European Journal of Respiratory Medicine
2019; 1(1): 118– 119 . doi: 10.31488/ejrm.104

Editorial

A Perspective on Airway Hyperresponsiveness in Asthma

Russell J. Hopp
Department of Pediatrics and Children's Hospital and Medical Center, University of Nebraska Medical Center, USA
Corresponding author: Russell J. Hopp, D.O., FAAP, FAAAAI, Department of Pediatrics and Children's Hospital and Medical Center, University of Nebraska Medical Center, Omaha, NE, USA, E-mail: rhopp@childrensomaha.org

Received: October 10, 2019; Accepted: November 13, 2019; Published: November 18, 2019

Keywords: methacholine, airway hyperresponsiveness, asthma

The vast majority of basic research and clinical applicability on non-specific airway hyperresponseviness (AHR) was conducted in the previous century. A more recent review of AHR provides a historical and mechanistic overview [1].

There are few 100% truisms in medicine, but several are nearly so in the expression and measurement of airway hyperresponsiveness, an intrinsic phenomenon of the asthmatic condition:

1. Given that an asthmatic is free of albuterol therapy they will have a robust pulmonary response to inhaled albuterol; (and/or)
2. Virtually 100% of asthmatics, without protection of albuterol and muscarinic antagonists, will respond in a dramatic fashion when given progressively increasing doses of methacholine, and the sequential dosing will need to be terminated for safety considerations

The measurement of non-specific AHR is best demonstrated during a methacholine challenge. Histamine can be substituted, although it's use is less widespread. Methacholine and histamine are direct smooth muscle stimulants, acting thru acetylcholine or histamine receptors. Although the post-receptor signaling mechanisms responsible for bronchial (airway) responsiveness is not well understood, a susceptible subject will have a significant change in pulmonary function, predominantly measured by the forced expiratory volume in one second (FEV1). Methacholine (histamine) must be given in a graded fashion to allow the individual to respond but not over-respond. A 20% drop in FEV1 will occur within the parameters of a standardized challenge.

A non-asthmatic will not have a 20% change in FEV1 under most circumstances. The extension of methacholine challenge dosing will not demonstrate responsivity (or minimal AHR) in non-asthmatics; while the asthmatic will have continued deterioration of pulmonary function if doses are extended after a 20% change in FEV1, and is not advisable.

Using methacholine (or histamine) challenges in epidemiological studies have shown a significant body of studied individuals who have measurable BHR, but by all "standard'" criteria do not have asthma. These responsive individuals generally cluster around allergic diseases, including allergic rhinitis, atopic dermatitis, and those who have asthmatic siblings [2-4]. Individuals who will develop asthma in the future also have AHR [5]. The tenets of non-specific AHR are summarized in Table 1.

The emphasis on asthma management in the past three decades has resolved around reducing airway inflammation; and the more recent, and likely future advancements, are largely targeted therapy of cells or cytokine activity blockade, thus reducing cellular activity [6]. Figure 1is a simplified conceptualization of asthma pathophysiology. The intrinsically present AHR becomes inundated with a cellular constituency, largely eosinophilic, ultimately resulting in a chronic inflammatory state.

Working top down, controlling inflammation with reduction of cellular presence and/or cell products (i.e. cytokines) has the potential to subtly influencing AHR; however, unless the intrinsic asthma state (condition) remits and never returns the native AHR persists.

The evidence that asthma symptoms recur when anti-inflammatory medications are stopped or reduced is well accepted. Asthma has to be gone or it's not gone! Current 2019 GINA (Global Initiative for Asthma) recommends inhaled corticosteroids for all persistent adult and adolescent asthma; while adding a biological modifier as an option for more severe forms [7,8]. Obviously, controlling inflammation and reducing cellularity is critical for asthma symptom control.

In essence the presence of a long-acting bronchodilator as a co-component of an inhaled corticosteroid (ICS) has the benefit of a sympathomimetic opposition of intrinsic parasympathomimetic (AHR) tendencies; but in clinical practice it's non-uncommon to find additional bronchodilation after short-acting bronchodilators, further delineating an active, albeit controlled asthmatic status. In essence, AHR is a "non-touchable" component of our proposed triad. Are there options?

Returning to the original truisms: methacholine responsiveness, an indirect measure of AHR, can be abrogated using an anti-cholinergic agent. In recent publications, long-acting anti-cholinergic agents (LAMA) are suggested as add-on therapy in severe pediatric asthma [9], and have long been additive therapy in severe adult asthma [10]. The use of LAMA

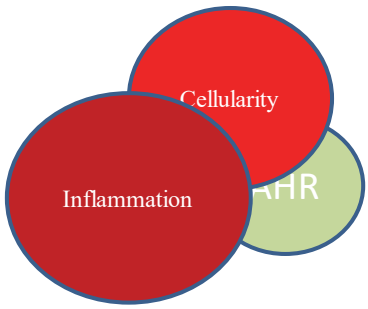

Figure 1. Triad elements of active asthma

Table 1. Tenets of Airway Hyperresponsiveness (AHR)

● AHR ≠ Asthma
● AHR is intrinsic to the asthma condition
● AHR is demonstrable in infants and young children even when not asthmatic
● AHR likely pre-exists before asthma starts
● AHR is minimally modified by asthma therapy
● AHR maintains even if asthma symptoms are gone
● AHR may slowly resolve after many years of clinical asthma remission

in asthma, pediatric or adult, appears to be a therapeutic modality to abrogate the long standing soldier in the asthma triad (Figure 1), namely, the intrinsic AHR of all asthmatics. Whether it's earlier use in mild to moderate patients might shift AHR tendencies, or act in concert with ICS with or without LABA to assist with disarming all three components of the active asthma state, is a fertile field for investigation.

Adding to the eventual potential of LAMA in a wide range of asthmatics are current agents that combine ICS, LAMA and LABA in different combinations; but which currently are out of the asthma therapeutic armamentarium [11]. The emphasis on asthma control has shifted to a focus on inflammatory and cellularity components of asthma, while minimal progress has been made in blocking or reducing AHR. Given no potential cures for asthma on the horizon, attacking as many of the individual components of active asthma should remain viable.

Author Disclosure Statement

No personal or financial support or commercial association or conflict is relevant to this submission

References

1. Chapman DG, Irvin CG. Mechanisms of airway hyperresponsiveness in asthma: The past, present and yet to come. Clin Exp Allergy. 2015; 45: 706-19
2. Clifford RD, Pugsley A, Radford M, et al. Symptoms, atopy, and bronchial response to methacholine in parents with asthma and their children. Arch Dis Child. 1987;62:66-73
3. Cockcroft DW, Murdock KY, Berscheid BA. Relationship between atopy and bronchial responsiveness to histamine in a random population. Ann Allergy. 1984;53:26-29
4. Longo G, Strinati R, Poli F, et al. Genetic factors in nonspecific bronchial hyperreactivity: an epidemiologic study. Am J Dis Child. 1987;141:331-334
5. Hopp RJ, Townley RG, Biven RE, et al. The presence of airway reactivity before the development of asthma. Am Rev Respir Dis. 1990; 141:2-8
6. Peters SP. Asthma treatment in the 21st century: what's next? Clin Rev Allergy Immunol. 2004; 27:197-205
7. 2019 GINA MAIN REPORT. https://ginasthma.org/gina-reports/ Accessed November 7, 2019
8. Reddel HK, FitzGeral JM, Bateman ED, et al. GINA 2019: a fundamental change in asthma management. Eur Respir J. 2019; 53: 1901046
9. Grigg J. Tiotropium in paediatric asthma. Eur Respir J. 2017; 49: 1602034
10. Kew KM, Dahri K. Long-acting muscarinic antagonists (LAMA) added to combination long-acting beta2-agonists and inhaled corticosteroids (LABA/ICS) versus LABA/ICS for adults with asthma. Cochrane Database Syst Rev. 2016; 21:CD011721
11. Virchow JC, Kuna P, Paggiaro P, et al. Single inhaler extrafine triple therapy in uncontrolled asthma (TRIMARAN and TRIGGER): two double-blind, parallel-group, randomised, controlled phase 3 trials. Lancet. 2019; 394: 1737-1749.

To cite this article: Hopp RJ. A Perspective on Airway Hyperresponsiveness in Asthma. European Journal of Respiratory Medicine. 2019: 1:1.