Interpretation of pulmonary function tests: beyond the basics

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ABSTRACT

Although the general framework described in the joint American Thoracic Society/European Respiratory Society guidelines provides a useful and practical method for the interpretation of pulmonary function tests, several other measurements and functional indices, if understood correctly, may help in diagnosis and management of patients with respiratory diseases and in design of research protocols. This review provides information on the underlying physiology, interpretative caveats, and the evidence supporting the use of a number of these indices. Some of these measurements, such as the inspiratory fraction, inspiratory capacity/total lung capacity (IC/TLC), may offer additional prognostic information, while others, such as residual volume (RV)/TLC and forced expiratory volume in 3 s/forced vital capacity (FEV_3/FVC), may help fill in the gaps between patient symptoms and more traditional indices of pulmonary function. Although most studies of non-traditional indices focus on airflow-limiting disorders, many can be fruitfully applied in other settings. Understanding the physiology that catalyzed these investigations will undoubtedly enrich the functional assessment armamentarium of the practicing clinician and researcher.

INTRODUCTION

The joint American Thoracic Society/European Respiratory Society (ATS/ERS) guidelines on the interpretation of pulmonary function testing[1] offer a succinct framework for assessing the pathophysiology of patients with lung disease. The main indices recommended are the ratio of forced expiratory volume in 1 s to the forced vital capacity (FEV_1/FVC), total lung capacity (TLC), and diffusing capacity of lungs for carbon monoxide (DL_{CO}) and their use in distinguishing the three basic patterns of pulmonary disease is summarized in table 1. However, modern equipment is capable of measuring and reporting a number of additional indices that can aid in diagnosis and the implementation of various management strategies. Not all of these indices are equally useful, however. In this review, we will present the basic physiology underlying several of the more common indices found in the medical literature, their use, the evidence supporting them, and some caveats of interpretation. Although none are poised to supplant the three 'essential' indices, many can be quite helpful on their own. Several derived indices, such as

FEV_3/FVC, FEV_6/FVC, residual volume (RV)/TLC, alveolar volume (V_A)/TLC, can help address the disparity between symptoms and FEV_1 in patients with airflow-limiting diseases. Others, such as DL/V_A, can point the way toward either a diagnosis or other useful diagnostic tests. Our approach is not meant to be exhaustive, as there are many other indices worthy of discussion, including maximal inspiratory and expiratory pressures, expiratory reserve volume/inspiratory capacity (ERV/IC), and tidal volume (Vt)/IC that could not be presented here. That said, the indices discussed in this review will no doubt be a useful addition to the functional assessment repertoire of any practicing clinician.

Anatomy of the flow–volume loop

The flow–volume loop (FVL) is obtained during normal spirometry,[2] with flow typically plotted on the y-axis and volume on the x-axis (figure 1A). By convention, the expiratory phase is represented on the positive side of the y-axis and the inspiratory phase on the negative side. By convention, volumes are also illustrated from the right to the left, with most pulmonary function laboratory systems using a higher value on the x-axis to represent lower volumes (as pictured). The distance between the RV and the TLC represents the vital capacity (VC). Vt is usually presented as a smaller loop within the larger FVL, with functional residual capacity (FRC) represented by the point at which the Vt loop crosses the x-axis on the side of the RV (figure 1B). Proper placement of the loop along the x-axis depends on knowledge of accurate lung volumes, underscoring the importance of lung volume assessment and reporting at the time of spirometry.

Forced expiratory flow at 50% of the FVC ($FEF_{50\%}$)

The forced expiratory flow at 50% of the FVC ($FEF_{50\%}$, also called maximal expiratory flow at 50% VC, $MEF_{50\%}$), alone or in combination with the FVC, has emerged as a potentially useful index, particularly in the evaluation of airflow-limiting diseases (figure 1C). Many studies evaluating the $FEF_{50\%}$ have found a good correlation with the FEV_1/FVC ratio in patients with airflow-limiting diseases, but it distinguishes itself in several settings by demonstrating abnormalities in patients with normal FEV_1/FVC ratios. Its usefulness is based on the

Table 1 Basic patterns of pulmonary function tests

| Airflow-limiting pattern	Restrictive pattern	Vascular pattern
$FEV_1/FVC < LLN$	$TLC < LLN$	$DL_{CO} < LLN$

The three primary patterns of disease distinguishable by traditional pulmonary function tests are summarized as follows: airflow limitation is characterized by a decrease in the forced expiratory volume in 1 s to the forced vital capacity (FEV_1/FVC) ratio, restriction is characterized by a decreased total lung capacity (TLC), and vascular disease is characterized by a decrease in the diffusing capacity of lungs for carbon monoxide (DL_{CO}).
LLN, lower limit of normal.

fact that the $FEF_{50\%}$ generally occurs at a level that will show significant differences between normal, airflow-limiting, and restrictive lung diseases (ie, small airways or 'distal' parenchymal disease). A higher value indicates elevated relative flows, and it is therefore higher in restrictive lung diseases and significantly lower in airflow-limiting diseases. The term 'dysanapsis' has been used to describe the anatomic phenomenon of smaller airway calibers at low lung volumes.[3] Given that the $FEF_{50\%}$ correction as $FEF_{50\%}/FVC$ or $FEF_{50\%}/0.5FVC$ may make sense. In one study, the ratio $FEF_{50\%}/0.5FVC$ was useful in distinguishing between various patterns of lung disease. The mean ratios were 2.10 ± 0.82, 2.55 ± 1.47, and 0.56 ± 0.29, for normal, restrictive lung diseases, and airflow-limiting diseases, respectively.[4] In the same study, a ratio under 0.79 was highly associated with airflow limitation and a ratio over 1.33 practically excluded it. In our own analyses on 21,253 subjects who had spirometry and body plethysmography, mean $FEF_{50\%}/0.5FVC$ was 1.48 in normal individuals, 1.79 in those with restriction, 0.96 in those with small airway disease, 0.75 in those with airflow-limiting disorders, and 0.74 in patients with mixed ventilatory impairments (unpublished data, $p < 0.0001$). The latter two categories (airflow-limiting and mixed processes) were statistically similar ($p = 0.99$), and are therefore not differentiated by this parameter. A value ≤ 1.0 is highly suggestive of airflow limitation or obstruction (92% positive and 80% negative predictive value), while a value ≤ 0.75 has a 99% positive and a 69% negative predictive value. A $FEF_{50\%}/0.5FVC > 1.8$ essentially rules out small airway disease (unpublished data).

Another study found correlations in a cohort of elderly patients between $FEF_{50\%}$ and smoking history, respiratory symptoms, and inhaler use, and in addition noted a significant correlation between a reduced $FEF_{50\%}$ ($< 60\%$) and newly detected heart failure as well as episodes of acute bronchitis.[5] The $FEF_{50\%}$ has also been used to characterize the contour of the FVL, as discussed in more detail below.

Airflow-limiting and restrictive patterns of flow–volume loops

The shape of the FVL can offer important clues to a patient's underlying diagnosis. Airflow-limiting diseases, such as asthma and emphysema, will reduce the flow at a given volume and cause a characteristic 'scooping' (or concave appearance) of the FVL. As this flow reduction can be caused by either a reduction in driving pressure gradient (as in emphysema) or an increase in airway resistance (as in asthma), it is best thought of as an airflow-limiting
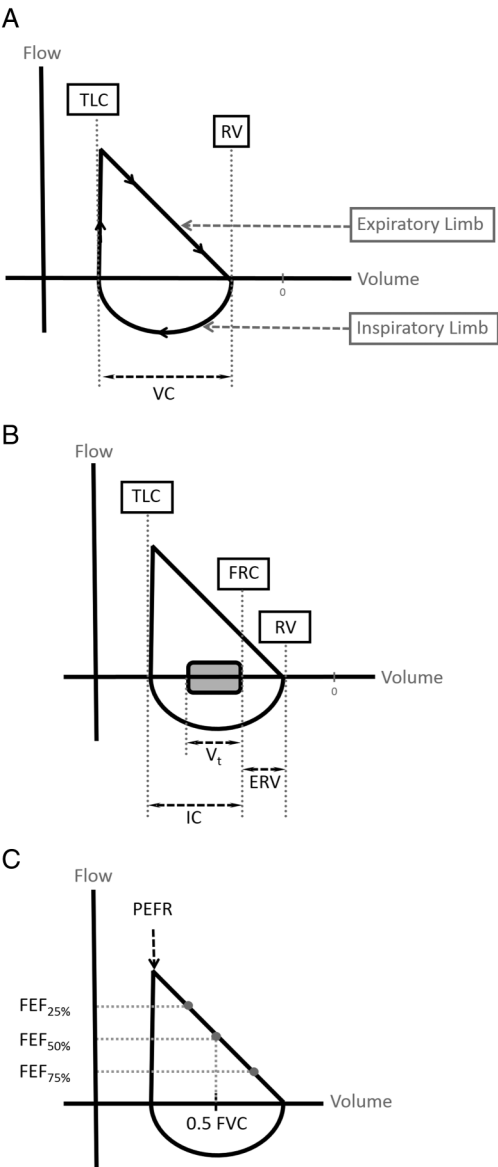
Figure 1 Anatomy of the flow–volume loop. (A) The flow–volume loop (FVL) is pictured here with volume on the x-axis (increasing toward the origin) and flow on the y-axis. By convention, the expiratory phase is depicted on the positive side of the y-axis and the inspiratory phase on the negative. Total lung capacity (TLC) is shown as the point on the x-axis after full inspiration, and residual volume is shown at the point of full exhalation, with vital capacity (VC) represented by the distance between the two. (B) The flow–volume loop is depicted here with a smaller tidal breath (V_t) in its interior. The point on the x-axis at which a tidal breath is exhaled is the functional residual capacity (FRC), and the distance between the FRC and the TLC is known as the inspiratory capacity (IC). (C) Peak expiratory flow rate (PEFR) is the highest positive value along the y-axis. $FEF_{25\%}$ is the point at which one-quarter of the VC has been exhaled, $FEF_{50\%}$ is the volume at which half of the VC has been exhaled, and $FEF_{75\%}$ is the point at which three-quarters of the VC have been exhaled. ERV, expiratory reserve volume.

pattern rather than an obstructive pattern. Provided lung volumes are also obtained, movement along the x-axis toward a higher value will reflect the presence of air

trapping and hyperinflation, and the V_t loop will often be shifted toward the TLC, reflecting an increase in FRC (figure 2A). A restrictive pattern, in contrast, is characterized by a shift along the x-axis toward zero. The distance between TLC and RV is also reduced, reflecting a smaller VC. Airflow may actually be increased at a given lung volume, reflecting reduced lung compliance. The appearance of the loop is often described as a 'bishop's mitre', referring to the tall ceremonial hat of some Christian church officials.

Several attempts have been made to mathematically characterize the shape of the flow–volume loop. Although none of these methods have entered standard practice, the principles underlying each are still instructive. An early attempt by Mead made use of tangent lines drawn along the expiratory limb of the FVL at discrete intervals and chord lines created by drawing a line between a tangent on the loop and the end of expiration to generate slope ratio curves[6] (figure 2B). Although the method was able to capture different patterns based on disease type (chronic bronchitis, emphysema, asthma), it does not appear to add much information to the FVL alone. Another attempt by Kapp et al[7] uses the FVL point at $FEF_{50\%}$ to draw two lines: one from the point of peak expiratory flow (PEF) to the $FEF_{50\%}$, leading to an extrapolated point on the x-axis, and the other from $FEF_{50\%}$ to RV (figure 2B). The angle β between those two lines can be used to determine whether the expiratory limb of the FVL is convex or concave. This approach, while relatively simple, relies heavily on the PEF and the proper termination of the expiratory phase, making it particularly vulnerable to errors in patients with severe airflow-limiting diseases. Further, the possibility that multiple values of TLC, PEF, and $FEF_{50\%}$ could result in the same angle β, also undermines the specificity of the assessment.[8] An approximated area under the maximum expiratory flow–volume curve, first proposed by Vermaak et al,[9] has also been studied in several settings. It appears to correlate well with the response to methacholine challenge in patients with underlying bronchial hyper-responsiveness[10][11] and with pharmacologic bronchodilation in patients with chronic obstructive pulmonary disease (COPD)[12] (figure 2C). When the method was first proposed, it assumed the curve to be a triangle, with the VC as the base, PEF as the perpendicular, and a line from PEF to RV as the hypotenuse. However, expiratory flow curves, particularly in patients with airflow-limiting diseases, are far from triangular in shape. A more recent attempt by Lee et al[13] makes use of more sophisticated graphical analysis tools to generate a more accurate estimation of the area under the curve of the FVL. To do this, they determined the area under an imaginary line between PEF and the volume at end expiration on the FVL (the 'area under the diagonal'). They then compared that value to the area under a triangle described by PEF, the exhaled volume at PEF, and the VC. By dividing the area under the diagonal by the area of the triangle, they are able to generate a value for the area of obstruction as follows:

$$\text{area of obstruction} = \text{area under the diagonal}/\text{area of the triangle} \qquad (1)$$

A scooped FVL will result in a larger area under the diagonal relative to the total area under the triangle and will therefore
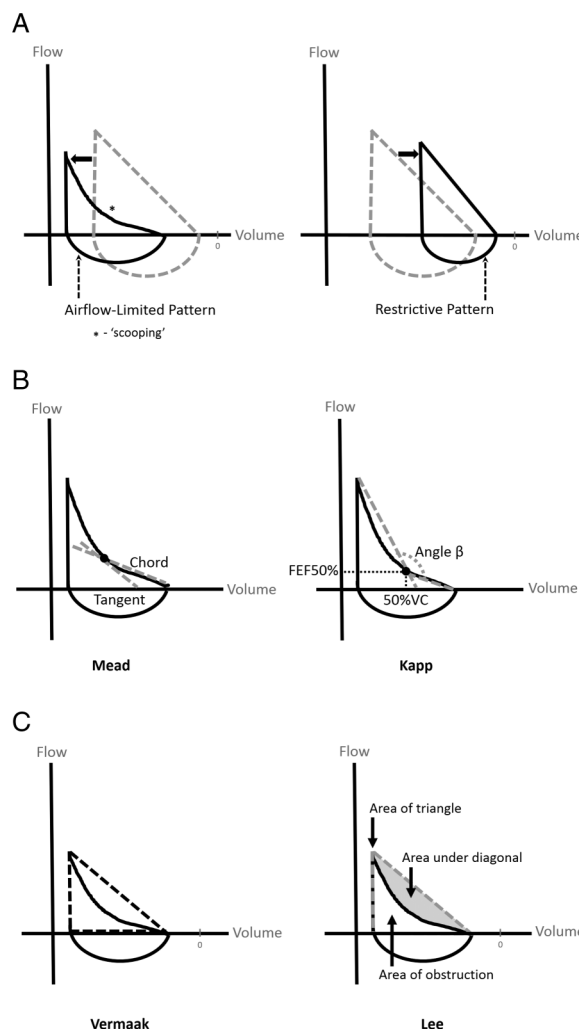
Figure 2 Abnormalities of the flow–volume loop (FVL). (A) The airflow-limiting pattern is distinguished by a 'scooping' of the FVL, in which the flow is lower at any given volume. In addition, provided lung volumes were obtained along with spirometry, the loop is often shifted to the left, reflecting an increase in TLC and RV. The restrictive pattern, in contrast, is distinguished by a shift of the loop to the right, reflecting a decrease in TLC and RV. Although lung volumes are decreased, at any given volume, flow is often increased. (B) Mead developed a method of FVL quantification that makes use of tangent lines drawn along the expiratory limb at discrete intervals as well as chord lines created by drawing a line between a tangent on the loop and the end of expiration to generate slope ratio curves. The method of Kapp involves the description of an angle β generated by two lines: one from the point of PEF to the forced expiratory flow at 50% of the FVC ($FEF_{50\%}$) that leads to an extrapolated point on the x-axis, and the other from $FEF_{50\%}$ to RV. (C) Vermaak's method of FVL quantification involves the creation of a hypothetical triangle using the VC as the base, the PEF as the perpendicular, and a line between PEF and RV as the hypotenuse. A later attempt by Lee makes use of a similar triangle but uses graphical analysis software to describe the area of obstruction (defined as the ratio of the area under the diagonal to the area under the triangle). The closer the ratio to 1, the more severe the obstruction. The closer it is to 0, the less obstructed the loop.

result in an area of obstruction closer to 1. A normal curve will result in an area of obstruction closer to 0. Although this method does help describe the contour of the FVL and the

area of obstruction correlated well with other indices such as the RV/TLC (described below), the reliance on PEF again makes it difficult to properly characterize patients with severe airflow limitation. The quantification of the actual area under the FVL, which can be performed by several modern systems, has also been shown to differentiate very well between different types of ventilatory impairment.[14] While all of these methods are meritorious in their attempt to quantify a complex phenomenon, it is difficult to see how much is added to the subjective analysis of the FVL at this point. Importantly, a recent study of pediatric patients confirmed the validity of the subjective assessment of the FVL relative to more quantitative techniques.[15]

Upper airway obstruction

A key use of the FVL is examination for the presence of upper airway obstruction. Although a formal diagnosis cannot be made by spirometry, it can often provide the impetus needed to pursue further more definitive testing (ie, with bronchoscopy or laryngoscopy). The physiology underlying alterations to the FVL can be understood by considering the balance of intrathoracic and extrathoracic forces during inspiration and expiration.[16] In the case of a variable intrathoracic obstruction, inspiration causes pleural pressure to drop relative to intrathoracic airway pressure leading to an increase in airway diameter that prevents any obstruction from occurring. During expiration, pleural pressure increases above tracheal pressure, narrowing airway diameter, causing airway obstruction and a cut-off of the expiratory limb of the FVL (figure 3A). In contrast, variable extrathoracic obstruction involves a balance between tracheal and atmospheric pressure. During expiration, tracheal pressure is elevated above atmospheric pressure, increasing airway diameter and preventing obstruction from occurring. During inspiration, tracheal pressure falls below atmospheric pressure (thus allowing airflow into the lungs) and airway diameter narrows as a result, leading to airway obstruction and a cut-off of the inspiratory limb of the FVL (figure 3B). Finally, a fixed obstruction will be reflected by cut-off of the inspiratory and expiratory limbs due to its lack of variation with the respiratory cycle (figure 3C). In terms of quantification, a ratio of $FEF_{50\%}$ to forced inspiratory flow at 50% of the FVC ($FIF_{50\%}$) >1 can support the diagnosis of extrathoracic obstruction.[17]

The volume–time curve

The volume–time curve, a graph with exhaled volume plotted on the y-axis (in liters) and time plotted on the x-axis (in seconds), is obtained during normal spirometry as a patient inhales to TLC before exhaling rapidly to RV (figure 4A). In addition to its usefulness in assessing the validity of spirometry,[2] the volume–time curve offers a useful framework in understanding a number of readily available, though often-underused, indices. First and foremost, the pattern of the curve can offer clues to the underlying diagnosis. In the case of airflow-limiting diseases, patients may continue to exhale beyond the duration of the test, which would be manifested by a lack of plateau to the curve. In that case, the FVC determined by the test will underestimate the true FVC (a pattern sometimes referred to as 'pseudorestriction') and could lead to a misdiagnosis of either restriction or normal airflow when hyperinflation and airflow
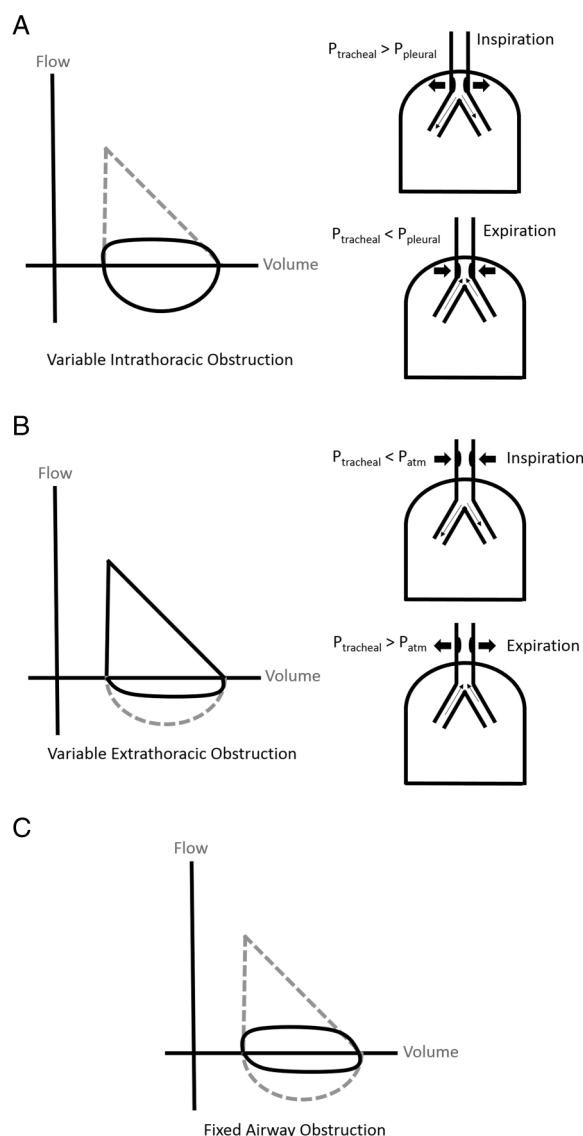
Figure 3 Upper airway obstruction. (A) Variable intrathoracic obstruction causes a plateauing of the expiratory limb of the flow–volume loop (FVL) due to worsening obstruction when tracheal pressure is exceeded by pleural pressure during expiration within the thorax. (B) In contrast, variable extrathoracic obstruction causes a plateauing of the inspiratory limb due to worsening obstruction when tracheal pressure is exceeded by atmospheric pressure during inspiration. (C) A fixed airway obstruction does not vary with the respiratory cycle and therefore causes plateauing of both limbs of the FVL. Figures adapted from Acres and Kryger.[16]

limitation are actually present. This problem can be mitigated somewhat by following the ATS/ERS guidelines, which suggests that the slow vital capacity obtained either during spirometry or plethysmography or the inspired vital capacity obtained during a DL_{CO} maneuver should replace the FVC in the FEV_1/FVC ratio to determine the presence of airflow limitation, if either one is larger than the original FVC value.[1] In addition, it should be noted the FVC is reduced in this scenario as a direct result of an increase in the RV, a key finding in airflow-limiting diseases (discussed further below under 'RV/TLC'). Finally, a restrictive pattern

will manifest on a volume–time curve as a rapid plateau that occurs at a lower-than-expected volume (figure 4B).

Ratio of forced expiratory volume in 1 s to forced expiratory volume in 6 s (FEV$_1$/FEV$_6$)

One index that helps mitigate the problem of an underestimated FVC leading to underdiagnosis of airflow limitation is to replace the FVC with the FEV$_6$ (figure 4A). Doing so potentially provides a better-defined end point for spirometric evaluation and could make the test easier to perform for patients who have difficulty sustaining forceful exhalation for as long as the FVC requires.[18] Unfortunately, the FEV$_1$/FEV$_6$ ratio sacrifices some sensitivity for the detection of airflow limitation when compared with the FEV$_1$/FVC.[19] Nevertheless, the number of studies validating the ratio, some of which include reference values, suggest that it is long since ready for daily use in the proper context.[20–22] In addition, some investigators have found usefulness in the FEV$_6$ as a surrogate for FVC for airflow-limiting spirometric patterns and for restrictive patterns.[23]

Forced expiratory flow at 25–75% of the FVC (FEF$_{25–75\%}$)

The FEF$_{25–75\%}$ (also referred to as the maximal midexpiratory flow) is defined as the average expiratory flow over the middle half of the FVC (figure 4C). It is calculated by identifying the points at which 25% and 75% of the FVC has been exhaled using data from the volume–time curve.[2] The change in volume is then divided by the change in time. Of note, the FEF$_{25–75\%}$ is distinct from the FEF$_{50\%}$, which is a measurement of the flow at a single point (50% of the FVC), rather than an average flow over a range of FVC values. The FEF$_{25–75\%}$ has often been described as a measurement of small airways disease due to its examination of flows that occur in the middle of an expiratory effort, presumably when smaller airways are more involved. However, most of this time period overlaps with the portion of exhalation in which effort is still present, so it does not truly represent small airway flows alone. Perhaps not surprisingly, several studies have demonstrated that FEF$_{25–75\%}$ adds very little to FEV$_1$ assessment.[24] It also suffers considerably from its reliance on the

FVC (which is needed to determine the points at which the relevant volumes have been exhaled).[2] In addition, bronchodilator responses become problematic given that the relevant points are assessed at different lung volumes (provided the FVC increases postbronchodilator). Some have advocated using the prebronchodilator volumes for better comparison of the relative flow rates,[25] but the physiologic rationale for doing so again calls into question the usefulness of the measurement relative to the FEV$_1$ alone. Despite these caveats, it may still be a useful adjunctive index in building a case for airflow limitation in patients with a normal FEV$_1$/FVC ratio who have other hints of dysfunction present in their pulmonary function test (PFT) results (eg, a concave FVL or an increased RV/TLC as discussed below). In addition, recent investigators have found a role for the FEF$_{25–75\%}$ as a biomarker of asthma severity (including blood eosinophilia and bronchial hyperreactivity).[26] Although it must be interpreted with caution, the FEF$_{25–75\%}$ may yet have a role as an adjunct in the interpretation of PFTs, particularly with regard to prognostication in asthma.

Ratio of forced expiratory volume in 3 s to forced vital capacity (FEV$_3$/FVC)

Given the apparent inadequacy of the FEF$_{25–75\%}$, a need still exists to determine the presence of mild airflow limitation that occurs despite a normal FEV$_1$/FVC ratio. The FEV$_3$/FVC ratio has proven to be a useful alternative for that purpose (figure 4A). Consistent with the concept that areas of the lung that have longer time constants (ie, are slower to empty) will manifest primarily with impairment of the 'terminal' or 'distal' expiratory flows, the FEV$_3$/FVC seems to be reduced in 'early' or mild airflow limitation.[27 28] Reference equations for FEV$_3$ and FEV$_3$/FVC have been validated as well.[29 30] A significant percentage of patients (~10%) has an abnormal FEV$_3$/FVC ratio in the presence of a normal FEV$_1$/FVC ratio, with the overall pattern of their PFTs otherwise consistent with mild airflow limitation.[31] However, the FEV$_3$/FVC has not fared well against the FEV$_1$/FVC in specific settings such as occupational health screening[32] (in part because air trapping by body plethysmography, which is the gold standard test, may not be present
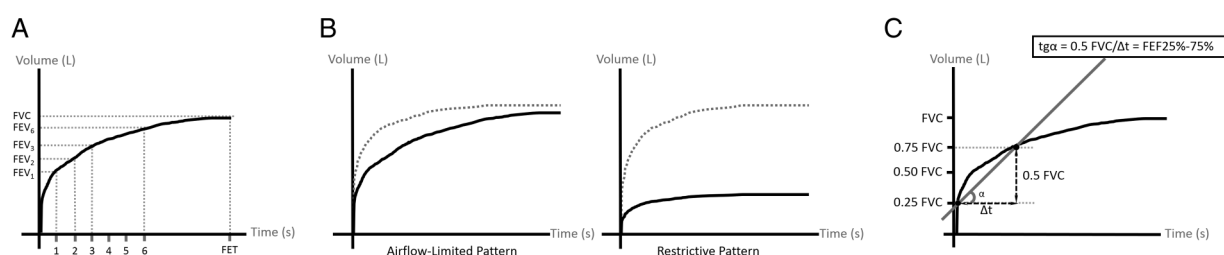
Figure 4 The volume–time curve. (A) The volume–time curve is presented with time along the x-axis and volume along the y-axis. The FEV$_1$ is the volume exhaled in 1 s, while the forced vital capacity is the volume exhaled during the entirety of the breath (the forced expiratory time, FET). The forced expiratory volumes at 2, 3, and 6 s are determined by the volumes exhaled at those respective times. (B) The volume–time curve has a characteristic shape depending on the underlying pathology. In airflow limitation, the curve rises more slowly and does not plateau appropriately (ie, additional volume continues to be exhaled even at the conclusion of the breath). In restrictive lung disease, the curve rises and plateaus prematurely. (C) The maximal mid-expiratory flow (FEF$_{25\%–75\%}$) is determined by drawing a line between the points at which 25% and 75% of the FVC has been exhaled. The triangle described by that line (as the hypotenuse), the change in volume (as the perpendicular), and the change in time (as the base) allow for assessment of the angle α, which is the FEF$_{25\%–75\%}$.

in mild airflow limitation). Further, the FEV_3/FVC ratio relies on the FVC, which makes it subject to the same problems inherent in the FEV_1/FVC ratio when the test is not of sufficient duration to fully assess the true FVC. In that context, the FEV_2 and the FEV_3 have been shown to adequately estimate FVC using the following equation based on a linear regression model[33] that is especially useful when forced expiratory times are short:

$$\text{Estimated FVC} = 0.261 + (0.842 \times FEV_3) \\ + (3.497 \times [FEV_3 - FEV_2]) \quad (2)$$

Although the equation does not eliminate the problem of underdiagnosing airflow limitation due to an underestimated FVC, it does help mitigate the problem of underestimating FVC due to an inadequate expiratory time.

Ratio of residual volume to total lung capacity (RV/TLC)

The RV is the amount of air remaining in the chest after a maximal exhalation. It is typically obtained with the following equation:

$$\text{TLC} = \text{FVC} + \text{RV} \quad (3)$$

The TLC can in turn be obtained by either plethysmography or multiple-breath washout test, and the FVC can be obtained during normal spirometry.[34] Thus, the RV/TLC ratio reflects the amount of air remaining in the lungs after a maximal exhalation compared with the amount of air present in the lungs after a maximal inspiration (figure 5A). As such, it has become established as a standard measurement of air trapping and hyperinflation in severe airflow-limiting diseases. Hyperinflation correlates with several clinical indices, for example, dyspnea and exercise intolerance,[35] as well as markers of inflammation.[36] It has been previously shown to reflect air trapping in smokers and patients with airflow-limiting diseases such as asthma and emphysema[37–39] as well as nitric oxide levels in asthma.[40] The RV/TLC ratio has also been used to assess response to treatment with inhaled corticosteroids.[41] In one small study, the RV/TLC ratio was abnormal in a larger subset of patients with underlying asthma (RV/TLC>35%) than FEV_1/FVC ratio.[42] Interestingly, the investigators observed no relationship between RV reversibility and FEV_1 reversibility and speculated that the RV may be a better measurement for persistent obstruction of the small airways. In obesity, it does not seem to vary with increasing body mass index (unlike FRC/TLC), suggesting that the two values tend to decrease proportionally in obesity.[43] Of note, several investigators have defined normal RV/TLC values, which may vary based on the method used to evaluate TLC, but are typically below 35%.[44] The variability of the index, as assessed by variability of its respective components, is fairly good.[45 46] Overall, the RV/TLC ratio seems to be most useful in the investigation of asthma and emphysema as a key marker of hyperinflation.[36 47]
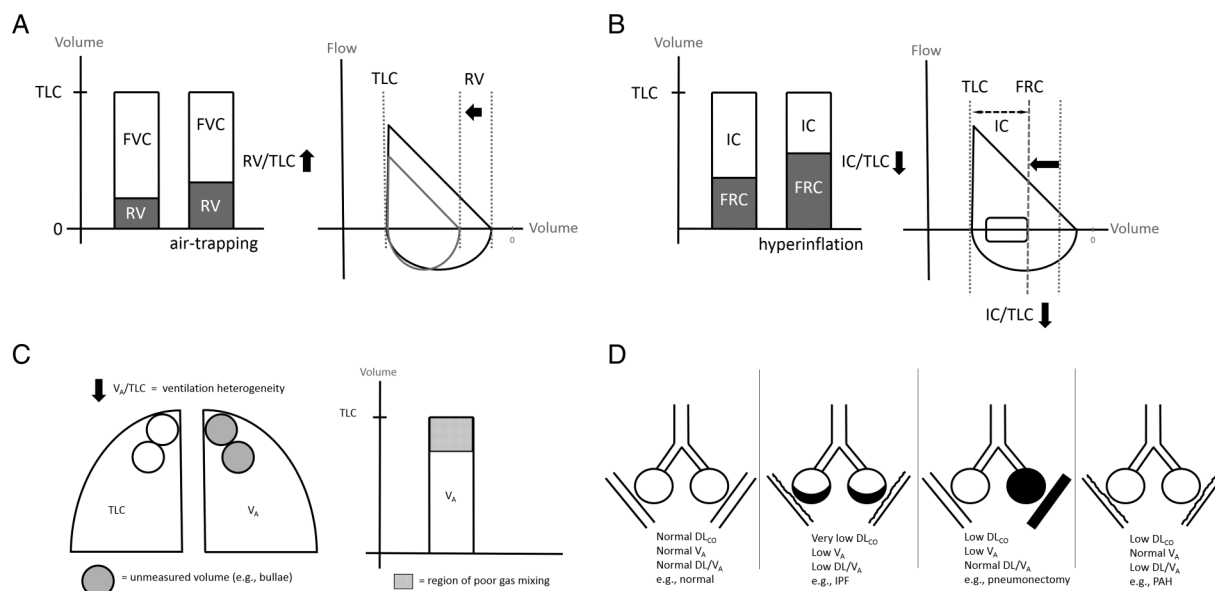
Figure 5 RV/TLC, IC/TLC, V_A/TLC, and DL/V_A. (A) The importance of a rising RV (assuming a constant TLC) is visualized first with volume on the y-axis and then with flow–volume loops (FVLs). (B) The relationship between inspiratory (IC) and functional residual capacity (FRC) is depicted here first with volume on the y-axis and then with FVLs. Assuming a constant TLC, as FRC increases, IC decreases. (C) The difference between alveolar volume (V_A) and TLC is depicted schematically. While TLC as assessed by plethysmography or multiple-breath dilution measures the total volume of air in the chest, V_A as assessed by inspiration of a tracer gas such as helium measures only the volume of air that reaches areas of the lung with normal gas mixing. With volume on the y-axis, the difference in volume between TLC and V_A reflects areas of poor gas mixing and ventilation heterogeneity. (D) In conditions causing a low diffusing capacity of lungs for carbon monoxide (DL$_{CO}$), the DL/V_A can be used to point toward the underlying pathology. A very low DL$_{CO}$ associated with a low V_A and a low DL/V_A suggests alveolar or microvascular destruction as is seen in idiopathic pulmonary fibrosis (IPF). In association with a low DL$_{CO}$, a low V_A and a normal DL/V_A suggest an increase in pulmonary capillary blood volume relative to alveolar volume, as is seen post pneumonectomy. A low DL$_{CO}$ associated with a normal V_A and a low DL/V_A suggests microvascular destruction or remodeling, as is seen in pulmonary arterial hypertension (PAH).

Inspiratory fraction (IC/TLC)

Symptoms in airflow-limiting diseases are not always related strictly to the FEV_1, a fact that has led many investigators to search for other objective indices that correlate better with patient symptoms. One such index that has shown promise in multiple studies is IC/TLC, also referred to as the inspiratory fraction (IF) which can be understood physiologically through the following relationships:

$$TLC - FRC = IC; IF = IC/TLC = 1 - (FRC/TLC) \quad (4)$$

Assuming a constant TLC, as the IC goes down, the FRC must go up[48] (figure 5B). An elevated FRC in turn reflects hyperinflation and increasing work of breathing. Given that, a lower IF reflects an elevated FRC and has been associated with numerous untoward outcomes. In addition, because IC can be measured without the use of plethysmography, it can also be used to track changes to FRC during cardiopulmonary exercise testing (though FRC is typically called end-expiratory lung volume in this setting) and thereby provide useful information on dynamic hyperinflation.[49]

The most common cut-off level studied for poor outcomes is an IF<0.25, though other cut-offs have been used as well (eg, IF<0.23). Studies have correlated IF with survival in emphysema,[50] to increased exacerbations,[51] exercise tolerance,[52] and also with symptoms.[53] One model of dynamic hyperinflation (as assessed by the IF) found that both IF and ΔIF are significantly related to emergency department visits and hospital admissions.[54] Another study found that an IF<0.28 was the best predictor of peak oxygen uptake <60% in Global Initiative for Chronic Obstructive Lung Disease (GOLD) stages II and III,[55] with a specificity of 89.6%, sensitivity of 80%, and an overall accuracy of 86.3%. Further, the IF responds to administration of bronchodilators as well, with an increase in IC representing a decrease in lung hyperinflation.[56] A longitudinal study found that a rapid rate of IC/TLC decline is closely related to high symptom score (modified Medical Research Council), high Charlson comorbidity score, and low postbronchodilator FEV_1.[57]

Although it has been studied mostly in COPD, investigators have found usefulness of IF in other settings as well, including the assessment of therapeutic response to continuous positive airway pressure (CPAP),[58] or in the setting of pulmonary arterial hypertension, where IC was found to be a more useful predictor of survival than the IF.[59] Despite its usefulness, the fact that the IF provides more information on prognosis than in diagnosis has likely limited its use in routine practice, though the number of available studies supporting its value, particularly in emphysema, certainly argue for more frequent use.

Ratio of alveolar volume to total lung capacity (V_A/TLC)

Physiologically, V_A/TLC relies on two different methods for calculating TLC, with the understanding that a difference between the two methods suggests a degree of ventilation heterogeneity[60] (figure 5C). The TLC (as calculated by plethysmography or multiple-breath dilution method) represents the total volume of the lungs, inclusive of bullae and other areas of poor gas mixing. The V_A is obtained during a measurement of DL_{CO} and represents the volume of gas in the lungs accessible to the gas exchange surface.[61] It is obtained by inhalation of a tracer gas during the single-breath DL_{CO} maneuver after subtracting an estimated anatomic dead space from the inspired volume (V_{insp}). As the V_A represents the volume of air accessible for gas exchange, the differences between the V_A and the TLC reflect poor gas mixing, as is seen in airflow-limiting disorders.

Despite its potential usefulness in evaluating ventilation heterogeneity in airflow-limiting diseases, the V_A/TLC has failed to achieve widespread acceptance thus far. This failure may be due in part to the fact that a normal V_A/TLC has been somewhat difficult to determine. Some investigators have found no correlation with age,[62] while others have found a slight decrease in the normal ratio of older patients.[63] A large study examining the spectrum of normal V_A/TLC ratios found that an FEV_1/FVC ratio >0.70 is correlated with a V_A/TLC of ~0.98.[64]

Another significant issue with the V_A/TLC is the lack of specific standards for V_A itself. The measurement is likely underestimated if a patient starts to inhale at a level above RV or does not inhale fully to TLC. The ATS/ERS criteria state that V_{insp} should be at least 85% of the highest VC and note that variation of as high as 15% reduces the DL_{CO} by <5%.[65] Basing the acceptable variance of V_A on variation in the DL_{CO} highlights the fact that the V_A measurement is optimized for DL_{CO} and not for TLC. Further, there does appear to be some variability in V_A/TLC depending on whether plethysmography or multiple breath dilution is used to evaluate TLC.[46] That said, data suggesting a fairly strong correlation between single-breath and multibreath values for TLC under normal circumstances and divergent values in patients with airflow-limiting diseases suggest that the V_A/TLC may be useful clinically as a measurement of ventilation heterogeneity.[64 66–68] Of recent clinical interest, a 2014 study on the V_A/TLC found that it correlates well with the degree of airway responsiveness in asthma during a methacholine challenge,[60] suggesting that the ratio may yet find a role in the management of specific patient populations.

Ratio of diffusing capacity of lungs to alveolar volume (DL/V_A)

The DL/V_A, often referred to as the K_{CO} or transfer factor, is based on measurements made during a single breath DL_{CO} maneuver. During this maneuver, a patient exhales to RV before rapidly inhaling a mixture of air, carbon monoxide (CO), and a tracer gas (usually helium). The patient performs a 10 s breath hold before rapidly exhaling. The expired gas is then collected for analysis, with the tracer gas used to calculate the V_A and the rate of uptake of CO from alveolar gas representing DL/V_A. The product of the two, DL_{CO}, is a key measurement of traditional PFTs.[69] A low DL_{CO} can imply microvascular destruction, loss of lung units, alveolar capillary damage, or lack of alveolar expansion.[61] An elevated DL_{CO} has been associated with diseases or pathologic states that increase pulmonary blood flow or increase alveolar capillary uptake.[70] DL_{CO} measurement is of great practical importance, being the overall measure of gas transport. Its interpretation is complicated by the fact that it does not measure a specific part of a multistep process: (1) first CO crosses the alveolar–capillary barrier or membrane (represented by D_M) and then (2) CO combines

with the hemoglobin in capillary red blood cells at a rate θ multiplied by the volume of available capillary blood (V_c). Since these steps are in series, the conductances add as the sum of the reciprocals: $DL_{CO}^{-1} = D_M^{-1} + (\theta \times V_c)^{-1}$. Readers interested in the details of the methodology are referred to an excellent review by Drs Hughes and Pride on the subject.[61]

When the DL_{CO} was first described, it was thought to be linearly proportional to the V_A and that the DL/V_A was a constant. Later studies showed that the relationship between DL_{CO} and V_A is not linear, which meant that DL/V_A is in fact not a constant, but rather reflects a DL_{CO} for a given value of V_A.[61] Nevertheless, the DL/V_A can be a useful adjunct when interpreted in concert with the DL_{CO} and the V_A. Given a low DL_{CO}, a low DL/V_A implies a reduced rate of CO uptake in the lungs and can represent microvascular destruction or remodeling (when associated with a normal V_A) and alveolar or microvascular destruction (when associated with a low V_A). In contrast, a high DL/V_A implies a relative increase in pulmonary capillary blood volume relative to alveolar volume and is associated with an increase in pulmonary blood flow (when associated with a normal V_A, as can be seen in asthma) or incomplete alveolar expansion, increased pulmonary blood flow, microvascular congestion, or alveolar hemorrhage (when associated with a low V_A) (figure 5D).

Despite the useful information it can provide in the proper context, the DL/V_A is still quite controversial, due at least in part to difficulties in interpreting the definition of 'diffusing capacity per unit volume' used in the joint ATS/ERS guidelines.[65] Although the phrase could be taken to mean that the DL/V_A represents DL_{CO} 'corrected' for alveolar volume, it is more appropriately thought of as representing alveolar CO uptake efficiency. Other significant issues with the index include the fact that diseases in which ventilation is uneven (such as emphysema) cannot be assumed to have the same diffusion properties as normal areas of the lung, making the index subject to a number of potentially inappropriate assumptions. In addition, some have questioned the value it adds to the DL_{CO} itself, in the case of predicting desaturation with exercise[71] or in adding to the diagnostic evaluation,[72] for example. Others have pointed out the difficulty in standardizing the DL/V_A in the face of an abnormal TLC.[73]

Despite those concerns, the DL/V_A can be a helpful diagnostic tool in particular settings, such as the work-up of diffuse parenchymal lung disease (by virtue of the different combinations of DL_{CO}, V_A, and DL/V_A found in different diseases depending on the pathogenesis)[74] and respiratory muscle weakness (by virtue of the increase in DL/V_A seen in inspiratory muscle or diaphragmatic weakness),[75] as long as its limitations are understood and the data it offers are properly contextualized. Even then, it is important for the practicing clinician to remain aware of the data that can be gleaned from DL_{CO} and the DL/V_A longitudinally and avoid placing too much emphasis on one particular test at any given time.

RESEARCH APPLICATIONS AND FUTURE DIRECTIONS

An expanded repertoire of indices allows for additional nuance in the design of research trials. For example, the indices described above that allow for an assessment of hyperinflation and air trapping could serve as useful benchmarks against which to measure the efficacy of novel biomarkers. Such studies would also benefit greatly from the use of indices that can aid in the diagnosis of early airflow limitation (eg, the FEV_3/FVC) in order to evaluate the ability of a biomarker to detect diseases before traditional indices of pulmonary function. In addition, these indices could serve as helpful adjuncts in efforts to establish phenotypes of disease, some of which could be categorized by degree of ventilation heterogeneity or altered inspiratory fraction, for example.

Although the focus of this review has primarily been on indices obtainable from traditional pulmonary function testing, many other techniques exist to fill the gaps created by standard testing. Exhaled nitric oxide levels, for example, offer useful information regarding chronic (eosinophilic) airway inflammation,[76] while techniques such as impulse oscillometry and flow interruption can provide useful information on the lung function of patients who are unable to participate in standard testing.[77 78] Further, as demonstrated by the discussion of FVL quantification above, tools of graphical analysis will no doubt offer new insights into traditional functional indices moving forward. Technological advances are also creating new opportunities for the study of lung function that do not require the use of full pulmonary function laboratories, including measurement of TLC using flow interruption techniques and diagnostic examinations based on the analysis of tidal breathing. Knowledge of the core physiologic principles described in this review will enhance the ability of researchers to apply new technologies to the study of pulmonary function.

CONCLUSION

The indices described here offer crucial data for diagnosis, management, and prognostic stratification in respiratory disease. Most helpfully, they can all be obtained through the use of spirometry, lung volume assessment (plethysmography or multiple-breath dilution), and diffusing capacity of carbon monoxide. Many modern pulmonary function laboratories are capable of deriving and reporting these measurements without the need for any additional equipment or software. Most importantly, a thorough understanding of these indices will lead to a better overall understanding of what lung function testing can tell us clinically and in research and how the numbers that clinicians use are generated. Although each of the indices must be interpreted in the light of certain important caveats, most can be useful if deployed and understood in the proper context.

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