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The pragmatic role of FEF₂₅₋₇₅ in asymptomatic subjects, allergic rhinitis, asthma, and in military setting

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Abstract

Introduction: The forced expiratory flow between 25% and 75% of forced vital capacity (FEF₂₅₋₇₅) is a spirometry parameter that may be useful in many clinical settings. Values <65% of predicted have been defined as abnormal.

Areas covered: The current report discusses the clinical value of FEF₂₅₋₇₅ in different settings, namely military medicine, primary care, and specialized clinic. Moreover, the predictive role of FEF₂₅₋₇₅ was discussed considering different patients' populations, including patients suffering from allergic rhinitis and/or asthma, as well as normal subjects. The most recent literature concerning the assessment of FEF₂₅₋₇₅ in these covered areas was searched.

Expert opinion: In clinical practice, impaired values have been defined as a reliable surrogate marker for bronchial airflow limitation associated with early onset of asthma, bronchial

hyperresponsiveness, lower airway inflammation, reversibility to bronchodilation testing, allergic sensitization, and uncontrolled asthma. In the military medicine setting, simple spirometry, including FEF₂₅₋₇₅, may suggest a series of fruitful information.

Keywords: asthma, rhinitis, FEF₂₅₋₇₅, spirometry, clinical practice, military setting

1. Introduction

Allergic rhinitis and allergic asthma share a common pathogenic mechanism sustained by a type 2 immune response, characterized by a T helper 2 polarization and eosinophilic infiltrate of airways. Allergic inflammation contributes to airways obstruction. Forced expiratory volume in the first second (FEV₁) is the gold standard measure to detect bronchial obstruction. However, it is common to observe asthmatic normal FEV₁ in clinical practice, whereas the forced expiratory flow between 25% and 75% of forced vital capacity (FEF₂₅₋₇₅) seems to be a more reliable marker to define early impairment of bronchial airways. There is growing evidence that FEF₂₅₋₇₅ could be useful in different settings and subjects. The current Report analyzes and discusses the most relevant information present in literature.

2. Body

The current special report discusses the main issues and problems concerning the pragmatic role of the forced expiratory flow between 25% and 75% of forced vital capacity (FEF₂₅₋₇₅) in some clinical settings, including asymptomatic subjects, allergic rhinitis, asthma, and military medicine. Asthma is characterized by airway inflammation, bronchial hyperresponsiveness, and variable obstruction of airflow as pointed out in the global initiative for asthma (GINA) document (1). Allergic rhinitis (AR) is the most common immune-mediated disorder as it may affect up to 40% of the general population (2). Both asthma and AR share common pathogenic mechanisms and interplay mutually as uncontrolled AR may promote asthma onset or worsen current asthma (3).

Asthma may also impact AR concerning over- or under-treatment (4). Therefore, upper and lower airways are closely linked and the term "united airways disease" has been coined to define this relationship (5,6). In this regard, the main physiological characteristic, shared by both disorders, is airflow limitation, but with a reciprocal difference: in asthma, it occurs primarily during the expiratory phase, while in rhinitis during the inspiratory one. Spirometry is the gold standard test to document bronchial obstruction that is mandatory for asthma diagnosis (7). The asthma diagnosis is based on clinical history and a demonstration of bronchial obstruction reversibility. However, it is rare to observe a positive bronchodilation testing in real-life as very frequently lung function (mainly concerning the forced expiratory volume in one second, FEV_1 , and the ratio between FEV_1 and the forced vital capacity, FEV_1/FVC , that are considered the gold standard to detect bronchial obstruction) is normal in the majority of subjects with suspected asthma (8). Alternative tests have been proposed to solve this drawback, including methacholine challenge and fractionated exhaled nitric oxide (FeNO), but they are expensive and usually performed in specialized centers. There has been therefore growing interest in the practical role exerted by FEF_{25-75} in this context. FEF_{25-75} measures the airflow during the middle expiratory phase, so it has been advanced that it may mirror the flow dynamics in small airways and proposed as a potential surrogate marker for impairment of small airways (9). There is also evidence that FEF_{25-75} may have clinical relevance especially when FEV_1 values are normal (10). FEF_{25-75} values $<65\%$ of predicted have been defined as abnormal (5). Therefore, a series of studies have been conducted both in asymptomatic subjects, in asthmatics, and AR patients. Indeed, reduced FEF_{25-75} value might precede FEV_1 impairment, so indicating early asthma and poor prognosis in current asthma (11,12). In AR, reduced FEF_{25-75} was associated with bronchial hyperreactivity (13), positive response to bronchodilation testing (14), and increased fractional exhaled nitric oxide (15). Thus, it was proposed that reduced FEF_{25-75} might be a surrogate functional marker of early bronchial involvement in AR, such as impaired FEF_{25-75} could predict the asthma development in patients suffering from AR. It has been also reported that impaired FEF_{25-75} is associated with airway inflammation in subjects with asthma-like symptoms

(16). So, it has been concluded that abnormal FEF_{25-75} might be considered an early marker of airflow limitation related to eosinophilic inflammation, suggesting a role for impaired FEF_{25-75} as a predictive marker of newly diagnosed asthma. Also, a recent cross-sectional study, conducted in 234 patients with respiratory symptoms, demonstrated that FEF_{25-75} , but not FEV_1 and FEV_1/FVC , predicted airway hyperreactivity (17). This finding underlines the clinical relevance of FEF_{25-75} when other conventional spirometry parameters are normal.

Notably, several studies were conducted to evaluate the role of FEF_{25-75} also in the pediatric population in the last year. A 24-year longitudinal study showed that lower infant airway function is associated with respiratory symptoms into adulthood, in particular, FEF_{25-75} was a reliable predictor of respiratory compromise (18). This study underlined the predictive role of FEF_{25-75} in identifying at-risk subjects from childhood to adulthood. Kong and colleagues reported that FEF_{25-75} was a more sensitive indicator of symptomatic asthma than FEV_1 in asthmatic children and better correlated with air trapping than FEV_1 (19). A retrospective cross-sectional analysis, conducted in 139 children with moderate to severe asthma, showed that reduced FEF_{25-75} was associated with peripheral airway impairment in 10% of adolescents (20). These studies reinforce the concept that FEF_{25-75} seems to be more sensitive than FEV_1 , when still normal, to predict future asthma worsening.

The CHAMACOS (Center for the Health Assessment of Mothers and Children of Salinas) study reported that prenatal maternal urinary concentrations of mono-ethyl phthalate were associated with lower FEF_{25-75} in their children at the age of 7 (21). The CHAMACOS study was a longitudinal cohort study examining the effects of in utero and childhood environmental exposures on growth, neurodevelopment, respiratory disease, and pubertal development in the Salinas Valley, California, an agricultural community. English or Spanish-speaking mothers who were eligible for low-income health insurance (MediCal), at least 18 years old, <20 weeks' pregnant, and who was planning on delivering at the county hospital were recruited to participate in the study in 1999–2000 from prenatal care clinics serving the Latino, farmworker population in the Salinas Valley. A total of 601

mothers were enrolled and 531 were followed through the birth of a live infant. Of those, 517 had at least one prenatal measurement of low molecular weight phthalates, parabens, or other phenols and 392 children additionally had information on respiratory or allergy symptoms, spirometry, or cytokine measurements. FEF_{25-75} was the most reliable marker able to document respiratory impairment after maternal exposure to chemical products. Another study, conducted in 53 asthmatic children living in Detroit, demonstrated that high-symptom respiratory viral infections significantly reduced FEF_{25-75} values (22). This study could be useful in clinical practice as asthma exacerbation is frequently preceded by a viral infection, thus impaired FEF_{25-75} may detect early bronchial involvement during viral infection.

Early-life exposure to air pollution was associated with lung function impairment, including FEF_{25-75} , at 17.5 years in Hong Kong Chinese birth cohort (23). Another study showed that in children, with controlled asthma and normal FEV_1 values, impaired FEF_{25-75} well correlated with small airway dysfunction (24). Also, it has been evidenced that FEF_{25-75} strongly correlated with FEV_1 , FEV_1/FVC , and reversibility to bronchodilation testing in a cohort of 116 asthmatic children (25). The authors concluded that besides the FEV_1 and FEV_1/FVC , the FEF_{25-75} may be a useful and early spirometry parameter to evaluate the children with asthma and or AR (25). Therefore, these studies provided convincing proof that FEF_{25-75} could be a reliable marker for suspecting asthma worsening due to different pathogenic mechanisms.

On the other hand, asthma is considered a disease that is regarded as incompatible with active military service. With that to diagnose asthma is mandatory in military personnel, also considering the contingency of simulation or dissemblance (26). Also, asthma and AR were very frequent in Italian conscripts and soldiers deserving careful attention in selection visits (27-29). To support these concepts and translate them into the Military Medicine field, some seminal studies were conducted in the Italian Navy setting. The first study involved a group of Navy soldiers suffering from seasonal AR (30). This study evidenced that early bronchial impairment, documented by pathological FEF_{25-75} value, is frequently detectable in patients with persistent allergic rhinitis and

BHR. Moreover, the nasal function was strictly related to bronchial airflow and BHR grade. A further series of studies investigated the impact of AR duration on lower airways in a group of Navy soldiers with AR. These studies demonstrated that long-lasting AR was associated with impaired FEV₁ (31), bronchodilation testing (32), and bronchial hyperresponsiveness (33). Therefore, it was hypothesized that long-lasting AR could be a relevant risk factor for developing asthma. As proof of concept, 99 frogmen with moderate-severe persistent allergic rhinitis were prospectively and consecutively evaluated for 8 years (34). The number of patients with abnormal FEF₂₅₋₇₅ significantly increased during the observation time. Interestingly, no subject had bronchial hyperresponsiveness at baseline; whereas 34 patients had bronchial hyperresponsiveness after 8 years. This study highlighted the close link between upper and lower airways, suggested that spirometry should be performed in patients with allergic rhinitis, and stimulated the proposal of a new definition: the “asthma march” (35), just like the concept of “allergy march” (36). Another study showed that impaired FEF₂₅₋₇₅ was significantly associated with increased FeNO in 211 Navy soldiers with persistent AR (37). This finding suggested the intriguing link between bronchial inflammation and airflow limitation in AR as the harbinger of overt asthma. In this regard, the *trait d’union* is allergic inflammation. Changing perspective, impaired spirometry, namely low FEF₂₅₋₇₅, has been demonstrated to be predictive of sensitization in a group of 283 Navy cadets who had to undergo spirometry for attending specific courses (38). This study provides evidence, relevant to clinical care, that mild spirometry impairment may generate the suspect of allergic disorders, thus spirometry could be more frequently performed in general population screening. A further study was conducted on a larger population, i.e. 2043 Italian Navy military personnel to confirm this outcome (39). Spirometry and skin prick testing were performed to predict sensitization. Sensitization, assessed by skin prick test, was documented in 658 (32.2%) subjects. Impaired FEF₂₅₋₇₅ was detected in 82 subjects, of whom 69 were sensitized. Therefore, impaired FEF₂₅₋₇₅ significantly predicted sensitization (OR 7.43). This study provided evidence, relevant to clinical care, that mild spirometry impairment should generate the suspect of allergic disorders, thus

spirometry could be more frequently performed in general population screening. A recent study, conducted on more than 2,000 Navy soldiers, provided evidence that smoking and $FEF_{25-75} < 65\%$ of predicted in sensitized subjects constitute significant risk factors for having bronchial hyperresponsiveness, $OR = 5$ and 19.9 respectively (40). Moreover, this study is clinically relevant, as, in a period of limited financial resources, simple spirometry and skin prick test may reasonably provide information on potential risk for asthma. This study underlines the concept that smoking is a relevant cofactor in asthma. In this regard, tobacco smoke remains one of the most significant triggers of asthma, despite increased public awareness of the detrimental effects of smoking. Asthma patients who smoke have more frequent emergency department visits and hospitalizations for an exacerbation than asthma patients who do not smoke (41,42). It is well known that smoking has a significant effect also on the development of asthma in AR patients (43). Moreover, second-hand smoke is also associated with deteriorated lung function, poor response to treatment, and frequent emergency room admission for asthma exacerbation (44).

A very recent study, conducted in the military setting, used the clustering analysis method to demonstrate that AR patients may have different phenotypes (45). The outcome was that impaired FEF_{25-75} was able to define the AR phenotype characterized by other variables associated with bronchial involvement, such as bronchial hyperresponsiveness and FeNO overexpression. Therefore, impaired FEF_{25-75} could identify AR patients probably prone to develop asthma.

Such data taken together are partially consistent with the outcomes of other studies conducted in the military setting in the last years. Morris and colleagues reported that asymptomatic airway obstruction, documented by impaired spirometry, including FEF_{25-75} , had a prevalence of 14% in young military personnel of the U.S. Army, most of them had worsening obstruction during exercise (46). Konarski and colleagues showed that divers had low FEF_{25-75} values compatible with the phenomenon of “large lung” due to hyperinflation (47). Skabelund and coworkers evaluated 1693 U.S. Army soldiers before deployment and found abnormal spirometry, including FEF_{25-75} , in 22.3% of participants (48). However, in those soldiers with pre-deployment abnormal spirometry,

there was also not identifiable change, including FEF_{25-75} , that indicated worsening lung function after deployment (49). This finding confirmed a study demonstrating a poor correlation between screening spirometry, including FEF_{25-75} , and asthma history (50). On the other hand, Butzko and colleagues reported that FEF_{25-75} was impaired in U.S. Army veterans who had distal airway dysfunction (51).

These inconsistent findings could depend on the low reproducibility and sensitivity of FEF_{25-75} , even if the specificity is very high as precisely demonstrated (40). The main limitation of FEF_{25-75} is that it is an indirect method to show bronchial impairment rather than a direct measurement. However, this drawback may be partially solved by correct spirometry performed by trained staff and the outcomes should be critically interpreted in the clinical context.

Summarizing these data, in presence of normal FEV_1 and FEV_1/FVC , two main information may derive from impaired FEF_{25-75} in clinical practice: in AR patients it may predict a possible asthma development (52) and in asthmatic patients a poor control (53).

3. Conclusion

FEF_{25-75} deserves an adequate and careful consideration in patients with asthma and/or allergic rhinitis as well as in the general population because low values can add fruitful information about asthma, rhinitis, and allergy in the common practice, as summarized in Table 1.

4. Expert opinion

Spirometry is a fruitful method to assess bronchial airflow. Spirometry may be performed in normal subjects to confirm normal lung function or to provide information about an airflow limitation that should be adequately investigated. FEF_{25-75} could be considered a reliable parameter useful to detect early bronchial impairment in patients with allergic rhinitis and if abnormal, such as $<65\%$ of predicted, could suggest a possible evolution toward overt asthma. In asthmatic patients, FEF_{25-75} could suggest early asthma worsening, mainly when FEV_1 is still normal. In addition, impaired

FEF₂₅₋₇₅ could suggest bronchial eosinophilic inflammation, bronchial reversibility to bronchodilation test, bronchial hyperreactivity in patients with allergic rhinitis and asthma. Moreover, impaired FEF₂₅₋₇₅ in normal subjects could suggest sensitization, such as allergen-specific IgE production. Therefore, careful interpretation of spirometry should be carried out in clinical practice, even when FEV₁ and FEV₁/FVC are normal.

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Declaration of interest

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Table 1 Clinical implications of impaired FEF₂₅₋₇₅ (<65% of predicted)

Clinical setting	Suspected risk	Reference
Normal subjects	Allergic sensitization	37,38
	Bronchial Hyperresponsiveness	39,41
Allergic rhinitis	Early bronchial involvement	29
	Subclinical asthma	14,30,33,34
	Bronchial Hyperresponsiveness	12
	Reversibility to bronchodilation	13
Asthma	Increased FeNO	36,40
	Uncontrolled asthma	9,10
	Increased FeNO	15
	Exacerbation	21
	Need to increase medication use	23