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Commentary

Is Exclusive Small Airway Asthma a Possibility?

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Abstract: Although the small airway component of chronic asthma is becoming a more important topic, its impact in the daily assessment of pediatric asthma is limited. The intrinsic airway autonomic control in asthma suggests some potential mechanisms by which more distal obstruction may dominate in some situations. We suggest theoretical possibilities for small airway dominance and present clinical data supporting this possibility.

Keywords: asthma; small airway disease; airway hyperresponsiveness; pediatrics

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1. Introduction

Older studies of methacholine (and histamine) responsiveness in asthmatic patients in the previous century provide a framework for a newer paradigm of small airway disease in asthma. A review of the older data is paramount to considering what the possibility is that an asthmatic patient has predominantly, or (possibly) exclusively, small airway obstruction. Considering this possibility, we review data of the methodologies used to find the location of direct airway responsiveness largely used in the previous century and compare this with current thoughts on small airway disease in pediatric asthma.

2. Assessing the Small Airway Compartment in Pediatric Asthma: The Conundrum!

The bottom line is that standard spirometry, including the forced vital capacity (FVC), the forced vital capacity during one second (FEV_1), and the forced expiratory flow rate from 25 to 75% of the FVC ($FEF_{25–75}$), with their corresponding percent predicted and z scores, provides immense information as a snapshot of lung health in children. What is continuously argued is if **any** spirometry measure provides information on the smaller and small airways. It is interesting that the investigations described in virtually all recent publications on small airways in adult asthma immediately utilize radiological procedures. Recent examples include segmental CT analysis [1], while a review has mentioned radiological procedures, nitrogen washout, and impulse oscillometry [2]. A significant question remains, however, is how available, or reasonable, are these procedures for pediatric asthma management?

During an initial pediatric asthma evaluation, therapy should be initiated if an FEV_1 % change after a bronchodilator of 10% or higher is obtained on a well-performed spirometry [3]. However, the presence of an isolated large $FEF_{25–75}$ change alone is minimized or ignored in most clinical practice [4]. Is that reasonable? Does it suggest a different compartment of asthma for that child? A different type of asthma? Cough variant asthma? An evolving asthmatic?

This perspective is not meant to be a refutation of these other important and evolving methodologies to determine small airway disease in an asthmatic, but to raise an issue for respiratory specialists and to provide perspective on a neglected topic of pediatric asthma care.

3. Direct Airway Hyperresponsiveness and Location of Obstruction

Comprehensive reviews of muscarinic receptor location and muscarinic antagonist responses and function are beyond the scope of this perspective but can be found in references [5–7]. In brief, muscarinic activity in airways is regulated by M_3 muscarinic receptors

more than M_2 muscarinic receptors. Both receptor types are found in tertiary bronchi, small bronchi, bronchioles, and respiratory bronchioles. A review of this information is available in publications by Cazzola et al. [6] and Ikeda et al. [5]. Methacholine, a muscarinic agonist, when inhaled by asthmatics in a challenge protocol, can cause proximal (large) and distal (small) airway obstruction [8]. The challenge end point is generally expressed as the change in the post-saline baseline FEV_1, and a 20% drop is considered positive [9]. Various other measures of small airway changes during a methacholine challenge occur and exceed the magnitude of the 20% FEV_1 in the large airways [9]. This includes information obtained using impulse oscillometry and body plethysmography, and smaller airway changes on spirometry (e.g., $FEF_{25–75}$) [9].

What possibilities exist, using receptor density and function concepts, to explain distal, rather than proximal and distal, airway responsiveness? In vitro studies have shown greater central muscarinic activity and more distal airway $beta_2$ adrenergic activity, which generally does not translate to a differentiated benefit of adrenergic agonists or muscarinic antagonists in humans [10,11]. If, however, proximal airway cholinergic control was more dominant than distal cholinergic control, then $beta_2$ responsiveness might lag in the proximal airway. Or if $beta_2$ receptor density or post-receptor activity is more dominant in the distal airway, then inhaled beta agonists might exert a greater distal response, and greatly exceed the proximal airway response. These options are likely uncommon but may have selective or occasional occurrence, or a presence in less defined asthma phenotypes, such as cough variant asthma (CVA) [12–14].

The level of methacholine responsiveness might provide information as to more central versus peripheral cholinergic activity in an asthmatic. If there is a greater cholinergic response peripherally, then a $beta_2$ agonist may preferentially dilate more peripherally, or vice versa. A recent review by Donovan and Noble summarizes that in animal models, both proximal or distal arguments can be made; while studies in humans have shown preferential small airway constriction, but other studies have shown medium and large airway responsiveness [15]. If an individual has more distal $beta_2$ receptors, then is it possible to have a greater distal $beta_2$ response [16–18]? If there is more balanced upper/lower methacholine hyperresponsiveness, then equal $beta_2$ upper and lower airway bronchodilation responsiveness should occur. This possibility ignores short-term "global" hyperresponsiveness changes (i.e., viral illness) [19], or long-term global or segmental inflammatory-induced obstruction/hyperresponsiveness (i.e., allergen) [20].

4. Beta$_2$ Receptor Density in Central and Peripheral Airways

$Beta_2$ receptors are distributed throughout the airway but increase in density with serial passages down the airways and are higher in distal airways and highest in the alveoli [16]. Indirect challenge studies in infants show salbutamol blocks challenge with water or histamine bronchoconstriction [21,22]. The issue in question is the relative density of upper and lower airway $beta_2$ receptors and the acquisition of the density of $beta_2$ receptors in children versus adults. Is there person-to-person variability in lower vs. higher $beta_2$ receptor density, or in children versus adults? Is the observation of exaggerated/exclusive small airway bronchodilation with $beta_2$ agonists more a pediatric oddity? Is there a genetic difference in lower vs. higher $beta_2$ receptor density, so that a particular person has a greater distal density versus proximal density counts, making distal overresponsiveness the exception in some individuals? Are distal airways more responsive in unique asthma phenotypes, such as CVA [12–14]? If any or some of these propositions are true, then selective individuals have long-term or permanent distal responsiveness to $beta_2$ agonists, and this makes more exclusive small airway asthma a possibility. The signaling pathways for beta-adrenergic signaling are complex, and distal up-regulatory functionality for the $beta_2$ agonist response could be possible.

It is also possible that spare $beta_2$ receptors are different in the upper and lower airways, either developmentally or selectively.

5. Potential Processes That May Result in Exclusive (Dominant) Small Airway Asthma

Any allergen load deposited in the respiratory tract should have nasal clearance due to particle size and adequate nasal function. This may not be totally true in nasally obstructed subjects, allowing for downstream (i.e., lung) deposition [23]. Depending on the native allergen size, or the individual allergenicity, regular downstream lung deposition may allow for chronic enhanced distal hyperresponsiveness and which may also include complex nasal–bronchial and/or systemic processes [24]. This has been recently seen in young children, with exaggerated airway hyperresponsiveness due to allergy to house dust mites [25]. Small airway changes were not measured in that report, but bronchoconstriction indued by methacholine will also induce small airway constriction. With continued deposition of small particle allergens, more distal obstruction may dominate, although the population of individuals with exaggerated or isolated small airway "asthma" may be minimal.

In every type of asthma in children, either highly allergic or non-allergic, a new viral illness is the major exacerbation trigger. A seminal discussion of this phenomenon was published in 1998 [19], while small airway dysfunction is a hallmark of prolonged COVID-19 lung disease [26].

A recent study looking at lower airway inflammation in recurrent wheezing children using bronchoalveolar lavage revealed both infectious and atopic phenotypes [27], while a review of modern data approaches to pre-school wheezing phenotypes revealed the massive complexity of the terminology of recurrent childhood wheezing, and vast differences in etiological findings across populations [28]. Genetic differences are evident, as pointed out by Custovic et al., with Group 2 innate lymphocytes playing an unexpected role [28]. It is very possible that the bulk of the genetic and acquired response to environmental and/or infectious impacts can target distal (small airway) changes, resulting in small airway asthma (possibly exclusively).

A CT study of adult asthma in 2016 showed small airway disease is a common finding in all asthma severity groups and may have absent proximal airway changes [29]. CT findings in children with asthma have been severely limited, but the potential for small airway change dominance likely exists.

6. Clinical Examples

At the onset of the preparation of this commentary, the author requested the respiratory therapy team at his center to provide print-outs of examples of small airway reversibility without significant proximal (FEV_1) airway reversibility (Table 1). The percentage of total tests was not determined, but over a 12-month period, representative children were found. These are presented in tabular form, although longitudinal data or clinical circumstances were not collected in parallel.

Table 1. Clinical examples of disproportionate $FEF_{25–75}$ improvement.

Pre- and Post-Albuterol Results in Selected Children Presenting with Asthma-like Symptoms							
	Age	**FVC**	**Post FVC**	**FEV_1**	**Post FEV_1**	**$FEF_{25–75}$**	**Post $FEF_{25–75}$**
Example 1	8	96%	93%	109%	107%	129%	167%
Example 2	5	79%	73%	84%	78%	83%	123%
Example 3	8	85%	88%	85%	93%	81%	134%
Example 4	6	98%	94%	93%	100%	78%	136%
Example 5	10	88%	82%	86%	86%	80%	99%
Example 6	6	114%	114%	126%	127%	138%	170%
Example 7	5	112%	107%	121%	116%	111%	157%
Example 8	6	97%	92%	104%	92%	117%	165%
Example 9	10	112%	113%	113%	117%	108%	143%

Table 1. *Cont.*

Pre- and Post-Albuterol Results in Selected Children Presenting with Asthma-like Symptoms							
	Age	**FVC**	**Post FVC**	**FEV_1**	**Post FEV_1**	**$FEF_{25–75}$**	**Post $FEF_{25–75}$**
Example 10	5	100%	102%	100%	106%	87%	127%
Example 11	5	98%	99%	106%	109%	127%	152%
Example 12	9	81%	81%	78%	82%	66%	116%

7. Clinical Considerations

A child presents or is referred to a pediatric respiratory specialist for a chronic cough, or other asthma-like symptoms. The outcome of the pre–post albuterol response on standard spirometry is often used to characterize symptoms into a diagnosis and a treatment plan. Very likely, a chest X-ray, possibly a sinus X-ray, and an allergy test are also performed. It is less likely that body plethysmography, fractional exhaled nitric oxide (FeNO), impulse oscillometry, nitrogen wash-out, or chest CT are performed. So, if the decision to treat for likely asthma occurs, is the smaller (small) airway component appreciated?

Table 2 provides the potential outcomes for the above clinical scenario, which also includes the $FEF_{25–75}$ results.

Table 2. Clinical scenarios for spirometry interpretation.

	FVC % Improvement [30]	**FEV_1 % Improvement [3,31]**	**$FEF_{25–75}$ % Improvement [12–14,32]**	**Reasonable Clinical Outcome**
Scenario 1	≥10%	≥10%	≥30%	Daily asthma care
Scenario 2	<10%	≥10%	≥30%	Daily asthma care
Scenario 3	<10%	<10%	≥30%	Follow longitudinally [33] or consider cough variant asthma [12–14]
Scenario 4	<10%	<10%	<30%	Consider alternative cough etiologies

8. Clinical Recommendations

1. Consider the $FEF_{25–75}$ improvement especially when there is more than 2 s of expiratory time. A disproportionate improvement in the $FEF_{25–75}$ as compared to the FEV_1 after albuterol should not be ignored [34].
2. Companion pre–post albuterol spirometry with simultaneous impulse oscillometry can assist with differences in upper and lower airway bronchodilatation [33,35].
3. Figure 1 delineates the opportunities for determining large, smaller, and small airway disability in pediatric asthma.

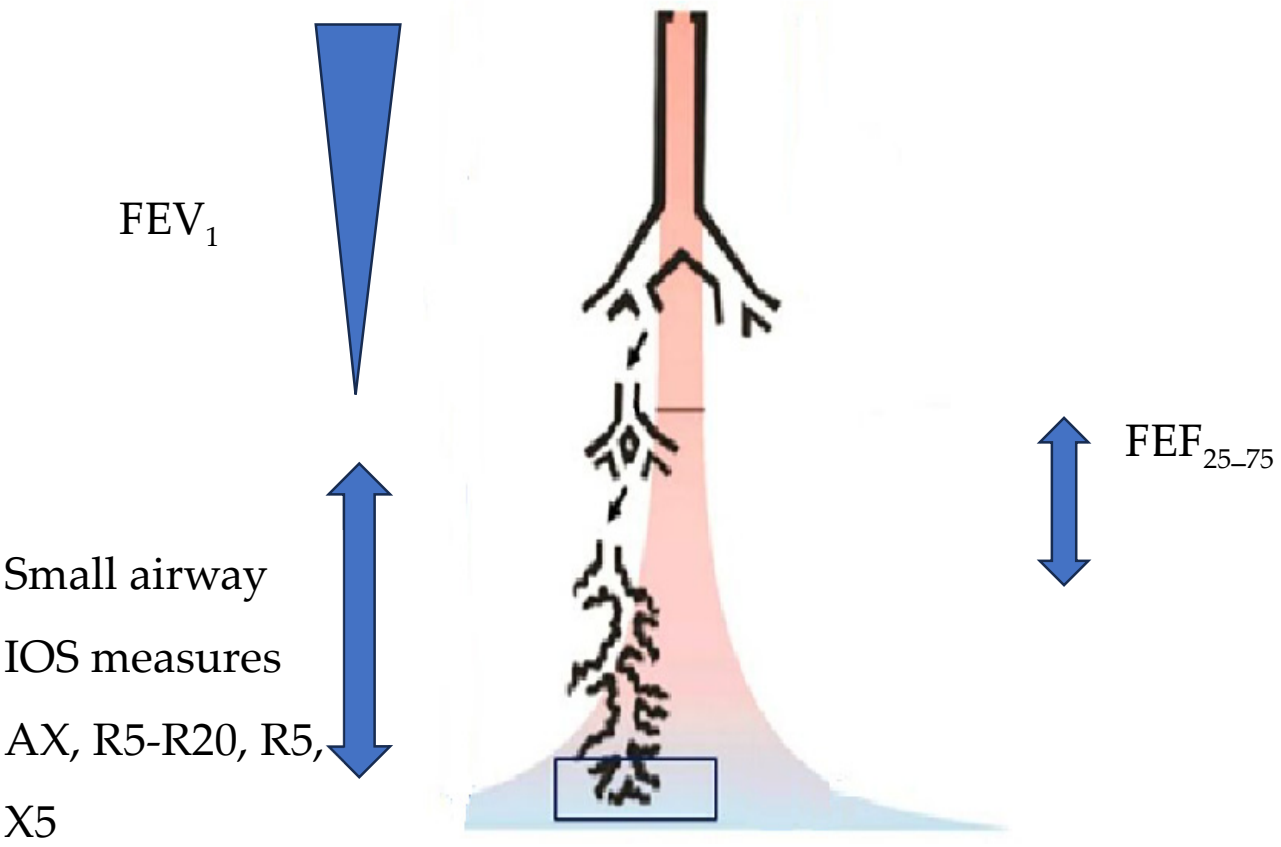

Figure 1. Schematic of the position of large, smaller, and small airways in pulmonary function testing [35].

9. Conclusions

Asthma is a disease of the airways [36]. Much has been made of the small airway asthma concept in this decade, largely because radiological determination of small airways is now possible, as imaging of the small airways conclusively demonstrates distal disease in asthma [37]. However, small airway disease in clinical practice is largely underappreciated/ignored. This commentary was not made to "localize" asthma to large or small airways, but rather to raise a theoretical question, as was carried out recently by Donovan [15]. The possibility that very selective subjects have the majority of their obstruction, either temporally or longitudinally, in the distal airways does lower the bar as to whom a diagnosis of asthma is attributed, but until the individual demonstrates more central/proximal obstruction, the diagnosis maintains less definition. This commentary raises the possibility of a spectrum of asthma not yet totally definable or recognized, points out clinical examples, and provides several suggestions for the clinical assessment of selective, but clinically relevant, small airway obstruction in children.

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