

The Future of Exertional Respiratory Problems

What Do We Know About the Total Airway Approach and What Do We Need to Know?



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KEYWORDS

- Exertional dyspnea • Exercise-induced laryngeal obstruction
- Excessive dynamic airway collapse • Exercise-induced bronchoconstriction

KEY POINTS

- Exercise is increasingly viewed as a preventative and therapeutic modality for a variety of medical and behavioral health disorders; therefore, it is imperative to minimize barriers that discourage exercise.
- This issue of *Immunology and Allergy Clinics of North America* details a “total airway approach” to the evaluation of exertional respiratory problems.
- This issue focuses on basic elements of 2 of sinonasal disease and excessive dynamic airway collapse; more complicated considerations are discussed with respect to exercise-induced laryngeal obstruction.
- A rigorous discussion of the mechanisms, diagnostics, and therapeutics for exercise-induced bronchoconstriction follows, reflective of more than 5 decades of research in the area.
- There is much room for growth in research in these areas, and in common inflammatory pathways and neurophysiologic coupling across all airway segments.

THE IMPORTANCE OF A TOTAL AIRWAY APPROACH TO EXERTIONAL DYSPNEA

In an age when exercise is viewed as a preventative or therapeutic modality for a variety of medical and behavioral health conditions, it is imperative that the medical, surgical, and behavioral health communities minimize barriers that discourage patients from exercising.¹ Exertional respiratory symptoms such as dyspnea, cough, and wheeze represent some of the most important problems acting as such a barrier faced by patients of general practitioners, allergists/immunologists, pulmonologists,

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otolaryngologists, and cardiologists. This collection of reviews has highlighted the history and recent improvements in our understanding of exertional symptoms attributable to the airway. The primary goal of this edition was to introduce a conceptual framework for clinicians to use in the approach to exertional respiratory problems, championing a “total airway” approach.

A secondary goal of this issue is to identify areas for growth in our scientific understanding of specific causes of exertional dyspnea attributable to the airway. Clearly, the medical and research communities have appreciated the impact of asthma during exercise for decades.² We propose the total airway approach as a conceptual framework for contextualizing asthma research as well as research devoted to sinonasal disease, the larynx, and the central airways.^{3–5} Using this framework, gaps in scientific knowledge become more apparent.

TOTAL AIRWAY APPROACH: WHAT DO WE KNOW?

From a clinical perspective, the collective expertise of the immunology/allergy, pulmonology, otolaryngology, speech-language pathology, and psychology communities featured in this edition can be pooled to develop diagnostic and treatment suggestions for providers of patients with exertional dyspnea. Although formal multidisciplinary teams are sparse, an appreciation of the multidisciplinary nature of exertional respiratory problems may lead to a more thoughtful approach by all providers.

In this issue, we began by discussing interactions between exercise and sinonasal disease (see Brecht Steelant and colleagues’ article, “[Exercise and Sino-Nasal Disease](#),” in this issue). This is a field in its infancy and rarely discussed in the literature despite the very high prevalence of sinonasal disease in the general population and increased prevalence among elite athletes.⁶ Seys and colleagues highlight some of the cellular mechanisms and physiologic consequences known to be involved in disease as well as the diagnostic and therapeutic options available to clinicians.

This issue of the *Immunology and Allergy Clinics of North America* is replete with a number of reviews (articles 2 through 6) devoted to exercise-induced laryngeal obstruction (EILO), which, since its initial recognition as a cause of exertional dyspnea in the 1980s, is increasingly recognized as an important cause of exertional dyspnea in specific populations.⁷ In the second article, Walsted and colleagues (see Leif Nordang and colleagues’ article, “[Exercise Induced Laryngeal Obstruction – An Overview](#),” in this issue) taught us that its prevalence lies in the 5% to 10% range in select demographic groups and societies, which is a prevalence comparable with that of asthma in the general population, and yet it remains almost completely unrecognized and certainly misdiagnosed in clinical practice.^{8,9} It may be completely distinct from inducible laryngeal obstruction caused by other triggers at rest, the condition described by Dunglison, Patterson, and Christopher, which has been described with many names including vocal cord dysfunction and paradoxical vocal fold motion.^{10–12} Halvorsen and colleagues (see Ola Drange Røksund and colleagues’ article, “[Working Towards a Common Transatlantic Approach for Evaluation of Exercise Induced Laryngeal Obstruction](#),” in this issue) described a variety of invasive and noninvasive diagnostic techniques that have been used in the past few decades, and noted that continuous laryngoscopy during exercise is emerging as the preferred diagnostic method for its ability to contextualize partial airway obstruction in relation to symptoms of interest, exercise intensity, and recovery.^{13,14} A variety of medical, behavioral, and surgical approaches to treatment have been proposed, each with potential benefits and shortcomings. Bergevin and colleagues (see Monica Shaffer and colleagues’ article, “[Speech-Language Pathology as a Primary Treatment for](#)

[Exercise-Induced Laryngeal Obstruction \(EILO\)](#),” in this issue) provide a detailed summary of speech-language pathology interventions that have been published since the 1980s.^{12,15} Olin and colleagues and Heimdal and colleagues (see J. Tod Olin and Erika Westhoff (Carlson)’s article, [“Exercise-Induced Laryngeal Obstruction and Performance Psychology: Using the Mind as a Diagnostic and Therapeutic Target”](#); and see John-Helge Heimdal and colleagues’ article, [“Surgical Intervention for Exercise-Induced Laryngeal Obstruction](#),” in this issue) follow with a summary of available therapeutic knowledge in the behavioral health and surgical realms respectively, fields in their infancy, ripe for future research.^{16–18}

Next, excessive dynamic airway collapse (EDAC) is covered, a condition only recently described as a potential cause of exertional dyspnea (see Michael J. Morris and colleagues’ article, [“Exertional Dyspnea and Excessive Dynamic Airway Collapse](#),” in this issue).^{5,19} Morris and colleagues taught us about the proposed physiology, presentation, and clinical relevance of the condition. Importantly, we present a discussion about this clinical entity in the context of our existing knowledge of tracheobronchomalacia. Finally, diagnostic and therapeutic approaches are proposed, although there is limited evidence to dictate whether they are truly robust or beneficial.

To complete the issue, a series of reviews (articles 8 through 13) cover exercise-induced bronchoconstriction with asthma and exercise-induced bronchoconstriction without asthma, conditions that have been the primary focus of airway literature both clinically and scientifically for the past several decades.²⁰ Bonini and Silvers (see Matteo Bonini and William Silvers’ article, [“Exercise-Induced Bronchoconstriction: Background, Prevalence and Sport Considerations](#),” in this issue) discuss the effect of different sports on the prevalence of these conditions.²¹ Kippelen and colleagues (see Pascale Kippelen and colleagues’ article, [“Mechanisms and Biomarkers of Exercise-Induced Bronchoconstriction](#),” in this issue) synthesize an incredible review of decades of mechanistic research in EIB, incorporating observations attributable to vascular phenomena into the now accepted osmotic hypothesis.^{22,23} In addition to cellular mechanisms, newer neurogenic mechanisms of disease are discussed. Rundell and colleagues (see Kenneth W. Rundell and colleagues’ article, [“Exercise-Induced Bronchoconstriction and the Air We breathe](#),” in this issue) followed with one of the most comprehensive reviews of interactions between asthma and the environment available, featuring knowledge on many commonly encountered environmental pollutants. Brannan and colleagues (see John D. Brannan and Celeste Porsbjerg’s article, [“Testing for Exercise Induced-Bronchoconstriction](#),” in this issue) discussed the latest advances in EIB diagnosis, highlighting the practical and physiologic advantages of surrogate testing.²⁴ Backer and Mastronarde (see Vibeke Backer and John Mastronarde’s article, [“Pharmacologic Strategies for Exercise-Induced Bronchospasm with a focus on Athletes](#),” in this issue) provide a comprehensive summary of pharmacologic options for clinicians, incorporating guidelines from the American Thoracic Society, American Academy of Allergy, Asthma, and Immunology, and American College of Allergy, Asthma and Immunology.^{20,25} Finally, Dickinson and colleagues (see John Dickinson and colleagues’ article, [“Non-Pharmacological Strategies to Manage Exercise Induced Bronchoconstriction](#),” in this issue) discussed several nonpharmacologic interventions for EIB, a topic of keen interest to many athletes.

TOTAL AIRWAY APPROACH: WHAT DO WE NEED TO KNOW?

This issue of *Immunology and Allergy Clinics of North America* has identified potential areas of immediate impact for potential future research across the airway. Our

understanding of diseases localized to specific locations in the airway varies greatly by location. With respect to other diseases of the airway, our understanding of lower airways disease is relatively sophisticated. Lower airways disease is increasingly understood to be a syndrome of clinical symptoms that occur as a final common pathway to a variety of insulted and dysregulated molecular and cellular pathways. On the other extreme, sinonasal disease, EILO and EDAC are poorly understood from the gross perspectives of mechanisms, physiology, and clinical impact. Moreover, there are currently no high-quality studies (ie, with a randomized, controlled intervention) assessing treatment in these areas.

With respect to understanding interactions between nasal processes and exercise, there are several clinical questions that require answering in the coming years. In the short term, it is critical to characterize the impact of nasal symptoms on exertional dyspnea as a whole. A functional assay of nasal air flow function could enable clinicians to quantitate nasal function, define threshold levels for abnormalities, and measure response to therapy. Such an assay could characterize the impact of changes in nasal flow on dyspnea more broadly.

From a more basic perspective, it will be helpful to understand the molecular and cellular mechanisms that lead to airflow obstruction. This understanding could help to characterize the effect of exercise on epithelial stress and nasal obstruction more broadly. Moreover, such an understanding will lead to understanding of the relative effects of various exercise modes on nasal function.

Turning to EILO, the publication of this issue coincides with the timing of the first international meeting of clinicians and researchers focused on EILO, in Bergen, Norway. The proceedings of this meeting featured focused discussion on available diagnostic and therapeutic strategies and serve as a useful guide to the identification of clinical and research gaps. Although there was broad consensus that continuous laryngoscopy during exercise is the diagnostic approach of choice among meeting participants, there is a need to reach agreement on protocols and exercise modalities used to provoke field symptoms, especially for the standardization of research protocols. There is a need to correlate observed upper airway obstruction and physiologic variables of clinical significance to define threshold levels of obstruction that define disease. The meeting participants agreed that there was an urgent need for a system that permits quantification of observed obstruction beyond the existing semiquantitative measures. There is also a need for a robust clinical outcome measure that is specific to exercise.

Beyond the immediate clinical gaps noted in EILO, it is notable that disease mechanism is poorly understood at the current time. It is not clear if EILO is a singular entity or a syndrome of related phenomena. The relative impact of absolute airway size, airway pliability, airway reactivity, extrinsic contributors (allergic rhinitis and gastroesophageal reflux), cortical processes and motor learning are currently unknown.

With respect to EDAC, active research is just beginning, and many clinical questions remain unanswered. From an applied clinical perspective, we do not have precise diagnostic techniques. For this reason, estimates of prevalence and characterizations of normal function are not available. The correlation of obstruction and symptoms is not clear at the current time and, thus, the importance of the phenomenon is not clear. Treatment remains quite a mystery, especially in light of the uncertainty as to whether this is a primary or secondary phenomenon. Symptom-based outcome measures could guide this process. On a similar note, from a more basic perspective, the disease mechanism must be elucidated somewhat moving forward if progress is to be achieved. Such knowledge could potentially lead to preventative strategies.

Finally, EIB presents a number of questions as well, albeit at a more refined level. Clinically, with our improved understanding of disease mechanism, it is reasonable to wonder whether more precise therapeutic targets are a possibility, analogous to the newer biologic agents available for refractory asthma. The true interaction between nonpharmacologic and pharmacologic interventions remain to be defined. There is also a need to study pharmacologic and nonpharmacologic interventions that protect athletes from noxious environmental stimuli and associated airway injury, with an eye toward disease prevention.

THE FUTURE OF "TOTAL AIRWAY" RESEARCH

Research devoted to specific causes of exertional dyspnea attributable to the airway will lead to increasingly precise characterization and treatment for patients in the future. However, a total airway approach will elucidate the mechanistic, physiologic, and clinical impact of interactions between conditions.

How does the inflammatory biology of the upper airway affect the physiology of the lower airways during exercise? How does the physiology of the lower airway affect the clinical characterization of central airways disease during exercise? Does the behavior of the larynx change in clinically important ways in response to extrinsic inflammatory triggers or intrinsic distal disease? Can the characterization of the relatively well-understood lower airways lead to early identification of dysfunction in other airway sectors? Does the molecular dysregulation that causes a specific asthma endotype affect all airway sectors in ways that will change our approach to treatment of that endotype in the future? These are only a few of the questions to answer related to biologic and physiologic coupling across the airway. More broadly, can we use the experience of asthma research, which has led to a model of distinct phenotypes and precision care, guide research about other dysfunction of other airway sectors, which may also be final common pathways to constellations of phenomena?

SUMMARY

This is an exciting time in the study of interactions between exercise and the airway. It is now clear that asthma and EIB do not explain many of the symptoms attributable to the airway in exercise, with nasal disease, EILO, and EDAC contributing in select populations. Our improved understanding of these more recently appreciated conditions will continue to improve the precision of patient care moving forward.

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