

What Long-Term Changes in Lung Function Can Tell Us About Asthma Control

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Abstract Asthma severity is typically classified according to lung function, but asthma control in relation to lung function is often harder to define. In this paper, we will review how lung function measured at rest, as well as over time, relates to asthma control. We will explore not only conventional lung function as measured by spirometry, such as peak expiratory flow and forced expiratory volume in 1 s, but also more sophisticated measurements of peripheral airway function related to respiratory system impedance and ventilation heterogeneity. In particular, we will review the emerging area of assessing the fluctuation of lung function over time and how it may correlate to both past and future asthma control.

Keywords Asthma control · Peak expiratory flow variability · Respiratory system impedance · Ventilation heterogeneity · Detrended fluctuation analysis · Airflow complexity

Introduction

Asthma is a disease characterized by persistent or periodic episodes of airway inflammation resulting in variable airflow limitation and airway hyperresponsiveness. The most recent

EPR3 guidelines make a strong distinction between asthma severity and asthma control. Asthma severity is related to the intrinsic intensity of the disease as measured by symptoms, lung function, and medication use, while asthma control is related to the degree to which the manifestations of asthma (i.e., the dynamic changes in symptoms, lung function, and medication use over time) are minimized [1]. Of these parameters, lung function is the most objective measure of disease severity and control. Relating lung function to severity is intuitive: Typically, the more that lung function is reduced, the more persistent and severe is the asthma. However, the relationship of lung function to asthma control is less obvious because patients may have poor control in the setting of normal lung function, and good control in the setting of reduced lung function. In the current paper, we will review the relationship between lung function and asthma control, with specific emphasis on how long-term changes in lung function not only relate to prior asthma control but also can help predict asthma control in the future.

How do Baseline Lung Function Measurements Relate to Asthma Control?

Given that there are a wide range of lung function measurements available, from the most simple to the more complex, it is essential to understand how these measurements differ in their relation to asthma control. Table 1 summarizes these measurements and their relationship to asthma control.

PEF

Historically, monitoring of lung function in asthma has been performed by measurement by peak expiratory flow (PEF) [2]. While PEF is known to be inaccurate in assessing the severity of airway obstruction [3], PEF is simple and

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Table 1 Lung function measurements and their relation to asthma control

Measurement	Relation to asthma control	Reference(s)
PEF	Long-term monitoring	[4]
	Variability in PEF a marker of asthma stability	[7, 39, 40]
FEV1	Lower FEV1 associated with greater risk of future exacerbations	[11]
	Change in FEV1 over time	[42•]
FEV1/FVC	Low FEV1/FVC after bronchodilator related to severe or poorly controlled childhood asthma	[15, 16••]
FEF 25-75	Lower FEF 25-75 associates with poor asthma control in children	[26]
AHR	Greater AHR (lower PC20) predictor of poor asthma control	[12, 13]
RV/TLC	Elevated RV/TLC indicative of airtrapping and related to poor asthma control	[27]
FOT-Rr	Elevated Rrs related to poor control	[28•, 35•]
	Increased variability associated with poor control	[50•, 51•]
FOT-Xrs	Elevated Xrs correlated with ventilation heterogeneity by MBNW (see below) and related to poor control	[36•]
SBNW	Elevated closing volume related to poor control	[29]
MBNW	Elevated acinar (Sacin) and conductive (Scnd) normalized Phase III slopes (greater ventilation heterogeneity) related to severity, response to inhaled corticosteroid withdrawal, and poor control	[30•, 31•, 32•]
DFA	Autocorrelation of PEF over time associated with asthma control	[41, 45, 46••]
Complexity	Reduced airflow complexity and increased fluctuation in heterogeneity relates to poor control	[53, 54•, 55•]

PEF peak expiratory flow, *FEV1* forced expiratory volume in one second, *FVC* forced expiratory volume, *FEF 25–75* forced expiratory flow between 25 and 75 % of vital capacity, *AHR* airways hyperresponsiveness, *PC20* provocative concentration causing a 20 % fall in FEV1, *RV/TLC* residual volume-to-total lung capacity ratio, *FOT-Rrs* respiratory system resistance by the forced oscillation technique, *FOT-Xrs* respiratory system reactance by the forced oscillation technique, *SBNW* single breath nitrogen washout, *MBNW* multiple breath nitrogen washout, *Sacin* index of acinar (diffusion-)dependent ventilation heterogeneity, *Scnd* index of conductive (convection-)dependent ventilation heterogeneity, *DFA* detrended fluctuation analysis

inexpensive and continues to be used to assess long-term outcomes to asthma control therapy [4]. Monitoring PEF is especially advocated for those patients who have poor perception of symptoms [5]. In a large network study of childhood asthma, lower PEF (<65 % predicted) was independently associated with poor asthma control [6]. In addition to baseline PEF, fluctuations in PEF have been considered a hallmark of asthma stability and control [7]. The variability in PEF is thought to reflect the unstable nature of airway caliber regulated, at least in part, by variability in underlying inflammation and

resultant airway smooth muscle function [8, 9••]. The role of airway smooth muscle is no doubt important, as evidenced by the importance of bronchodilator therapy and the recent development of bronchial thermoplasty as a treatment for asthma [10].

FEV1

Lung function as measured by forced expiratory volume in one second (FEV1) is also related to asthma control. In fact, Kitch and colleagues demonstrated that a low FEV1 was an independent risk factor for subsequent asthma exacerbations over the next 3 years [11]. In addition to baseline FEV1, the response of FEV1 to methacholine has also been shown to be a predictor of asthma control. Sont and colleagues conducted a landmark study comparing two strategies of adjusting anti-inflammatory therapy for asthma: one based on symptoms, PEF variability and FEV1, and the other based on airway hyperresponsiveness (AHR) [12]. They demonstrated that the AHR strategy resulted in an improved FEV1, a lower exacerbation rate, and a greater reduction in the subepithelial reticular layer, indicative of reduced airway inflammation and remodeling. Nuijsink and colleagues demonstrated similar findings in children, but the beneficial effects of an AHR-guided treatment strategy were lost after a mean of 4 years of usual care following the intervention [13]. Interestingly, AHR may persist even in children who “outgrow” their asthma. Koh and colleagues studied AHR in children whose asthma remitted by adolescence and found they had a reduced maximal airway response to methacholine despite similar levels of airway hypersensitivity compared to asthmatic children who remained symptomatic into adolescence [14]. There was no change in maximal response to methacholine in the group who had remission of asthma after 6 months of inhaled corticosteroid therapy, whereas inhaled corticosteroid therapy reduced the maximal response to methacholine in the symptomatic asthma group. These findings suggest that those children who outgrow their asthma have a persistent maximal airway response to methacholine that may be due to more structural, rather than inflammatory, changes in their airways.

This persistence of abnormal structural airway changes may also explain the residual airflow limitation as measured by a reduced ratio of FEV1/FVC after bronchodilator found in patients with previous severe chronic asthma in childhood [15, 16••]. In fact, Tai and colleagues found that, during a longitudinal study spanning nearly 43 years, children with severe asthma had a 32 times higher risk of developing chronic airflow limitation compared to children without asthma [16••]. Ongoing eosinophilic inflammation is thought to be the primary cause of the persistent, long-term remodeling and airflow limitation seen in allergic patients with poor asthma control [17], highlighting the importance of early anti-inflammatory therapy in these patients [18]. Even repeated

bronchoconstriction in the absence of inflammation has been implicated in the airway remodeling that contributes to chronic airflow limitation, reinforcing the importance of airway smooth muscle constriction and its treatment with bronchodilators in asthma [19].

Small Airways Measurements

One aspect of measuring lung function that has gained attention recently is the ability to detect and monitor small airway abnormalities in asthma [20•, 21]. Multiple methods have been used to demonstrate that the function of the lung periphery is abnormal in asthma [20•]. Perhaps, the most direct measurements were made by Wagner and colleagues, who demonstrated that peripheral airway resistance was elevated more than sevenfold compared to healthy subjects, even in asthmatics with no symptoms and normal spirometry [22]. Subsequent studies, including our own, have demonstrated that the lung periphery is also hyperresponsive to provocation with bradykinin, cold air, or histamine [23–25].

Abnormalities in small airway function in asthma are strongly associated with asthma control [20•]. In the presence of a normal FEV1, the forced expiratory flow between 25 and 75 % of the vital capacity (FEF25-75) is commonly interpreted as representing small airways function, and low values have been found to associate with poor asthma control in children [26]. Other aspects of small airway function linked to poor asthma control include gas trapping as measured by the ratio of residual volume-to-total lung capacity (RV/TLC) [27], peripheral airway heterogeneity indicated by low frequency resistance and elastance from the forced oscillation technique (FOT) [28•], airway closure as measured by the single breath nitrogen washout [29], and ventilation heterogeneity as demonstrated by the multiple breath nitrogen washout (MBNW) [30•, 31•, 32•]. The latter technique has yielded specific insight into peripheral airway function related to ventilation heterogeneity in both the conductive and acinar airways in asthma [33]. Unstable asthma is characterized by abnormalities in both regions of the lung periphery [30•, 31•, 32•]. One theory to explain poor asthma control on the basis of ventilation heterogeneity is the avalanche-like behavior of airway narrowing and closure that is predicted to occur based on computational models of uneven bronchoconstriction [34].

Combinations of modalities have also been used to assess small airway function and its relation to asthma control. Manoharan and colleagues have demonstrated that persistent abnormalities in the small airways as measured by mid-expiratory flows and oscillatory resistance are associated with poor asthma control, even when FEV1 was normal [35•]. Using FOT, Kelly and colleagues recently demonstrated that respiratory system reactance (Xrs) was an independent determinant of asthma control [36•]. Using concomitant measures of ventilation heterogeneity from MBNW, these authors

demonstrated that heterogeneity and airway closure were correlated with changes in Xrs, implicating these features as critical to determining asthma control. Most recently, Hanon and colleagues described in patients with well-controlled asthma persistent abnormalities in multiple indices reflecting peripheral lung function, such as airway resistance measured by FOT, ventilation heterogeneity measured by MBNW, and bronchial nitric oxide production, which were not normalized by inhaled corticosteroid therapy [37•]. Such abnormalities appear to be quite common in the community despite adherence to international treatment guidelines [38•], implicating the small airways of the lung periphery as an important, undertreated aspect of asthma care. This consideration may be as important in patients with mild disease as it is in patients with more severe disease.

Changes in Lung Function Measurements over Time Related to Asthma Control

One of the fundamental features of asthma is its periodic, often effervescent, presentation. Indeed, this is one aspect that clearly differentiates asthma from many other chronic lung diseases. In this sense, changes in lung function over time may reflect, and possibly even predict, asthma control (Table 1).

Changes in PEF and FEV1

Variability of PEF correlates with respiratory symptoms and impaired lung function in the general population [39]. In patients with asthma, increased variability in PEF measurements over time are indicative of poor asthma control [7]. Recently, Kamiya and colleagues demonstrated that increased PEF variability may be indicative of worsening asthma even when asthma symptoms are absent [40]. Thamrin and colleagues demonstrated that an increase in PEF variability over 2 weeks was associated with subsequent loss of asthma control among patients previously stable on inhaled corticosteroids in whom corticosteroid therapy was withdrawn [41].

With regard to FEV1, the rate of change of FEV1 over time is also indicative of asthma control and relates to disease progression. Matsunaga and colleagues have demonstrated that, among patients with good asthma control at baseline, the rate of change of FEV1 over time relates to asthma control [42•]. Patients who had a more rapid decline in FEV1 over 3 years (−53.3 ml/year vs −13.6 ml/year) had more frequent exacerbations and lower levels of control. The more rapid decliners were older and had higher levels of sputum eosinophils and fractional excretion of nitric oxide, suggesting more severe, or less well controlled, underlying eosinophilic airway inflammation.

Detrended Fluctuation Analysis

In addition to tracking lung function over broad periods of time, more recent studies have looked at relatively short-term fluctuations in lung function as indicators of asthma control and possible predictors of future exacerbations. A number of studies have focused on fluctuations in PEF using detrended fluctuation analysis (DFA). DFA is a method of analyzing series of data over time to look for long-term correlations among the data [43]. Frey and colleagues analyzed time series data from 300 consecutive twice daily PEF values from 80 asthmatic subjects involved in a randomized, cross-over study comparing regular short-acting beta agonists (SABA) and regular long-acting beta agonists (LABA) to placebo during three 6-month treatment periods [44]. The authors demonstrated not only higher PEF during the SABA and LABA phases, but also more variability of PEF in the SABA phase resulting in periodic worsening of PEF, and less variability in the LABA phase resulting in more persistent increased lung function. Further work in this area was conducted by Thamrin and colleagues, who showed that higher autocorrelation of lower PEF over time (i.e., self similarity) correlated with worse asthma control [41]. However, low lung function (low PEF) and its variability over time appeared to be the more important determinant of asthma control than the autocorrelation of PEF over time. Our own group has found similar findings using data from a large clinical trial of controller therapy in asthma [45]. Thamrin and her colleagues have subsequently demonstrated that the probability of an asthma exacerbation in an individual patient can be estimated by combining the autocorrelation properties of PEF time series data together with the distributive properties of such data, indicating that both are significant in determining future asthma control [46•]. Because of the computational nature of such calculations and access to modern communication, it is likely that future care of asthma will involve downloading of periodic fluctuation of PEF data using handheld electronic spirometers for use by health-care providers in order to predict future asthma control and alter therapy accordingly to prevent exacerbations and maintain clinical stability [47].

Variability in FOT Measurements

Analysis of variability over time has been applied to other aspects of pulmonary function, such as oscillatory resistance and respiratory system impedance. Que and colleagues first demonstrated that asthma was characterized by short-term (over minutes) variations in airway caliber as inferred from measurement of respiratory system impedance using the FOT [48]. They suggested that such information on variability of airway caliber might be used to predict subsequent airway narrowing over the next 24 h. Lall and colleagues demonstrated that variability in airway resistance measured by the FOT in

children decreased in response to bronchodilator therapy more than the improvement in FEV1 or airway resistance, so it could be used to monitor response to therapy [49]. Gullota and colleagues showed that variability in inspiratory resistance over 8 days was able to predict subsequent loss of asthma control over the next week based on mathematical modeling of individual probabilities [50•]. Most recently, Robinson and colleagues demonstrated that day-to-day variability in respiratory system resistance measured by FOT in children attending an asthma summer camp was able to differentiate between levels of severity and control, although PEF variability was not [51•].

It is important to point out, however, that not all studies support the usefulness of short-term variability in lung function as an indicator of asthma stability. Diba and colleagues were unable to confirm that the variability of respiratory system impedance correlated with variability in PEF or with AHR. The authors attributed their inability to confirm previous similar work to differences in sample size, methodology, and analytic technique [52]. Thus, it remains uncertain how valid and clinically significant the findings of increased variability of respiratory system impedance and its association with asthma control are in patients with asthma, but the concept and supportive data are intriguing.

Examining Airflow Complexity

Another approach has been to analyze the complexity of breathing pattern using the measure of approximate entropy, an indicator of the complexity of a signal [53]. Veiga and colleagues have shown that airway obstruction in asthma is associated with a reduced complexity of the airflow pattern, which may lower the ability of the respiratory system to adapt to increased workloads or stress, which, in turn, could theoretically lead to loss of asthma control. Of note, a subsequent study by the same group demonstrated that the loss of airflow pattern complexity with increasing obstruction was correlated with an increased variability of respiratory system impedance, suggesting that both measures provide complementary information about the status of airway narrowing and asthma severity [54•]. Gonem and colleagues have recently demonstrated similar findings using sample entropy, which is a measure of variability of heterogeneity over time. They found that increased impedance, heterogeneity of impedance, and fluctuation of heterogeneity of impedance over time were associated with the phenotype of asthma characterized by frequent exacerbations or loss of control [55•].

How do reduced complexity and increased variability of heterogeneity relate to asthma control? As summarized so eloquently by Peter Macklem, life itself needs to exist in the delicate balance of order and chaos so as to remain stable yet adaptable to change [56]. Asthma appears to be a disease of an abnormally increased order of breathing pattern (i.e., reduced

complexity) coupled with an airway tree characterized by excessive and highly variable airway smooth muscle activation (heterogeneity variability), causing wide fluctuations in airway caliber that may lead to periodic, widespread, avalanche-like airway narrowing and closure [34] and reduced ability to adapt to a changing environment [48]. These features translate clinically into more frequent asthma exacerbations and poor asthma control.

Conclusions

In summary, changes in lung function over time reflect both past control as well as possibly future control of asthma. The literature supports the view that persistent, poorly controlled asthma, especially from childhood, may result in fixed airway obstruction as seen by a reduced post-bronchodilator FEV1 or FEV1/FVC. As a reflection of the characteristic underlying variability of clinical asthma, monitoring fluctuations in lung function over time allows quantification of the variability of lung function, which may be associated with current and future asthma control. Newer methods of measuring lung function, such as the FOT and MBNW, and analyzing fluctuations over time, such as by DFA and airflow complexity, are yielding further insight into the mechanisms of asthma stability and may allow better prediction of future asthma control and disease progression.

Compliance with Ethics Guidelines

Conflict of Interest Dr. Kaminsky and Dr. Irvin have declared no potential conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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