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Spirometric Indices of Early Airflow Impairment in Individuals at Risk of Developing COPD: Spirometry Beyond FEV_1/FVC

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Abstract

Spirometry is the current gold standard for diagnosing and monitoring the progression of Chronic Obstructive Pulmonary Disease (COPD). However, many current and former smokers who do not meet established spirometric criteria for the diagnosis of this disease have symptoms and clinical courses similar to those with diagnosed COPD. Large longitudinal observational studies following individuals at risk of developing COPD offer us additional insight into spirometric patterns of disease development and progression. Analysis of forced expiratory maneuver changes over time may allow us to better understand early changes predictive of progressive disease. This review discusses the theoretical ability of spirometry to capture fine pathophysiologic changes in early airway disease, highlights the shortcomings of current diagnostic criteria, and reviews existing evidence for spirometric measures which may be used to better detect early airflow impairment.

Keywords

early COPD; spirometry; obstruction

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1. Introduction

Chronic obstructive pulmonary disease (COPD) is a leading cause of morbidity and mortality worldwide[1]. Unfortunately, COPD is also often recognized late in the clinical course. Because adequate and timely pharmacologic management and lifestyle modification can impact the disease progression[2–6], early identification of COPD is a top priority in global efforts to control this disease.

Spirometry is non-invasive, inexpensive, widely available, and easily reproducible; it remains the gold standard for diagnosis and monitoring of COPD. A wide range of spirometric parameters are routinely reported, but clinical use of measures other than the forced expiratory volume in one second (FEV_1), forced vital capacity (FVC), and the ratio of these two measures has been limited. While COPD is defined by a post-bronchodilator ratio of $FEV_1/FVC < 0.70$, pathophysiologic changes in the airways and lung parenchyma that characterize COPD start well before this criterion is met[7,8]. This review discusses the theoretical ability of spirometry to capture fine pathophysiologic changes in early airway disease, highlights the shortcomings of current diagnostic criteria, and discusses existing evidence for selected spirometric indices reflecting early airflow impairment in individuals at risk of COPD.

2. Airway disease preceding COPD

Important pathophysiologic changes occur in the lung prior to the development of a FEV_1 to FVC ratio below the threshold of normal (i.e. less than 0.70 or the lower limit of normal)[9,10]. Early airways changes preceding COPD are localized in small airways[11,12] with the development of emphysema in some patients[13,14]. Small airways, the term which anatomically corresponds to terminal or respiratory bronchioles with a luminal diameter of 2mm or smaller, represent the key anatomic point in the development of COPD. Inflammation in small airways is a determinant of the progression and severity of disease[15] and mucus plugging or narrowing and obliteration of the small airways lead to large increase in resistance subsequently leading to development of hyperinflation and emphysema[16]. Not easily captured by FEV_1 and FVC, these smoking-induced changes in small airways are pathologically visible well before conventional spirometric measures change[8], and can also be directly measured by catheterization of post-mortem lungs[17,18], impulse of forced oscillometry techniques[19] or via imaging[20].

It is known that tobacco smoke influences epigenetic reprogramming, remodeling, and hyperplasia of airway basal cells[21], and compromises regeneration of small airway epithelium[22,23]. Forty-two percent of current and former smokers with normal spirometry have evidence of emphysema or airway thickening on chest computed tomography (CT) scans[24]. Low diffusing capacity of the lung for carbon monoxide (DL_{CO}) in smokers with normal FEV_1/FVC ratio is not uncommon, and these individuals are at significant risk of developing COPD[25,26]. Some smokers without COPD, *i.e.* with “so-called” preserved spirometry, have significant respiratory symptoms, activity limitation, exacerbations and evidence of airway disease in a similar fashion to those who have COPD and similar

symptoms[27]. Initial airway disease extends across a spectrum of spirometric results, including values above an abnormal FEV_1/FVC.

Celli and Augustí[28], as part of an effort to update COPD taxonomy, drew a parallel with medical concepts of pre-diabetes or pre-hypertension to propose a more general definition for "pre-COPD" as respiratory symptoms with emphysema on CT. The concept of "pre-COPD" syndrome is not new though. Preserved ratio impaired spirometry (PRISm) refers to normal FEV1/FVC ratio but decreased FEV_1[29]. Previously widely used GOLD Stage 0[30], refers to individuals with respiratory symptoms (i.e. cough and sputum production) in the absence of abnormal FEV1/FVC ratio. While individuals with PRISM have higher risk of developing COPD over time[31], airway abnormalities present in these clinical scenarios may or may not evolve into COPD over time. Martinez *et al*[32] recognized the need for clear, objective criteria to distinguish these early airway changes from "early" COPD. They proposed that an ever-smoking individual (≥10 pack-years), aged <50 years with either reduced FEV_1/FVC below the lower limit of normal (LLN), airway abnormality and/or emphysema on CT, or FEV_1 decline ≥60 mL per year may be considered to suffer early COPD. Several other attempts to unify subjective and objective measures in order to more clearly define the early COPD patient[33,34] were made, yet no consensus definition exists.

The syndrome encompassing these early airway abnormalities may not be clearly defined, but it is evident that it should be distinguished from "mild" COPD, where the formal diagnosis of COPD is established based on FEV_1/FVC[34,35] or "early" COPD where manifestations of COPD are present at younger age[33]. In the search for metrics capable of distinguishing early airway disease from simply mild COPD, a measure of early airflow impairment should:

1. be present in individuals with FEV_1/FVC >0.70 or >LLN *and*,
2. serve as an objective correlate to subjective respiratory symptoms *and/or*,
3. correlate with other objective features of COPD such as emphysema on computed tomography, reduced DL_{CO} or air trapping *and/or*,
4. predict future outcomes, such as accelerated decline in pulmonary function, hospitalization for acute respiratory symptoms consistent with an exacerbation, or mortality

Detailed analysis of lung function decline over time may allow for better understanding of the concept of early disease and help distinguish whether such a measure is predictive of progression to COPD[36] or is associated with a separate smoking-related condition, which does not necessary progress to spirometrically defined COPD[37].

3. Spirometry in diagnosing COPD

Spirometry is a safe, reproducible, and practical test that is widely used as an objective measure of lung function. While standard spirometric analysis offers a number of parameters, most often used are FEV_1 and FVC, and their ratio is considered necessary for the diagnosis and staging of COPD. Pulmonary function tests are generally highly repeatable[38] and FEV_1 and FVC are more reproducible than expiratory flow

measurements[39]. Nonetheless, some limitations related to the use of FEV_1 and FVC in diagnosing COPD need to be pointed out. FEV_1 and FVC are variable on a diurnal basis[40], and considerable between-test variability has been observed in relation to patient age, sex, smoking status, region, COPD severity[41] and even spirometer device selection[42]. The challenge posed by measurement variability even in the research setting is compounded by variability in the disease itself. There is a growing recognition of various pathologic and clinical phenotypes of COPD[43–45], for which different spirometric indices may be relevant. The sensitivity of FEV_1 to capture early smoking-related airway disease is limited. It best captures flow-based changes in early portions of forced exhalation, and much less so in later stages of expiration, which is exactly where small airway disease changes could be captured. The FEV_1/FVC ratio has limitations for detection of early airflow obstruction. Compared to slow expiratory vital capacity (SVC) or forced inspiratory vital capacity (FIVC), FVC drops to a greater extent in early airflow obstruction due to dynamic air trapping[46]. This relative decrease in FVC with airway obstruction blunts the sensitivity of FEV_1/FVC ratio. Prior international spirometry standardization statements have treated the FEV_1/VC denominator differently, including the following: ECCS/ERS 1993[47] – FIVC or "relaxed expiratory" VC should be used; ATS/ERS 2005[48] – largest VC should be used (and the ATS 2017 spirometry reporting recommendations[49] note measurement of SVC is "a useful adjunct in patients with suspected airflow obstruction"); and GOLD 2016[35] – only utilizes FVC but mentions ATS/ERS statements are "increasingly suggesting" use of SVC.

There is disagreement between different guidelines and literature[50] as to the use of a fixed FEV_1/FVC ratio or the LLN for diagnosis of airflow obstruction. It is well recognized that FEV_1/FVC declines with age and as such, a fixed ratio leads to high rates of COPD diagnosis in elderly and under-diagnosis of COPD among younger individuals[51–53]. It is not clear to what degree the increased diagnosis of COPD in the elderly represents overdiagnosis of normal age-related changes versus unrecognized disease. Individuals with FEV_1/FVC <0.70 but above LLN have been shown to have more emphysema, air-trapping on CT[54,55], lower $FEF_{25-75\%}$ and to use more respiratory medication[55], as well as to have more hospitalizations and higher mortality,[56] than patients with normal lung function by both parameters[56]. These findings suggest using LLN rather than fixed ratio may fail to identify cases of early airflow compromise, especially in an elderly population. However, in retrospective analysis of the NHANES-III database, Hansen *et al*[57] found an unacceptably high proportion of misdiagnosis with a fixed ratio. Approximately half of abnormal young adults were identified as normal and a fifth of normal older adults were identified as abnormal when compared to LLN[57]. ATS/ERS 2005 guidelines[48] recommend use of LLN for interpretation of FEV1/FVC. GOLD 2016 guidelines[35] utilize a fixed ratio, but note that "many experts recommend use of [LLN]" and "FEV_1/FVC ratio may need to be lowered to 0.65" as the threshold for abnormality among individuals over 70 years old. Using FEV_1/FVC of 0.70 as a threshold for COPD diagnosis is also problematic as significant variability is seen on repeated testing[58], suggesting that repeated spirometric assessments may be required. Additionally, it should be noted that there is lack of standardization of pre- versus post-bronchodilator (BD) measurements of FEV_1 and FVC. GOLD guidelines recommend post-bronchodilator measurements, but it is not clear that this is necessary or superior to pre-bronchodilator measurements. In the Lung Health Study[59] pre- and post-BD

measurements predicted mortality equally well. In the more recent COPDGene cohort[60], both pre and post-BD predicted certain cardinal features of COPD including symptoms and exercise tolerance. However, post-BD was a better predictor of long-term mortality in COPDGene[60] and a prospective study[61]. There is insufficient data to define which should be used when examining early airflow obstruction preceding COPD, but bronchodilator administration must be accounted for when comparing spirometric indices.

Finally, one conceptual remark relates to the clinical requirement to dichotomize whether the disease is “present” or “absent”, where strict spirometric criteria are needed. However, from a pathophysiologic standpoint, the development of airflow obstruction occurs over many years and the point where these changes are considered a “disease” is arbitrary (Figure 1). Taken together, these arguments suggest that clinically relevant dysfunction may exist despite normal current diagnostic criteria, and additional parameters able to objectively evaluate subtle airway abnormalities could be useful in interpretation of borderline FEV_1/FVC.

4. Spirometric indices of early airflow impairment beyond FEV_1 and FVC

Spirometry offers abundant information about the function of the respiratory system, and it extends beyond measures such as FEV_1 and FVC. Modern spirometers are built with sensitive real-time flow sensors which directly measure the flow of inhaled or exhaled air and obtain volumes by electronic or numerical integration. They can immediately display the real-time graphical spirogram and calculate reference values including the lower limit of normal. Analysis of spirometric data in the era of digital technology and machine learning, combined with a focus on recognition of early pathologic changes, offers the ability to explore and better understand other, less frequently used spirometric measures than FEV_1 and FVC and develop novel parameters which could be used for detection of small airways disease and early airflow impairment. These indices are divided into five categories based on the mathematical approach used to analyze spirometric data. A summary of previously reported parameters and their categorization follows in Table 1.

4.1. Lung capacity indices

A number of lung capacity maneuvers are obtained during PFTs. An advantage of measuring lung capacities is predictability of normal ranges based on genetic sex, age, weight, height and race/ethnicity of the subject[62]. Spirometry allows for measurement of vital capacity (VC) - a sum of tidal volume (V_T), inspiratory and expiratory reserve volumes (IRV and ERV) - and inspiratory capacity (IC), a sum of V_T and IRV (Figure 2). VC can be measured while doing a slow (SIVC) or forceful (FIVC) inspiratory maneuver starting from residual volume (RV) up to the level of total lung capacity (TLC), or a slow (SEVC, commonly referred to as SVC) or forceful (FEVC, commonly referred to as FVC) expiration starting from TLC down to the level of RV[63]. Since airways resistance and effort differ between inspiration and expiration, VC varies in these maneuvers. The differences between the four types of VC are minimal in those with no obstruction. In patients with obstruction, FIVC is usually the largest and FVC the smallest of measured capacities, the latter being most frequently and most significantly affected in COPD[63].

Although forced maneuvers are effort-dependent, they provide more information on flow-resistive characteristics than tidal maneuvers[64]. The high pressure generated in forced expiration pre-disposes to air trapping due to dynamic airway compression, leading to a fall in FVC in obstructed lungs. This effect is not as dramatic with a slow expiratory maneuver (SVC) or an inspiratory maneuver. The **difference between SVC and FVC** (Figure 2) has been described as a marker of air trapping, an early step in the development of obstruction[63,65]. This difference is also an independent predictor of diminished exercise tolerance and peak oxygen uptake in COPD patients[66]. However, interpretation of this index is complicated by the observation that body mass index (BMI) has a large impact on baseline vital capacities. In individuals with low BMI, FVC is larger than SVC, whereas FVC is smaller than SVC in individuals with high BMI[67]. A related index, **FVC to SVC ratio** (FVC/SVC) may give insight to changes in small airways - an important early step in COPD development. FVC/SVC decreased from baseline in lung transplant patients who develop bronchiolitis obliterans syndrome, a primarily small airways obstructive disease[68]. Compared to FVC, the stability of SVC may increase the sensitivity of spirometry to detect mild airflow obstruction, regardless of the defining criterion of obstruction (FEV_1/FVC <0.70 or <LLN)[63,69]. Since the discrepancy between FVC and SVC increases with age, a decrement below a fixed **FEV_1/SVC** ratio may better indicate obstruction in young individuals than in the elderly, where specificity may be reduced[70]. The obvious limiting factor for wider use of this metric is the lack of validation studies that would refer to clinical benefits of this more sensitive metric of diagnosing obstruction. In addition, lack of accepted LLN values for SVC makes interpretation more difficult given the significant impact of age or body habitus. Since expiratory time is usually longer than inspiratory time, and any leak caused by the patient or spirometer can affect expiration more than inspiration, and thus lead to lower FVC than FIVC. While assessing the **difference between FIVC and FVC** may help in detection of technically inadequate forced expiratory maneuvers, reduced FVC in comparison to FIVC can also be the consequence of the initiation of inhalation before the exhalation is complete in the FVC maneuver, which can be a sign of gas trapping (Figure 2) and can happen in individuals with severe airway obstruction[63,65,66,71].

The relationship between FIVC, SVC and FVC remains to be studied in mildly obstructed patients, but the ability to detect air trapping and potentially small airway changes may be useful in identifying early steps in COPD pathophysiology.

Inspiratory capacity (**IC**) may be helpful in assessing severity, prognosis and response to treatment of airway obstruction. Worsening obstruction and alteration in the elastic properties of the lungs of patients with COPD are associated with the development of progressive lung hyperinflation and decline in the resting IC[72]. Since bronchodilator (BD) administration can reduce lung hyperinflation in the absence of significant improvement in FEV_1 in advanced emphysema, improvement in IC can indirectly reflect the effect of a BD on hyperinflation reduction. Reduced IC in COPD as a consequence of increased functional residual capacity correlates with decreased exercise tolerance[73], increased dyspnea[74], and all-cause and respiratory mortality[75]. Compared to FEV_1, IC better correlated with symptom severity during acute COPD exacerbation[76]. IC/TLC ratio <25% has been shown to be a predictor of exacerbations and death in patients with emphysematous COPD[77].

4.2. Time-fractioned lung volume indices

Time-based lung volume fractions have the benefit of reproducibility, simplicity of calculation, and familiarity. The most widely used metric is FEV_1. There are several alternatives to FEV_1 which provide information about different components of the forced expiratory maneuver (Figure 3).

The forced expiratory volume in six seconds (**FEV_6**) has been used as a potential alternative to FVC. Measuring FEV_6 instead of FVC reduces duration of exhalation to six seconds, allowing for standardization of expiratory maneuver and limiting the effect of conscious effort to prolong the maneuver. FEV_6 is more reproducible and less difficult to perform than FVC[78] and performs well with office-based, hand-held devices[79]. In patient with COPD, an **FEV_1/FEV_6** ratio in the lowest quartile (<74% predicted) and second lowest quartile (74-84% predicted) was shown to be an independent predictor of mortality and hospitalizations, and low FEV_6 may predict future lung function decline[80]. A meta-analysis of eleven studies showed reduced FEV_1/FEV_6 ratio to be a sensitive and specific measure of airflow obstruction[81]. In the NHANES-III cohort, a LLN cutoff for FEV_1/FEV_6 outperformed FEV_1/FVC in identifying smokers[78]. The most direct evidence of benefit in predicting early airway disease comes from work by Bhatt *et al*[82] using the COPDGene cohort. Patients with FEV_1/FEV_6 <0.73 but FEV_1/FVC above 0.70 or LLN had greater air trapping and airway wall thickness, poorer functional capacity, and a greater number of respiratory exacerbations at follow-up in comparison to those with reduced FEV_1/FVC in isolation[82]. Similar results have been demonstrated in other large cohorts[52,83]. FEV_1/FEV_6 was found to be less sensitive than FEV_1/FVC to detect obstruction, but those with isolated reduction in FEV_1/FEV_6 had greater physiologic abnormalities in spirometry, diffusing capacity, and metrics of air trapping[83]. Based on these data, while FEV_1/FEV_6 may not be a replacement for FEV_1/FVC, inclusion may facilitate the detection of more individuals near conventional diagnostic cutoffs with important features of early airway disease.

In comparison to FEV_1, extending the measurement of expired volume to the first three seconds of forced exhalation has the advantage of offering additional insight into air flow through small airways. The forced expiratory volume in three seconds (**FEV_3**) has shown value for detecting early obstruction. Morris *et al*[84,85] in a single center study of over 13,000 patients, demonstrated that an isolated reduction in **FEV_3/FVC**, with normal FEV_1/FVC, was associated with greater degrees of hyperinflation (higher RV and TLC), air trapping (RV/TLC ratio), and loss of diffusing capacity of the lung for carbon monoxide (DL_{CO}) compared to those with normal FEV_3/FVC and FEV_1/FVC. While it has been argued that FEV_3/FVC may simply be an overly sensitive measure of mild obstruction of any etiology that lacks specificity[86], Hansen *et al*[78,87] established mean and 95% confidence limits for the LLN values for FEV_3 and demonstrated that FEV_3/FVC and **FEV_3/FEV_6** identified significantly more smokers in the NHANES-III dataset than FEV_1/FVC or FEV_1/FEV_6 respectively[78].

$FEV_{0.5}$/FVC and **$FEV_{0.75}$/FVC** are used in measuring obstruction in infants and children with wheezing[88]. However, despite inclusion in spirometry reference values in the past[89,90], these measures have been rarely used in adults.

4.3. Flow-based indices

Instantaneous and mean flows may be derived from various points on the flow volume curve to capture flow dynamics at different portions of the forced expiratory maneuver (Figure 4). Flow-based indices may serve as a more direct measure of small airways than time-based indices as the former may be measured over only the later, effort-independent, portion of the flow-volume curve.

The mean forced expiratory flow between 25% and 75% of the forced vital capacity (**FEF_{25-75}**) is the most studied and most widely reported forced expiratory flow measure. There is a wealth of information linking FEF_{25-75} to small airway disease in a variety of conditions. It is reduced in early bronchial impairment in allergic rhinitis[91], is a marker for early diagnosis of bronchiolitis obliterans[92,93] and correlates with eosinophilic inflammation[94]. In regard to COPD, FEF_{25-75} is lower in current and former smokers with no evidence of airflow obstruction as conventionally defined in comparison to healthy individuals[95]. It also correlates with second hand smoke exposure in adolescents[96] and with air trapping seen on chest CT imaging[97]. Nonetheless, the clinical utility of FEF_{25-75} has been limited, primarily by the wide range of normal values and within-subject variability. Different cut-off values have been proposed to be considered abnormal, the most commonly used cut off being < 65% of predicted flow[98]. But percentile LLN varies greatly among different patient populations; for example, the 5th percentile LLN is <35% predicted for those over 80 years old[99]. In NHANES III healthy controls[100], height, weight, gender and ethnicity all account for a relatively small portion of variability in FEF_{25-75}, making standardization of this metric challenging. The problems with interpretation of forced expiratory flows are even greater in patients with airway disease. Expiratory flow in small airways is, in part, dependent on the interplay of inward force of high pleural pressure and outward force of elastic recoil – which is dependent on lung volume. It is not practical to measure flows as a percentage of total lung volume, so percentage of FVC is used as a surrogate. FVC occurs at different total lung volumes depending on individual patient characteristics, introducing variability that contributes to large reference intervals for predicted values[99,101]. Furthermore, as obstruction develops, RV typically increases and FVC occurs at higher lung volumes, which limits even comparison of forced expiratory flow measures in any individual subject as his/her disease progresses. Abston *et al*[102] attempted to address the effect of body mass on lung volumes and flow by describing **FEF_{25-75}/FVC** and found association with several outcomes including exacerbations and mortality. A systematic study of PFT results from 22,676 consecutive patients at multiple tertiary centers called into question whether maximal mid-expiratory flows add meaningful information to FEV_1/FVC, as there was very little discordance between FEF_{25-75} and FEV/FVC in properly performed spirometry[101]. When discordant results have been found, Detels *et al*[103] showed that FEV_1/FVC identified a greater percentage of smokers as abnormal when the FEF_{25-75} was normal than vice versa. Similarly, in the NHANES-III database discordant results with FEF_{25-75} <5th percentile LLN and normal FEV_1/FVC often miscategorized never smokers as abnormal and smokers as normal[87].

Mean forced expiratory flow at 75%-85% of FVC (**FEF_{75-85}**), which falls further into the effort-independent portion of the flow volume curve, does distinguish smokers from

nonsmokers[104]. Predicted normal values were found to correlate with height, age, and smoking history[105]. However, FEF_{75-85} is highly sensitive to the FVC volume and expiratory time[106]. FEF_{50-75}, FEF_{75-85} and **FEF_{85-95}** do not predict mortality as accurately as FEV_1[107].

The instantaneous maximum expiratory flow at 50% of FVC (**FEF_{50}** or **MEF_{50}**) is the flow where half of forced vital capacity (FVC) remains to be exhaled and, unsurprisingly, it strongly correlated with FEF_{25-75}[108]. It is considered reduced when < 60 % of predicted and may be used as a surrogate of early small airways disease (defined by an abnormally low mid-expiratory flow in the presence of normal FEV_1)[109]. Significant decreases in forced expiratory flow at both 75% (**$FEF_{75\%}$**) and 50% (**$FEF_{50\%}$**) of the forced vital capacity were detected in GOLD stage 0 COPD patients compared with those in nonsmokers[110]. A related metric **FEF_{50}/0.5FVC** correlates with FEV_1/FVC ratio[111]; however whether any additional information is gained remains unclear. Forced expiratory flows are all sensitive to variability in FVC, and their utility for diagnosis of early airflow obstruction remains undefined.

The peak expiratory flow (**PEF**) is commonly obtained and is generally used as a dynamic measure for monitoring severity of airflow obstruction during an exacerbation. A protocol using PEF and a simple symptom based score identified patients with COPD in the primary care setting[112], and handheld peak flow meters seem to perform better than screening questionnaires alone at identifying undiagnosed COPD[113]. This may reflect late diagnosis of COPD in practice rather than detection of early disease. Variability among PEF values in healthy subjects is high, particularly females[100], which may limit utility for detection of mild deficits. The **$FEF_{200-1200}$** is based on the average expiratory flow rate between 0.2 and 1.2 liters of the FVC[114]. It has been considered a substitute for PEF, nevertheless it becomes progressively less accurate as the vital capacity becomes smaller[106].

Inspiratory flow features have also been reported to correlate with the status and progression of COPD even at early stages. Studies have shown that **peak inspiratory flow rate** (**PIFR**) may be reduced among females and advancing age, without a clear correlation between FEV_1 and PIFR[115]. PIFR can be reduced during COPD exacerbations. Reduced PIFR is associated with worse COPD-related symptom burden, increased odds of COPD-related hospital readmissions[116], and improved responsiveness to nebulized therapy[117].

Another ratio, **FEF_{50}/FIF_{50},** is based on maximal flows in inspiration and expiration during the flow-volume–loop maneuver. The flow during the middle of inspiration, measured at 50% of the FVC (FIF50% or MIF50%), is usually greater than the maximal expiratory flow at 50% of FVC (FEF50% or MEF50%). A FEF_{50}/FIF_{50} ratio is, therefore, usually less than 1. In lesions associated with variable extrathoracic airflow obstruction, the ratio is increased (usually greater than 1), while in lesions associated with variable intrathoracic obstruction, the ratio is diminished (0.2 or less).[64] FEF_{50}/FIF_{50} has been correlated with presence of emphysema on CT[118], although its clinical usefulness in detecting early airflow limitation has not been shown.

4.3.1. Measures of maximal expiratory flow volume curvilinearity (MEFVC)—

In addition to known spirometric indices, several attempts have been made to model

different aspects of a maximal expiratory flow-volume curve (MEFVC). A common hypothesis behind these approaches is that parameters obtained from modelling MEFVC may capture early pathophysiologic changes associated with COPD, as the shape of the MEFVC becomes abnormal before numerically derived spirometric measurements[119]. These modelling approaches could be broadly divided into two main categories. **Classic geometric indices** quantify the *degree of concavity* (section 4). **Novel computational indices,** *shape analyses* (section 5), model distinct elements of the MEFVC shape.

4.4. Classic geometric indices

The concavity of the flow volume curve is often utilized by experienced clinicians to provide a gestalt of a patient's obstructive pattern, although objective criteria for analysis are lacking. The degree of curvature has been of interest since the 1980s, with the development of indices such as angle-β by Kapp *et al*[120]. Classic geometric indices are relatively simple calculations based on discrete points on the flow volume curve or on first to second order equations which approximate the curve in order to quantify the degree of concavity. Recently, the number of such approaches has expanded, facilitated by the ease of computerized calculation.

The **angle-β** measures concavity by quantifying the angle between the slopes of the first and second halves of the expiratory limb of the flow volume curve (Figure 5A). Angle-β has been shown to be lower in patients with asthma, bronchitis, dyspnea, and wheezing than controls[117] and improves in response to bronchodilators. However, this measure is highly sensitive to attained FVC; if FVC is artifactually low due to incomplete exhalation, the mid-point will move to a lower volume which on an obstructed curve is closer to the initial steep, exponential decline in flow and thus may dramatically change the angle. In the 1990s O'Donnell *et al*[121] proposed a parameter called **flow-ratio at 75% FVC (FR_{75}).** FR_{75} was calculated as the deviation of FEF_{75} from a straight line joining FEF_{50} and RV and expressed as a percentage of FEF_{75}. A $FR_{75}>0$ indicates a convexity of the MEFVC with respect to the volume axis (Figure 5B), while an $FR_{75}<0$ indicates concavity (Figure 5C), and the magnitude reflects the degree of curvature. O'Donnell *et al* showed that FR_{75} was significantly more negative in smokers than in non-smokers and could be used as a sensitive index for early obstructive ventilatory impairment.

More recently, Johns *et al*[122] have put forward two related indices of concavity. They argue that the ***global concavity index*** is based on $FEF_{50\%}$ and quantifies concavity that usually involves the entire descending limb, and the ***peripheral concavity index*** is based on $FEF_{75\%}$, which quantifies concavity present near the terminal portion of the curve (Figure 5D). The authors found strong correlation with other measures of forced expiratory flow, greater detection of abnormality than standard indices, and some discordance between global and peripheral indices which may distinguish between different phenotypes of obstruction. More examples of mathematical equations to model the flow volume curve and quantify the concavity of MEFVC include slope ratio[123] curvature index (kmax)[124], flow-decay[125] and β-MMEF[126]; the last was also associated with increased risk of subsequent hospitalization.

Researchers have also studied the clinical significance of the **area under MEFVC (AUFVC)** and its other derivatives. AUFVC has been shown to be more sensitive to

bronchoconstriction and bronchodilation when compared to FEV_1 and other traditional parameters[127]. It is a good alternative for measuring lung function in pre-school children, especially when FEV_1 cannot be obtained due to short expiratory times[128]. Lee *et al*[129] calculated several ratios involving AUFVC that correlated well with six-minute walking distance in COPD patients. Das *et al*[130] proposed a parameter called **AreaFE%** where they express AUFVC as a percentage of a healthy reference AUFVC, estimated using predicted values of PEF, FEF_{25}, FEF_{50}, FEF_{75} and FVC. They concluded that AreaFE% is superior to traditional parameters in detecting the presence of air-trapping (RV/TLC > upper limit of normal) and severe hyperinflation (RV/TLC > 60% and IC/TLC < 25%) in COPD patients. The area under the curve in the first 3 seconds relative to the FVC has been shown to be an adequate substitute for FEV_1/FVC in suboptimal spirometry[131].

4.5. Novel computational indices

The curvilinearity of the MEFVC has held a major interest among researchers. Intuitively, in view of the variety of underlying pathophysiologic changes which converge to obstruction, there is more information to be gained by analyzing the unique shape of individual flow volume curves rather than simply the degree of concavity. As with classic geometric indices, the availability of computerized analysis, and now machine learning, is rapidly expanding the number of indices developed and the power to validate such indices.

The presence of a particular expiratory flow volume curve shape - the spirographic “kink” - due to pressure-dependent airway collapse in emphysema has long been a known concept[132], but Topalovic *et al*[133] provided a mathematical model to quantify it termed the **angle of collapse** (AC). They did so by calculating the angle between two best fitting regression lines that approximate the flow after PEF (Figure 5E). They showed that an AC below 131 degrees could be considered as a specific cut-off for predicting the presence of emphysema on CT scans in heavy smokers. Wang *et al*[134] further demonstrated that AC correlated significantly with emphysema extent quantified by percentage of low-attenuation areas less than −950 Hounsfield units (%LAA-950) in CT. They also concluded that AC ≤137 degrees could be used as a surrogate criterion for diagnosing asthma-COPD overlap.

Dynamical models describe time-dependent changes of volume or airflow during a spirometric maneuver. In mathematics a dynamical system is one which evolves over time according to a fixed rule. In spirometry the fixed rule may reflect intrinsic characteristics of the lung – i.e. elasticity, airway diameter and branching – which determine the characteristics of flow at a particular volume. One of the earliest works can be traced to the 1970s with Webster *et al*[135] in the early phases of spirometry development, who calculated **instantaneous time constants** as the ratio of remaining expiratory volume to maximal flow. Mead et al[136] developed a similar index called **slope ratios** (SR) in the late 1970s. SR is the ratio of instantaneous tangent slope (prior to point of interest) to corresponding chord slope (after point of interest) on MEFVC curves (Figure 5F). The plot of SRs against fractional expiratory volumes are sensitive to the shape of the MEFVC. Although Mead concluded that SR plots showed systematic changes with age and they were noticeably different in the abnormal curves of smokers, he speculated that they were not likely to detect early disease. Recently, Dominelli *et al*[123] showed that mild COPD patients had a significantly larger mean

SR than healthy individuals. They further concluded that the shape of the instantaneous SR and lung volume plot could, in fact, differentiate age-related changes in non-smokers (where SR was elevated and gradually increased during exhalation) from mild COPD in smokers (where SR was initially more elevated and gradually decreased throughout exhalation).

More complex dynamical models are now being developed through computerized modelling. Topalovic *et al*[137] proposed a **transfer function model** to describe flow in time after PEF and explained the baseline differences of model parameters such as poles and steady state gain between COPD and non-COPD. In a subsequent work, he applied **machine learning** to these model parameters as input to detect the presence of small airway disease in a cohort of discordant subjects (FEV_1/FVC between LLN and 0.70)[138]. Recently, Bhatt *et al*[139] derived a metric for airflow-obstruction called **parameter D** by describing the volume as an exponential function of time. They revealed that parameter D could identify additional subjects, who would be considered normal by traditional criteria, with mild disease or abnormal lung function with greater likelihood of structural lung disease.

The application of machine learning (ML) on spirometry data in detecting early obstruction may hold a promising future. ML has already been successfully applied to data from pulmonary function tests, CT, forced oscillation tests, sounds from lung auscultation and exhaled breath for diagnosing obstructive lung diseases[140]. The advantage of ML lies in the fact that it can learn complex yet subtle patterns which may distinguish early pathophysiologic changes from the effects of normal aging or smoking. We believe that there will be two different paths in the development of such algorithms. One path will involve extracting parameters through mathematical modelling of flow-volume data and feeding them as an input into a ML model, which then outputs a probability measure of a clinically relevant outcome[138]. The other path will involve a direct application of ML algorithms to flow-volume data, which in-turn will detect patterns that may associate with early COPD development. While the former approach could work in datasets with very limited samples, we believe the latter approach may require larger datasets as these models would be much larger in terms of computational complexity. However, it is still very early to comment on their comparative advantages.

4.6. Indices outside of the maximal flow volume curve

While not the focus of this review, it should be noted that several indices derived from routine spirometry other than the maximal expiratory or inspiratory flow volume curves have been studied. For example, Williams *et al*[141] analyzed the **centroids of flow-time and flow-volume waveforms** obtained from tidal breathing in spirometry. They concluded that breathing rate is faster and time to reach PEF is shorter in COPD patients with the centroids left-shifted with increasing asymmetry with airflow obstruction. In one of the only studies involving frequency domain analysis, Anogeianaki *et al*[142] studied the power spectrum characteristics of forced expiratory airflow. They showed that **airflow resonances** are sub-audible (<20 Hz) and that COPD patients have different power spectral characteristics than healthy individuals below 3.66 Hz. Combined with traditional indices, these approaches may increase the power of spirometry as a single test to distinguish unique patterns of obstruction.

5. Future of spirometry for detecting early obstruction and predicting COPD development

While it has been widely available for decades, the clinical use of spirometry remains primarily limited to FEV_1 and FVC analysis. Advances in understanding of the biologic mechanisms underlying early airway abnormalities in smokers hold promise for development of early interventions, highlighting the clinical imperative to identify early disease. In this context, spirometry may be an ideal diagnostic tool as it is widely performed and remains a crucial test in diagnosing and managing COPD. As we broaden our knowledge about early disease through large observational COPD cohorts, in an era of digitalized spirometry and increasingly ubiquitous complex analytic tools, we are offered the possibility to better understand and utilize spirometry. This review highlights simple measures of early airflow compromise such as FEV_1/FEV_6 or FEV_3/FEV_6. We also acknowledge the growing interest in measures of curvilinearity, which can provide more granular assessment of lung function. Machine learning holds promise for curve analysis which may detect subtle patterns that distinguish early pathophysiologic changes from the expected changes of aging and may allow synthesis of a variety of measures to form better predictive models for relevant outcomes.

Many of the investigations into alternative indices have been single center and retrospective. There is a need for organization within the field of spirometry to prioritize and expand investigation into promising metrics to drive clinical practice. We hope that classification schema for spirometric indices of early airway disease proposed in this review may provide a framework for further investigation and comparison between various indices of early airflow impairment. It is of crucial importance that investigational efforts in this field continue, in line with the premise that spirometry goes far beyond FEV_1/FVC.

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HIGHLIGHTS:

- Clinically relevant airway abnormalities may precede formal diagnosis of COPD by FEV_1/FVC ratio.
- Evidence for spirometric indices of early airflow impairment preceding COPD is summarized.
- This review offers a classification scheme of existing indices based on mathematical approach.
- Digital analysis of spirometry and machine learning provide new avenues to characterize early disease.

Significance:

Spirometry is well-validated in diagnosis of COPD, nevertheless the evidence suggests that early airway abnormalities often start before the formal spirometric diagnosis of COPD. While alternative approaches to identify these subjects (symptom-based, imaging techniques) have been investigated, the full potential of spirometry to identify early disease has not been completely exploited. Multiple spirometric indices - some previously investigated and some being novel - may deserve more systematic evaluation in the era of spirometry digitalization and availability of data from large observational longitudinal cohorts. In this review, we summarize published evidence about alternative spirometric indices of airflow obstruction and propose their systematic categorization which could be utilized in future studies focused on early airway disease.

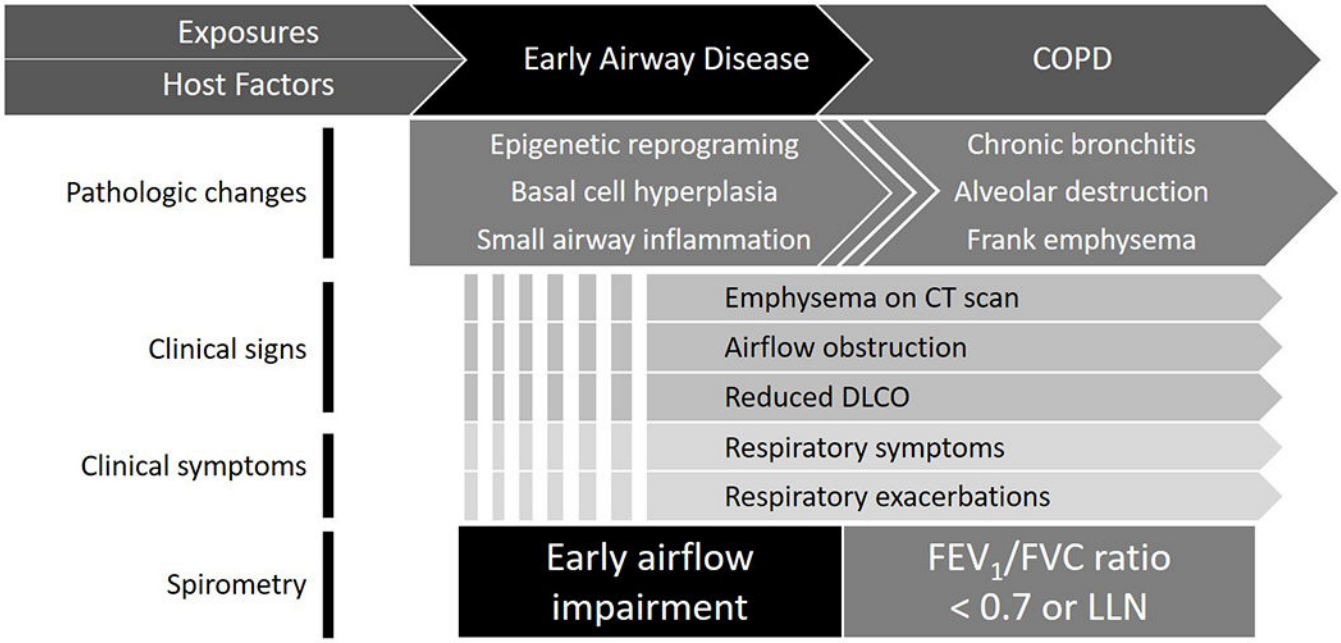

Figure 1. Select pathologic and clinical changes leading to development of early airflow impairment.

Summary of features underlying early airway disease which may be detected as early airflow impairment. Broken lines indicate variability in onset of described features. *COPD = chronic obstructive lung disease; CT = computerized tomography; DLCO = diffusing capacity of lungs for carbon monoxide; FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity; LLN = lower limit of normal.*

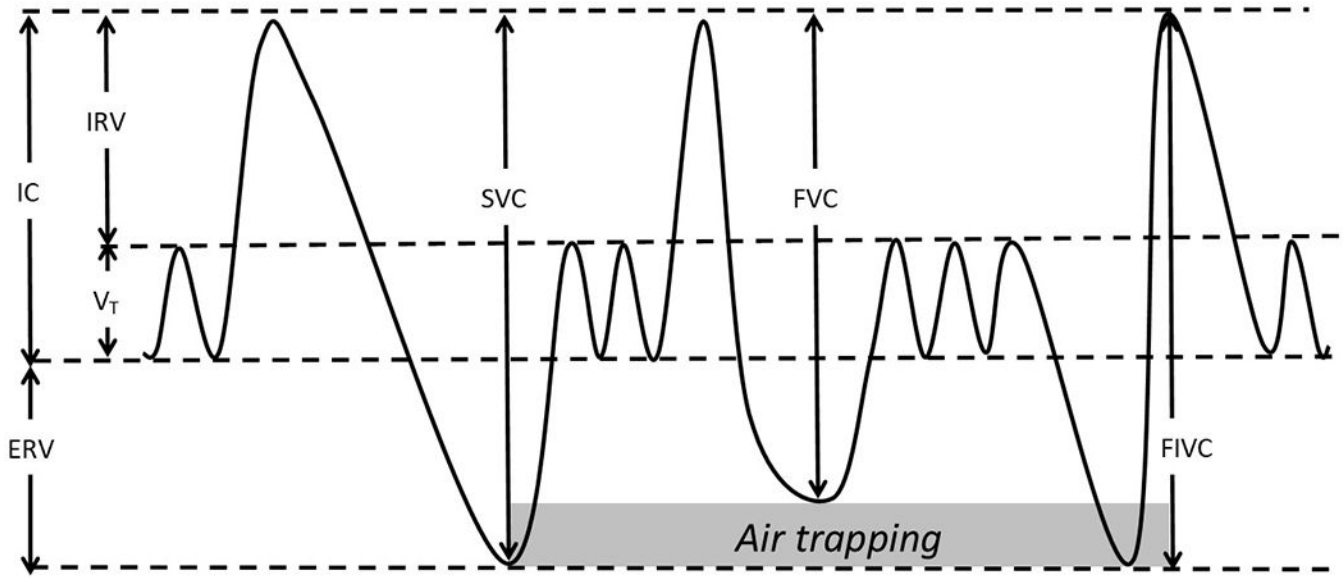

Figure 2. Difference between vital capacities.

Theoretical time-volume curve for patient with obstruction demonstrating the difference between slow vital capacity *(SVC)* or forced inspiratory vital capacity *(FIVC)* and forced vital capacity *(FVC)* due to dynamic air trapping. Other volumes of note, *IC = inspiratory capacity; ERV = expiratory reserve volume; IRV = inspiratory reserve volume;* V_T *= tidal volume.*

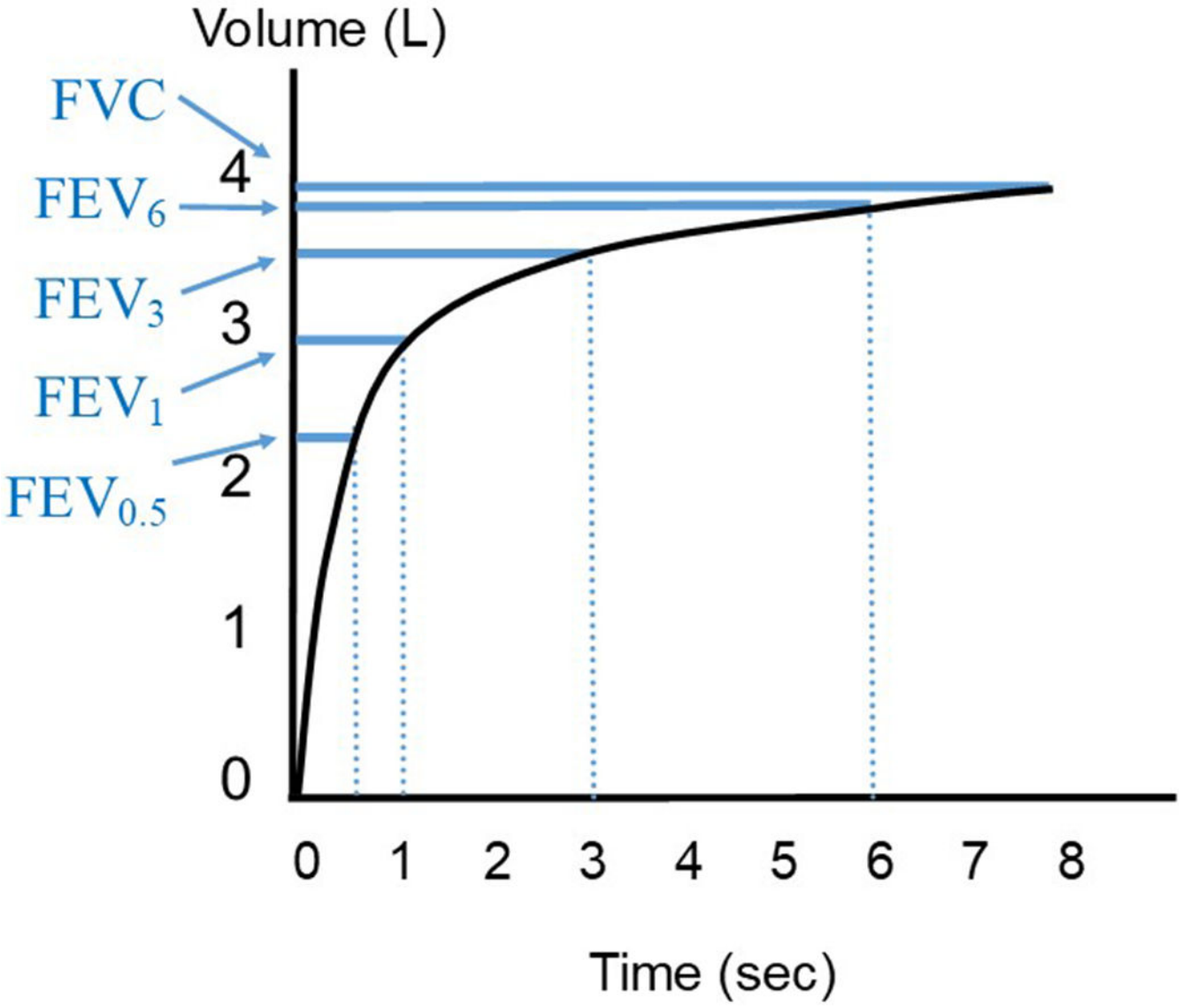

Figure 3. Time-fractioned lung volumes.

Plot of maximal expiratory volume-time curve, in a theoretical patient with mild obstruction, with commonly obtained time-fractioned lung volumes illustrated in blue. *L = liters; sec = seconds; FEV = forced expiratory volume, subscript denotes time in seconds since initiation of force expiratory maneuver; FVC = forced vital capacity.*

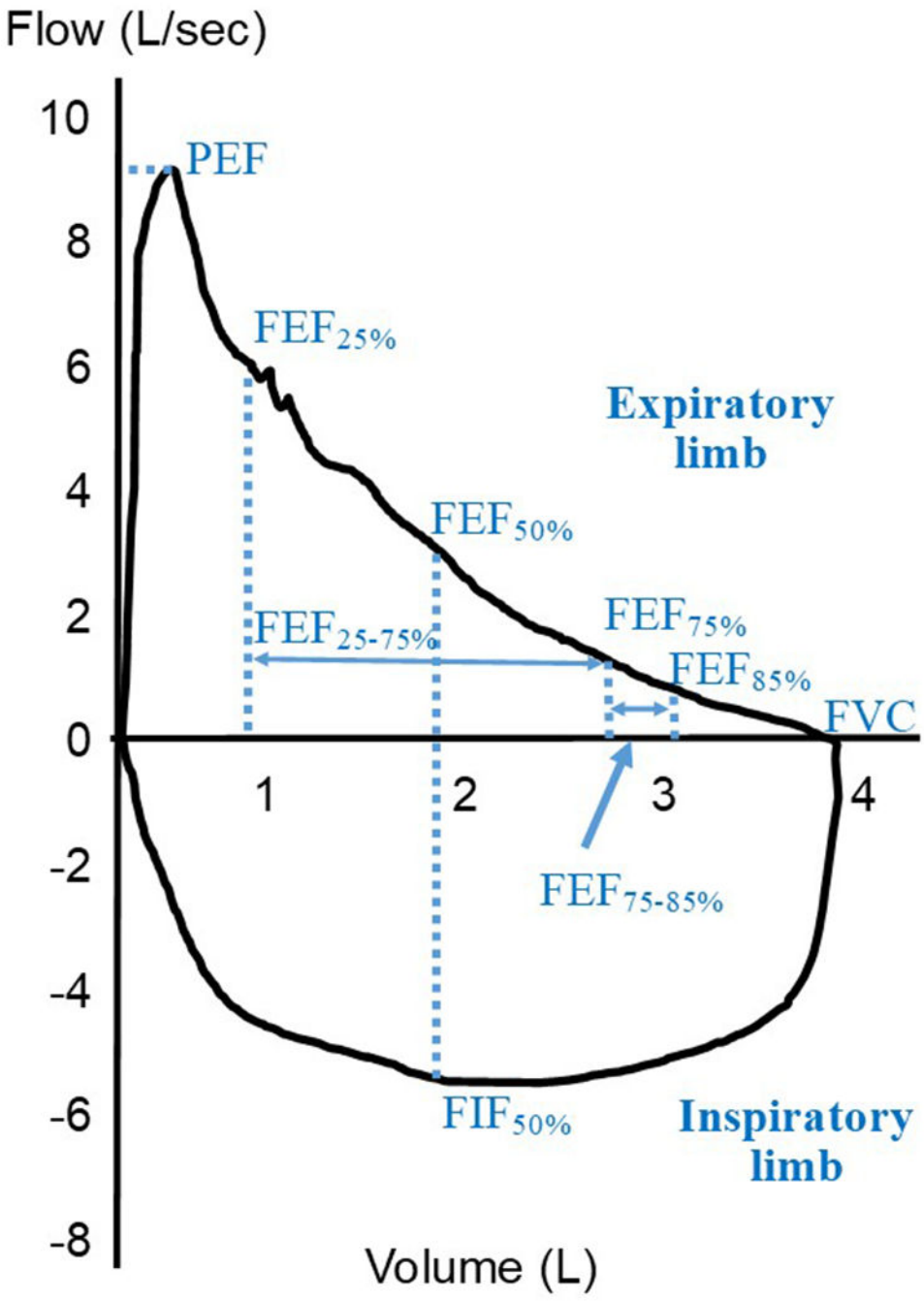

Figure 4. Flow-based indices.

Flow-volume loop of a maximal inspiratory and expiratory maneuver from a theoretical patient with mild obstruction. The location where commonly obtained instantaneous and averaged flows are obtained are demonstrated by dotted lines and solid arrows, respectively. *L = liters; sec = seconds; PEF = peak expiratory flow; FEF = forced expiratory flow, subscript denotes percentage of FVC; FIF = forced inspiratory flow; FVC = forced expiratory vital capacity.*

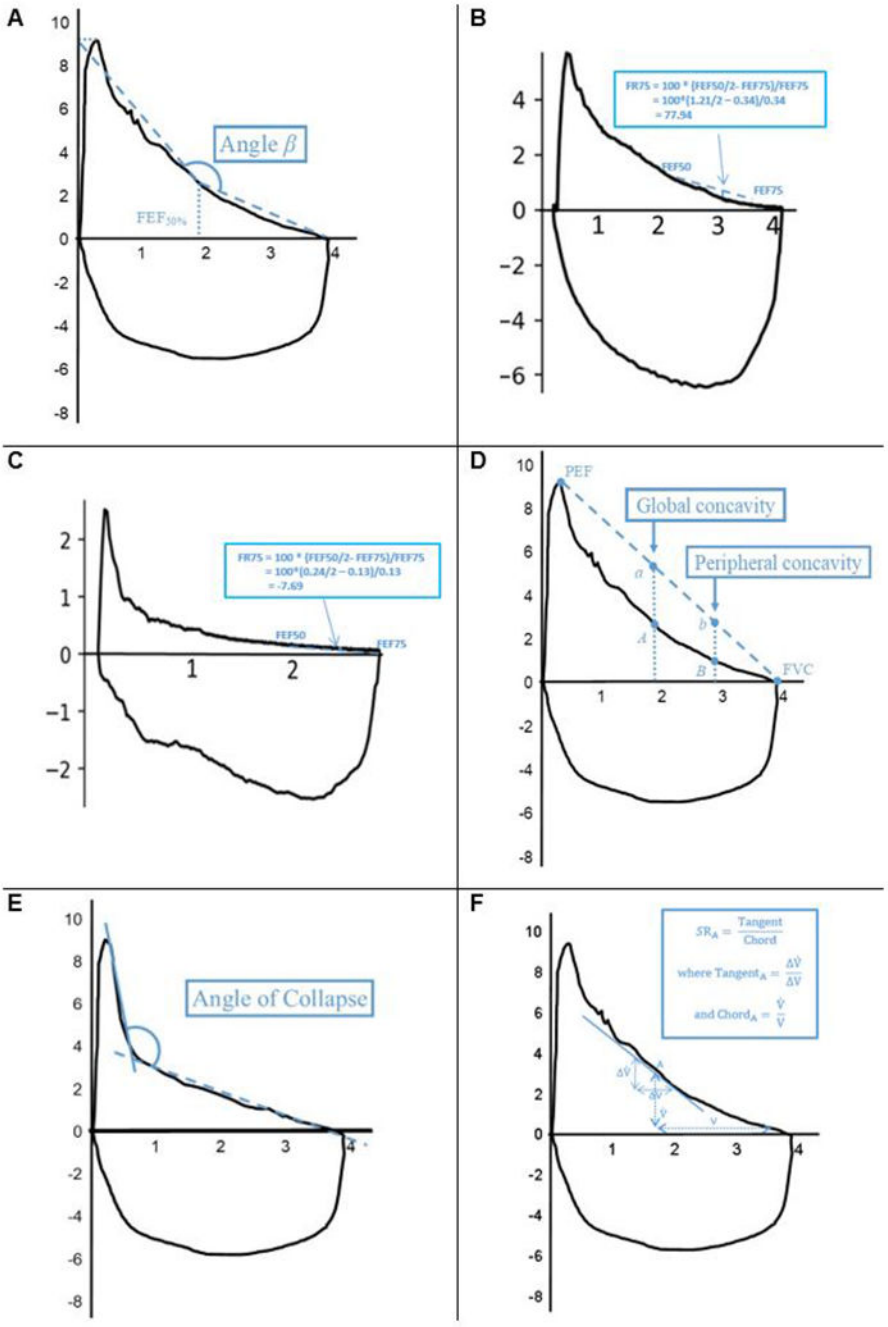

Figure 5. Selected curve analyses of maximal expiratory flow volume curve.

Flow-volume loop of a maximal inspiratory and expiratory maneuver from a theoretical patient with mild obstruction. *X-axis = volume in liters, y-axis = flow in liters/second.* **A.** Angle- *β. $FEF_{50\%}$ = forced expiratory flow at 50% of forced vital capacity (FVC)* **B.** FR_{75}, positive value. *FR75 = flow-ratio at 75% FVC.* **C.** FR_{75}, negative value. **D.** Global and peripheral concavity index. *Global concavity index = 100* (reference $FEF_{50\%}$ (*point a*)—measured $FEF_{50\%}$ (*point A*)/ (reference $FEF_{50\%}$); peripheral concavity index = (reference $FEF_{75\%}$ (*point b*)—measured $FEF_{75\%}$ (*point B*)/ (reference $FEF_{75\%}$). PEF = peak expiratory*

flow. **E.** Angle of collapse. Angle between two optimal regression lines (solid and dashed lines) of the descending limb of the expiratory curve. **F.** Slope ratio. Example instantaneous slope ratio calculation at point *A* (SR_A). V = *volume remaining to be expired* and $\dot{V}$ = *flow at this point*, chord ($Chord_A$) is defined as the *ratio of* $\dot{V}$ *to* V. If an *instantaneous change in volume and flow at this point* are denoted by $\Delta\dot{V}$, the tangent ($Tangent_A$) is defined as the *ratio of* $\Delta\dot{V}$ *to* ΔV. SR_A is calculated as the *ratio of* $Tangent_A$ *to* $Chord_A$.

Table 1.
Spirometric indices of airflow impairment.

All suggested cutoffs are for airflow obstruction unless otherwise noted. *FEV = forced expiratory volume, subscript denotes time in seconds; FVC = forced expiratory vital capacity; FIVC = forced inspiratory vital capacity; SVC = slow vital capacity; IC = inspiratory capacity; TLC = total lung capacity; FEF = forced expiratory flow, subscript denotes percentage of FVC; PEF = peak expiratory flow; LLN = lower limit of normal; -- = cutoff value is not well defined or not applicable.*

Category	Index	Suggested cutoff	Potential clinical applicability
Lung capacity indices	SVC – FVC	--	Marker of air trapping; predicts exercise tolerance
	FIVC – FVC	--	Marker of air trapping
	FVC/SVC	--	Indicator of small airway disease
	FEV_1/SVC	< 0.7 or LLN	Obstruction in young individuals
	IC	--	Indicates hyperinflation; predicts respiratory mortality
Time-fractioned lung volume indices	FEV_6	LLN	More reproducible and less difficult to perform than FVC; predictor of lung function decline
	FEV_1/FEV_6	< 0.73 or LLN	In normal FEV_1/FVC, associated with air-trapping, diffusion abnormalities, and respiratory exacerbations; identifies smokers
	FEV_3/FEV_6 and FEV_3/FVC	LLN	In normal FEV_1/FVC, associated with hyperinflation, air trapping, diffusion abnormalities; identifies smokers
	$FEV_{0.5}$ or $FEV_{0.75}$/FVC	LLN	Obstruction in infants and children
Flow-based indices	FEF_{25-75}	< 65% predicted or LLN	Lower in some smokers normal FEV_1/FVC; correlates with air trapping on CT
	FEF_{75-85}	LLN	Distinguishes smokers from nonsmokers
	FEF_{50} (MEF_{50}) or FEF_{75}	< 60% predicted	Reduced in GOLD zero patients
	FEF_{50}/0.5FVC	--	Correlates with FEV_1/FVC
	$FEF_{200-1200}$	--	Substitute for PEF
	PEF	Males < 350 L/min Females < 250 L/min	Simple screening for undiagnosed COPD
	PIFR	< 60L/min	Predicts COPD-related hospital readmissions
	FEF_{50}/FIF_{50}	--	Evaluates upper airway obstruction; correlated with emphysema by CT
Curvilinearity Measures			
Classic geometric indices	Global concavity index	Males > 38.4 units Females > 26.3 units	Based on FEF_{50}, quantifies end-expiratory spirogram concavity
	Peripheral concavity index	Males > 61.2 units Females > 63.1 units	Based on FEF_{75}, quantifies end-expiratory spirogram concavity
	Angle β	< 180° (concavity)	Lower in patients with dyspnea and wheezing than controls; improves in response to bronchodilators
	Slope ratio (SR)	> 1 (concavity) > 2.5	Indicates heterogenous lung emptying, obstruction
	Flow ratio at 75% FVC (FR75)	< 0 (concavity)	More negative in smokers than non-smokers

Category	Index	Suggested cutoff	Potential clinical applicability
	Coefficient of maximal mid-expiratory flow (β-MMEF)	> 0.4	Correlates with risk of hospitalization
	Curvature index (k_{max})	--	Exponentially associated with FEV_1
	Flow decay	Upper limit of normal (0.802 L^{-1})	Correlates with other measures of obstruction; not sensitive to artifactually low FVC
	Area under the curve in 3 seconds / Area of triangle 3 seconds (AUC_3/AT_3)	LLN	Surrogate for FEV_1/FVC when 6 second expiratory effort not met (particularly young patients with obstruction)
	Area under the flow volume curve (AUFVC)	--	Detects air trapping and hyperinflation; correlates with 6-minute walk
Novel computational indices	Angle of collapse (AC)	< 131° ≤ 137°	< 131° correlates significantly with emphysema extent; ≤137°asthma-COPD overlap syndrome
	Volume dependence of slope ratio	SR decreases through exhalation in early COPD; SR increases through exhalation in elderly	Distinguish spirogram concavity caused by mild COPD from concavity due to physiologic changes with age
	Transfer function model of flow decline	--	Correlates with traditional measures of obstruction well; offers additional inputs for machine learning algorithms
	Parameter D	--	Identifies individuals with mild disease or unrecognized disease who have CT findings of structural lung disease
	Deep learning algorithms and other machine learning approaches	--	May detect subtle patterns that distinguish disease from normal variation; may synthesize various indices to improve predictive power for relevant outcomes