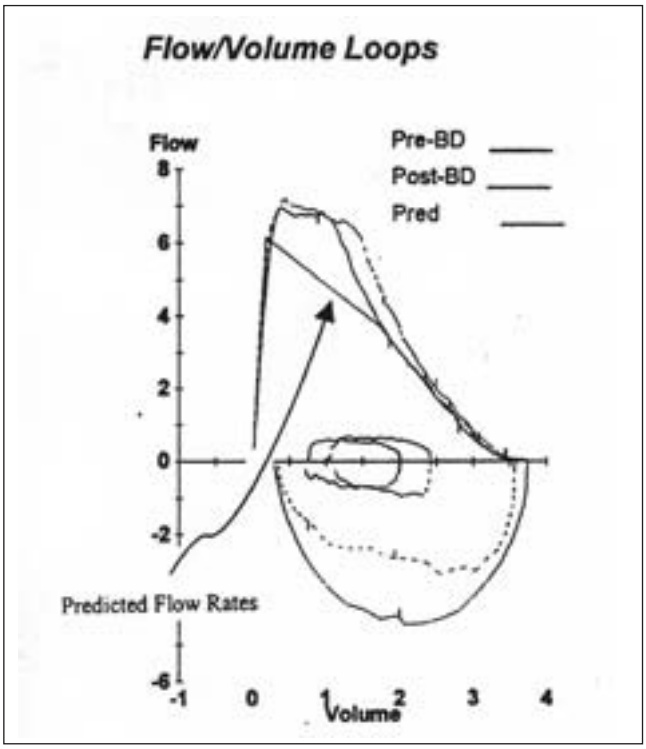

Figure 17. FVL is a normal variant, which appears similar to the pattern seen with intrathoracic UAO due to the initial plateau of expiratory flow and concave downward shoulder at the right end. Note that the flow rates are above normal. Outward "bumps" are seen in the upper descending portion of the expiratory limb in some normal young people.

results are graphed as the percent reduction in FEV_1 from baseline vs inhaled concentration. The concentration of inhaled agent that causes a 20% reduction in FEV_1 (PC_{20}-FEV_1) is interpolated from the graph (Fig 18). The ATS guidelines have suggested cutpoints for interpretation.[17] Assuming a pretest probability of asthma of 30 to 70%, a PC_{20}-FEV_1 > 16 mg/mL is normal; 4.0 to 16 mg/mL is borderline bronchial hyperresponsiveness (BHR); 1.0 to 4.0 is mild BHR (positive test); <1.0 mg/mL is moderate to severe BHR. The threshold below which a test is considered positive shifts to higher concentrations when the pretest likelihood of asthma is higher. Conversely, a lower concentration is required to designate a test positive when the pretest suspicion of asthma is lower.

The test is also sometimes performed using the body plethysmograph to measure airways resistance (Raw) and its reciprocal, conductance (Gaw), which is measured by the equation, Gaw = 1/Raw. This is usually expressed as specific airway conductance, G/TGV (conductance divided by the thoracic gas volume at which it is measured). The advantage of Gaw over Raw is its linear relationship to lung volume. A 45% reduction is considered positive due to greater variability in this measurement than for FEV_1.

Bronchoprovocation and the Diagnosis of Asthma

Most consider bronchoprovocation highly sensitive for asthma, but nonspecific. Consequently, a negative test is a strong argument against the diagnosis of asthma. False-negatives can be due to currently inactive asthma. Other illnesses that are associated with a positive study, although in a smaller percentage of patients, include rhinitis, sarcoidosis, COPD, and congestive heart failure. Most of these other conditions are easily ruled out by clinical evaluation. The lower the PC_{20}, the more likely it is that the patient has asthma.

A negative study can be used as supportive evidence for vocal cord dysfunction mimicking asthma, especially if a flattened inspiratory limb of the FVL is present.

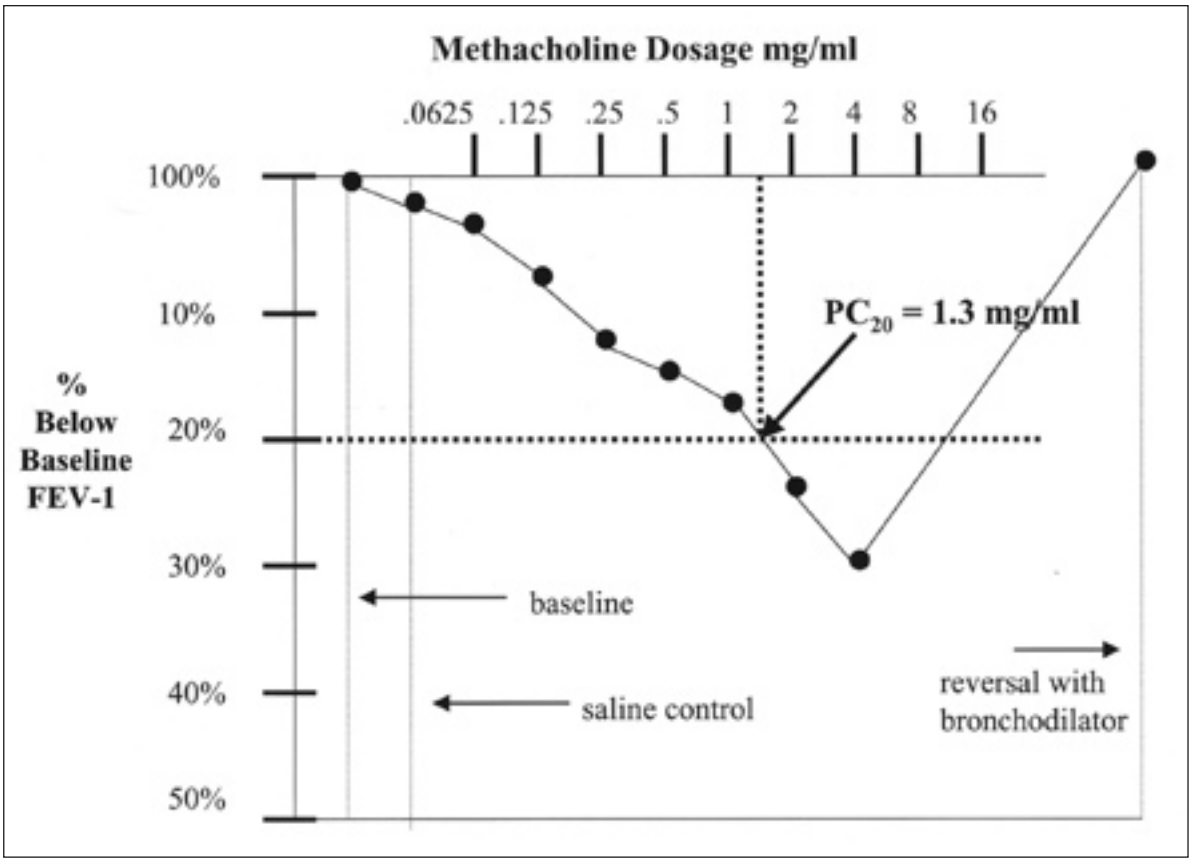

Figure 18. Methacholine bronchoprovocation study. The concentration of methacholine that causes a 20% fall in FEV_1 is interpolated from the graph. The PC_{20} in this patient indicates a positive study and mild bronchial hyperreactivity. There is brisk reversal with bronchodilator to above the baseline FEV_1.

Exercise Bronchoprovocation

Exercise bronchoprovocation is best performed on the treadmill, with a target heart rate of 80 to 90% of predicted maximum (220 – age in years) maintained for 4 to 6 min, with a total exercise duration of 6 to 8 min. Having the patient inhale cold, dry air during the study increases the yield of this test. Drying and cooling of the airways during exercise is the presumed stimulus for bronchospasm in this condition. Paradoxically, bronchoprovocation testing is usually used to diagnose exercise-induced bronchospasm, because it is simpler to perform and more sensitive for the diagnosis. Some patients with exercise-induced bronchospasm will have negative methacholine bronchoprovocation studies, and only exercise testing will be positive.

Role of PFTs in Preoperative Assessment

Lung Resectional Surgery

Surgical treatment of non-small cell lung cancer offers the only chance for cure. However, many lung cancer patients have reduced pulmonary reserve due to comorbidity with COPD. All patients must undergo a staging workup for resectability, and a PFT evaluation to assess physiologic reserve, or operability. The goal of this PFT evaluation is to aid in predicting the likelihood of poor outcome (postoperative death, ventilatory dependence, or severely disabling dyspnea) and the extent of resection that can be tolerated.

Step 1: Routine PFTs including spirometry, lung volumes, diffusing capacity, and arterial blood gas studies are performed. In general, if FVC and FEV_1 are ≥ 2 L or 80% of predicted, and the D_{LCO} ≥ 75%, the patient can tolerate pulmonary resection up to pneumonectomy without further investigation.

Step 2: If the FVC, FEV_1, or D_{LCO} is below the threshold values in step 1, predicted postoperative values need to be calculated to assess the extent of operation that can be tolerated. In general, the right lung contributes 55% to overall lung function and the left lung 45%, although comorbid disease or the lung cancer itself may modify these significantly. Currently, this regional contribution to overall lung function is best estimated by a perfusion lung scan. The ventilation scan is not needed because defects due to COPD, or atelectasis or mass effect from the cancer, produce matched ventilation and perfusion abnormalities. The perfusion scan needs to be performed as a quantitative split perfusion scan, in which percent of function is split into right vs left lung, and upper vs lower lobe on each side (right middle lobe cannot be separately identified).

Predicted postoperative values for FEV_1 and D_{LCO} are obtained by multiplying the preoperative values by the percentage of lung that will remain after lobectomy and pneumonectomy, using the data from the perfusion scan. In the past, more focus was placed on the FEV_1 and a fixed lower limit of 0.8 L was used as an acceptable lower limit for postoperative values. Now that lung cancer is an equal-opportunity disease, it has become clear that using the same absolute number for a 6-foot-tall man and a 5-foot-tall woman is not reasonable. Currently, most consider predicted postoperative FEV_1 and D_{LCO} values > 40% of predicted to be the acceptable lower limit for proceeding to resection without performing exercise testing.

Although not well studied, it has been conventional to consider significant hypercapnia to be a contraindication to lung resection. This was initially based on the poor prognosis of COPD associated with hypercapnia. Although most still consider this a relative contraindication, step 3 evaluation can help select those high-risk patients who are acceptable candidates for surgical resection.

Most data suggest that hypoxemia alone is not a contraindication to surgical resection.

Step 3: Cardiopulmonary exercise testing (see separate chapter) is an elegant way to dissect the factors contributing to exercise intolerance. Looked at from another angle, exercise is a metabolic stress that requires the integrated function of many organs that are important to surviving the stress of surgery. For this purpose, the integrative parameter, maximum oxygen consumption (V_{O_2} max) achieved during the exercise test, is predictive of outcome. Those patients with adequate pulmonary, cardiac, and muscular function who are also sufficiently motivated and cooperative to achieve a high V_{O_2} max have good overall function and low risk. If V_{O_2} max is > 75% of predicted or > 20 mL/kg/min, the patient can undergo pneumonectomy. When V_{O_2} max is < 40% of predicted or < 10 mL/kg/min, the patient is inoperable. In the intermediate group, the perfusion scan is combined with the V_{O_2} max to calculate a predicted postoperative V_{O_2} max. If

predicted postoperative V_{O_2} max is > 10 mL/kg/min and > 35% of predicted, the patient can be considered physiologically operable up to the calculated extent.[18] This model assumes that cardiac risk has also been evaluated and appropriate testing performed as necessary.

Surgery Other Than Lung Resection

Although pulmonary complications are among the most important postoperative complications, and COPD is a risk factor, the independent role of PFTs in predicting complications is controversial for surgery other than thoracic surgery. The frequency of pulmonary complications is site-dependent, inversely proportional to the distance from the diaphragm: thoracic > upper abdominal > lower abdominal > orthopedic, and head and neck surgery > other sites.

Circumstances in which PFTs are likely to be important are the following: (1) when nonsurgical therapies might be preferred if severe lung disease is present, PFTs should be part of the clinical evaluation; and (2) when preoperative medical evaluation identifies a significant tobacco history, or the patient has signs and symptoms of previously undiagnosed pulmonary disease. In this situation, aggressive perioperative therapy for newly diagnosed COPD or other illness may be helpful.

Pending more definitive data, the American College of Physicians recommends PFTs in the following circumstances: (1) before coronary artery bypass grafting or upper abdominal surgery if the patient has a history of tobacco use or dyspnea; (2) in patients undergoing lower abdominal surgery if there is uncharacterized pulmonary disease with anticipated prolonged or extensive surgery; (3) in patients undergoing head and neck surgery or orthopedic surgery with uncharacterized pulmonary disease; and (4) in all patients undergoing lung resection.[19]

Cardiac Effects on PFTs

The cardiac and pulmonary systems have a joint function in the delivery of O_2 and elimination of CO_2 to support the metabolically active tissues. Clinically, we are well aware of their interactions. Of note, the Framingham longitudinal studies have found that reduced FVC is an independent predictor of cardiac events even in people without established cardiac disease.

Congestive Heart Failure

In patients with congestive heart failure, the PFT findings are well explained by the mechanisms and stages of pulmonary congestion. In mild stages, with vascular congestion but without frank pulmonary edema, the increased capillary blood volume will result in an increased diffusing capacity. With more blood volume (and hemoglobin) to accept CO and nothing interfering with the transfer of gas from alveolus to capillary, uptake of CO is enhanced. This corresponds to the radiologic phase of cephalization of vascular flow. As congestion worsens with the development of interstitial and alveolar edema, a restrictive process with a reduced diffusing capacity develops.

One study found that patients who had a reduced D_{LCO} due to congestive heart failure had crackles.[20] The suggestion is that another cause of a reduced D_{LCO} should be sought if crackles are absent in this setting.

Amiodarone Toxicity

Amiodarone pulmonary toxicity is a difficult diagnosis to establish, and largely a diagnosis of exclusion. Serial PFTs, including the measurement of D_{LCO}, have not proven useful in screening for early disease caused by this agent. Despite this, otherwise unexplained restriction and low D_{LCO} is part of the clinical pattern suggesting toxicity from this drug. Other tools have included chest CT, gallium scans, BAL, and transbronchial lung biopsy.

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Notes

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