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The Importance of Airway Hyperresponsiveness in Asthma: A Clinical Perspective

Announcer:
Welcome to ReachMD. This medical industry feature, titled "The Importance of Airway Hyperresponsiveness in Asthma: A Clinical Perspective" is sponsored by Amgen and AstraZeneca. This program is intended for physicians. Your host is Dr. Charles Turck.

Dr. Charles Turck:
Airway hyperresponsiveness is the heightened bronchoconstrictive response to stimuli that would produce little or no effect in healthy individuals.[1,2] But, there are some big questions regarding its relation to asthma, like how is airway hyperresponsiveness involved, and why is it clinically important?

This is ReachMD, and I'm Dr. Charles Turck. Here to discuss airway hyperresponsiveness are Professor Chris Brightling and Professor Bruce Levy. Professor Brightling is the NIHR Senior Investigator and Clinical Professor in Respiratory Medicine at the University of Leicester in the UK. And Professor Levy is the Division Chief of Pulmonary and Critical Care Medicine at Brigham and Women's Hospital in Boston, Massachusetts. He's also the Parker B. Francis Professor of Medicine at Harvard Medical School.

Professor Levy and Professor Brightling, thank you both for being here today.

Professor Brightling:
Dr. Turck, thanks for that kind introduction and delighted to join you today!

Professor Levy:
Thank you very much for including me and I'm delighted to be here as well!

Dr. Charles Turck:
Great to have you both with us. And I'd like to begin by handing it over to Professor Brightling, who will discuss the involvement of airway hyperresponsiveness in asthma alongside Professor Levy.

Professor Brightling:
Thank you, Dr. Turck. So, Bruce, let's start with the basics. Can you describe what airway hyperresponsiveness, or AHR, is, and how it relates to asthma?

Professor Levy:
Of course. So as Dr. Turck mentioned at the start of the podcast, AHR is the heightened bronchoconstrictive response to stimuli that would produce little or no effect in healthy individuals.[1,2] It is a cardinal feature of asthma, alongside other factors such as variable or reversible airflow limitation and airway inflammation.[1] AHR can play a part in the diagnosis and management of asthma, as well as classification of the asthma severity.[1,2] And what's really interesting is that the severity of AHR is also associated with increased asthma severity, as measured by symptoms, lung function, and risk of exacerbations.[2,3]

Professor Brightling:
Those are all great points, Bruce, and I'd like to just add that AHR is very dynamic, as its severity and even presence can vary over time with disease activity, specific exposures, or treatment.[1]

Professor Levy:
That's a good point, Chris. And with that in mind, I'd like to say that AHR is dependent on multiple factors; the main ones being airway

inflammation and structural changes, including mast cell effects on airway smooth muscle and airway smooth muscle hypercontractility.[1,2,4–6]

Now if we dive into this idea a little further, airway inflammation is persistent in individuals with asthma and can be exacerbated by exposures to allergens, infections, occupational triggers, and various environmental factors.[1,7] As part of these inflammatory pathways, the epithelial cytokines thymic stromal lymphopoietin, or TSLP for short, interleukin-33, and IL-25 are released from epithelial cells and other immune and airway cells, and can induce the release of downstream cytokines, including IL-4, IL-5, and IL-13.[1,8–10] This release leads to further inflammation, measured by biomarkers such as eosinophils and IgE, as well as bronchoconstriction.[1,8–10]

Airway inflammation is also considered to have variable contributions to AHR,[1] with the severity of AHR being associated with the number of inflammatory cells, including eosinophils, mast cells, and neutrophils in the airway.[2] But it's important to note that AHR can also occur independently of airway inflammation.[11]

Chris, another aspect of AHR is the related structural changes;[1,2,4–6] please can you tell us a bit more about this and about the role of mast cells?

Professor Brightling:
Thanks, Bruce. As we know, airway remodeling encompasses a range of structural changes,[12] some of which are involved in AHR,[1,13] and these are considered to have permanent or persistent contributions to the process.[1,13] Structural changes associated with bronchoconstriction include epithelial damage, airway wall thickening or subepithelial fibrosis, reticular basement membrane thickening, loss of airway tethering to the parenchyma, airway smooth muscle hypertrophy and hyperplasia, and altered extracellular matrix; these structural changes have all been associated with AHR.[14–19] Airway structural changes and their contributions to AHR are an area of evolving research,[2,12,20] so I think we are all excited to see further development in this area.

Now mast cells also appear to play an important role in AHR. Mast cell infiltration into airway smooth muscle and the resultant interactions between the two cell types is associated with structural changes and AHR.[5,6] And I'd like to call out that TSLP acts on and can be released by mast cells and airway smooth muscle cells.[21]

Additionally, in-vitro studies have shown that patients with asthma exhibit fundamental physiological changes in their airway smooth muscle, known as airway hypercontractility.[4,22] Compared with healthy individuals, airway smooth muscle from patients with asthma display enhanced shortening and increased contractility, which is hypothesized to involve mast cell infiltration, and these changes can be another driver of AHR.[4,22–32]

Dr. Charles Turck:
Thank you so much, Professor Brightling and Professor Levy, for breaking all of that down for us. And for those just tuning in, you're listening to ReachMD. I'm Dr. Charles Turck, and today I'm speaking with Professor Chris Brightling and Professor Bruce Levy about airway hyperresponsiveness, or AHR for short.

Now you both just spoke about how airway inflammation and structural changes contribute to AHR in asthma,[1,2,4] but now let's shift over to why AHR is clinically important. Professor Brightling, feel free to take it away.

Professor Brightling:
Thank you Dr. Turck. So, Bruce, we know that AHR is important clinically for a number of reasons, but can you run us through how AHR affects asthma prognosis in patients?

Professor Levy:
Yes, so AHR is associated with a number of clinical aspects of asthma.[2,3,33–35] The severity of AHR is associated with an increased risk of exacerbation, as well as increased asthma severity.[2,3,33] And the presence of AHR has also been associated with accelerated loss of lung function,[34] and airflow limitation in adults.[1]

Now if we look at this from a clinical perspective, multiple factors can also affect AHR, including level of treatment and exposure to environmental stimuli.[36–38] However, it is important to note that AHR is very variable, both among patients and at the individual patient level.[1,2]

Professor Brightling:
And since AHR is so important, when would we measure it?

Professor Levy:
So there are a number of reasons why AHR may be measured in the clinic.[1] It is most commonly used to confirm or exclude a diagnosis of asthma, for example in a patient who has asthma symptoms but with no documented airflow limitation, or in patients suspected of having occupational asthma or exercise-induced respiratory symptoms.[1,39–41] AHR can also be used to help monitor asthma control.[1,42,43]

So, Chris, now that we know why AHR may be measured clinically, how exactly it is measured?

Professor Brightling:
AHR can be measured directly or indirectly and involves stimulation of airway smooth muscle with various agents.[1,2,44] Direct tests are sensitive but not very specific; therefore, direct testing is useful to rule out an asthma diagnosis.[45] Indirect tests are more specific but often less sensitive than direct tests; therefore, indirect testing is useful to diagnose asthma.[45]

Now the two most common methods for testing AHR are methacholine, a direct challenge, and mannitol, an indirect challenge.[1,41,46] For the direct methacholine challenge, inhaled methacholine mimics the neurotransmitter acetylcholine to directly interact with muscarinic receptors on the airway smooth muscle, resulting in bronchoconstriction.[41] This is measured through provocative concentration or provocative dose to methacholine, the provoking concentration or delivered dose of methacholine required to induce greater or equal to 20% reduction in FEV_1 from baseline, also known as PD_{20}.[41]

For the indirect mannitol challenge, inhalation of mannitol rapidly increases the osmolarity of the airway surface liquid.[1,43,46] Inflammatory cells such as mast cells become activated owing to this change in osmolarity, releasing downstream mediators and cytokines involved in inflammation.[1,43,46] This causes bronchospasm and bronchoconstriction, mimicking active airway inflammation.[1,43,46,47] This is measured by PD_{15} to mannitol, meaning the provoking cumulative total dose of mannitol required to induce greater or equal to 15% reduction in FEV_1 from baseline or a 10% decrease in FEV_1 between two consecutive mannitol doses.[1,46]

Both of these tests have different defined cutoff levels for AHR, which can provide beneficial detail regarding the severity of AHR in patients.[41,46]

Professor Levy:
Thanks for breaking all of that down for us, Chris. And I'd just like to highlight one more thing: there are a number of contraindications for performing indirect tests, including hypersensitivity to mannitol and moderate airflow limitation.[46] Contraindications for performing direct tests include moderate or severe airflow limitation, cardiovascular problems, or recent eye surgery.[41]

Now Chris, if we dive a bit deeper into the importance of AHR to patients, what would you do if a patient presented in the clinic with active AHR?

Professor Brightling:
So, in my experience, in the clinic, breathlessness, wheeze, chest tightness, and cough can all be associated with AHR in patients with asthma, particularly when these symptoms have triggers such as exercise, cold air, and allergens. Evidence of these symptoms in a patient could possibly indicate that AHR is a disproportionate factor in their asthma. These symptoms can also impact the patient's ability to work, undertake caring roles, and adversely affect their overall wellbeing.

Professor Levy:
And in a clinical trial setting, would you perform tests for AHR?

Professor Brightling:
Yes, so in clinical trials, we can use AHR to assess the efficacy of new or existing therapies for treatment of asthma. Not only that, but the ability of these treatments to affect AHR also provides additional information on the mechanisms of AHR in asthma.[43]

Professor Levy:
Well, I think we have covered a lot of the key topics on AHR today, Chris, but if you had a final take-home message for our audience on AHR, what would it be?

Professor Brightling:
I'd like everyone to remember that AHR is a cardinal feature of asthma, comprising intricate interplay between airway inflammation and structural changes, but AHR can be present in the absence of significant airway inflammation.[1,4] With that in mind, AHR can play a role

in the diagnosis and the management of asthma, with the severity of AHR being associated with increased asthma severity.[2,3,33] And so if we're able to better understand the mechanisms of AHR, this can provide greater insights into asthma pathophysiology.[1,2]

Dr. Charles Turck:
What an interesting discussion, and those final insights are great for us to think on as we come to the end of today's program. I want to thank my guests for helping us better understand the importance of airway hyperresponsiveness in asthma. Professor Brightling and Professor Levy, it was fantastic speaking with you both today; thank you very much.

Professor Brightling:
Thank you to you and thank very much for those of you who have been listening.

Professor Levy:
Thank you Dr. Turck and thank you to all those listening in today!

Announcer:
This program was sponsored by Amgen and AstraZeneca. If you missed any part of this discussion, visit ReachMD.com/industryfeature. This is ReachMD. Be part of the knowledge.

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