Editorial: Small Airways Disease and Asthma

G Pesola, U Ahmed

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Abstract

The term small airway generally refers to about 7 to 19th generation airways with an inner diameter of about 2 to 0.5 mm ([1,2]). These airways are felt to be an important site of inflammation in both early chronic obstructive pulmonary disease ([1,3]) and asthma ([4]). It is felt that small airway resistance contributes 15 to 24% of airway resistance in normals and much more in the severely diseased ([4,5]) The maximum mid-expiratory flow rate or MMEFR (often known as the FEF_{25-75}) has been suggested as a measure of early small airways disease (SAD) in subjects with a preserved FEV_1 ([3]) and it has been shown to be completely reversible in some subjects who quit smoking and use bronchodilators ([3]). Traditionally, the physiologic method of detecting early SAD was to define an abnormally low MMEFR in the presence of a normal FEV_1, normal FVC, and normal FEV_1/FVC ratio. Once either the FEV_1 or FVC are reduced below predicted norms, by definition the MMEFR will be reduced and is no longer needed to detect abnormal lung function and should not be used. It should also be remembered that in the presence of a normal FEV_1 and FVC, a low FEV_1/FVC ratio can be a normal variant ([6]) and can give a falsely low MMEFR ([7]). Therefore, the FEV_1/FVC ratio must also be normal for age.

A problem with the MMEFR is the lack of correlation with actual resistance measurements in the small airways in subjects with otherwise normal spirometry. Only one study has clearly shown an isolated reduction in the MMEFR, normal spirometry and an isolated measured increase in small airways resistance in mild asthmatics relative to normal controls ([4]). This study revealed a significant difference between the mean MMEFR in asthmatics versus normals, albeit some of the asthmatic MMEFR would still be included in a 95% confidence interval.

The main problem with the MMEFR is the variability in measurement and what appears to be its evanescent nature at times. All pulmonary physicians who regularly read lung function tests have seen only an abnormal MMEFR in the presence of otherwise normal spirometry which over time often becomes normal. This variability may be secondary to the intrinsic variability of the test with a coefficient of variation described as 25% ([8]) and the fact that it is partly dependent on the FVC. If the FVC changes due to variable effort so will the MMEFR. However, it is also possible that some of the variability is related to intermittent increased resistance in the small airways due to inflammation that is reversible. This possibility would clearly account for some of the variability of the test and would explain why it can be abnormal at times and then become normal.

Potentially the most interesting aspect of the MMEFR would be when it is abnormal in the face of otherwise normally predicted spirometric measures. Then, it might be a signal that there is early increased small airways resistance ([4]) that is presumably secondary to inflammation of some sort. In asthma, this might mean persistent inflammation that has resulted in increased small airways resistance and otherwise normal spirometry. In this scenario, the finding may be transient even without treatment or may improve only with anti-inflammatory therapy. More interestingly, a subset of asthmatics may have this finding as the only abnormality initially and as their asthma progresses there will be a reduction in the FEV_1 and FEV_1/FVC ratio consistent with obstruction as currently defined ([6]). The only way to prove this in asthmatics would be to measure small airway resistance (and look for a cause ie small airway inflammation) in asthmatics during periods of low MMEFR and during periods when the MMEFR becomes normal (assuming otherwise normal spirometry). A prospective positive correlation between the two would go a long way toward proving that the MMEFR spirometric measure is

indeed a measure of increased airway resistance in asthma. Presumably, this airway resistance would be secondary to airway inflammation. However, it is possible to have early airway inflammation that does not immediately manifest as increased airway resistance or a low MMEFR ([9]). In addition, it is possible to have recurrent airway damage with permanent SAD and no longer have inflammation present. Therefore, measurement of peripheral airway resistance would be the most important factor to follow to help validate that the MMEFR is detecting early SAD in asthma and other diseases. The assumption of a reduced MMEFR with airway inflammation per se may not be correct.

The study by Cirillo et. al. in this issue of the IJAAI finds SAD as defined by a MMEFR less than 80% in 20/58 subjects with allergic manifestations of disease without a history of asthma. All 58 subjects had normal spirometry defined as a FEV_1, FVC and FEV_1/FVC ratio in the predicted range. All twenty with a low MMEFR were atopic with at least mild airway hyperresponsiveness and 8/20 had allergic rhinitis. In addition, when evaluating the numbers there was a statistically significant difference between the mean MMEFR for the 20 patients with a low MMEFR compared to those with a normal MMEFR ($p < 0.05$). This is important since it can be appropriately argued that the 95% confidence interval would encompass most of the low MMEFR values. Therefore, are these values really low or abnormal? A credible answer is that the only study that measured the MMEFR in normals and asthmatics and also measured actual peripheral airways resistance found a statistically lower mean value for the MMEFR in asthmatics compared to normals, all of whom had otherwise normal spirometry ([4]). As noted above, the group of 20 with allergic disease or at least bronchial hyperreactivity (with atopy) and no asthma also had significantly different (decreased) MMEFR compared to normals. In addition, most of the MMEFR in these allergic nonasthmatic subjects were probably located within the 95% confidence interval for the MMEFR despite being statistically lower than those in normals.

The above situation poses a dilemma. The MMEFR appears to differentiate “groups” on average. However, due to the intrinsic variability of the test, when used as an “individual “test in subjects with either asthma or in this case atopy, bronchial hyperresponsiveness and in some also allergic rhinitis, it is possible an individual value could still be defined as normal (within the 95% confidence interval) despite being less than 80% of predicted. This variability and dilemma is undoubtedly why the MMEFR is not considered a very useful test to detect early SAD. Tests with improved sensitivity for the detection of early SAD before spirometry is abnormal are needed.

An interesting question to pose for the future is will the group of patients with a relatively low MMEFR, atopy, and at least bronchial hyperresponsiveness with or without allergic rhinitis develop asthma at a rate greater than either the general population or others with allergic rhinitis, normal bronchial hyperresponsiveness and a normal MMEFR? It could be argued that a prospective longitudinal study is needed in different groups of patients with and without SAD and the presence or absence of allergic manifestations. In reality, the answer is already known. Subjects with bronchial hyperresponsiveness alone ([10]), atopy alone ([11],[12]), or allergic rhinitis ([12]) are known to have a higher incidence of asthma; this is independent of whether or not SAD is present since it was not measured in any form in these studies. The only question then would be in subjects without asthma with allergic manifestations of disease and a measurement suggestive of early SAD (otherwise normal spirometry), is the disease actually present? A definitive answer would have to start with measurements of airway resistance compared to controls. If the airway resistance was elevated, this suggests early SAD. If, in addition, inflammation was present, this suggests an increased resistance in the small airways secondary to inflammation related to allergic diseases.

It has been proposed that allergic rhinitis, rhinosinusitis, and asthma are simply different clinical manifestations of the location of significant airway inflammation ([13]). Is it possible that early SAD as manifested by some measurement consistent with this idea, is part of this spectrum of disease? Is it possible that subjects with nonasthmatic allergic disease (atopy, allergic rhinitis, atopic dermatitis) or airway hyperresponsiveness who develop a manifestation consistent with SAD are simply part of an atopic march that can start from more than one baseline and end up in the lung with the final manifestation asthma? The atopic manifestation just prior to asthma could be early SAD and then if inflammation persists, asthma would appear.

Cirillo et. al. have suggested that predominantly allergic manifestations of disease in those without asthma appear to be associated with a putative marker that may reflect early SAD. Future research will help determine whether or not this marker or more sensitive ones will reflect early airway resistance secondary to inflammation before asthma

develops. If this were the case, pre-emptive anti-inflammatory therapy might be considered to prevent progression of SAD to frank obstruction that could be detected by routine spirometry.

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Author Information

Gene R. Pesola, M.D., M.P.H.
Dept. of Medicine, Section of Pulmonary/Critical Care Medicine, Harlem Hospital/Columbia University

Ubair Ahmed, M.D.
Dept. of Medicine, Section of Pulmonary/Critical Care Medicine, Harlem Hospital/Columbia University