

Wheezing after Respiratory Tract Infection in Athletes

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Abstract:

Wheezing is a commonly encountered complaint by patients seen in sports medicine practice. Wheezes are a continuous musical sound heard best on expiration and can originate from one or more of several defined anatomical locations in the human airway. While common causes of wheezing include exercise-induced bronchoconstriction, postnasal drip, and asthma, wheezing also follows specific respiratory infections and can persist for months after the onset of symptoms. Abnormal lung physiology following pneumonia can persist for decades. These postinfectious pulmonary changes affect the ability of athletes to return to sports. In addition to history and physical examination, diagnosis may require pulmonary function testing and exercise challenge testing. The cornerstone to management is an accurate diagnosis and using lifestyle and pharmacologic intervention. Return to play should be gradual and allowed only after individuals demonstrate adequate pulmonary capacity to meet the demands of their sport. Providers also should be aware of governing body regulations regarding treatments and required therapeutic use exemptions.

asthma, and WARI in children. Discussion addresses management of the common wheezing syndromes, return-to-play issues, and therapeutic use exemptions (TUE) for National Collegiate Athletic Association (NCAA)/World Anti-Doping Association (WADA)-prohibited substances.

Definitions

“Wheezing” is defined as a continuous musical, whistling breathing sound that lasts longer than 250 ms (29). Local narrowing of the airway causes increased velocity of moving air, which produces the vibration (26). The high-frequency vibration is audible to the human ear but is heard best with the diaphragm of the stethoscope. Wheezing

can occur with inspiration, expiration, or both. When wheezing is associated with the upper airways as in tracheal or laryngeal obstruction, the sound is termed “stridor” (17). Stridor requires emergent assessment as it can be a sign of impending airway compromise.

The timbre or quality of the wheezing sound can prove useful in determining the location of the obstruction (11). A polyphonic timbre created by multiple musical notes usually is caused by dynamic compression of large upper airways, *i.e.*, above the carina. Monophonic wheezing, heard as a single musical tone, usually represents the smaller lower airway, *i.e.*, below the carina. Monophonic wheezing is characteristic of bronchoconstrictive disorders. Expiratory wheezing classically is associated with intrathoracic lower airway obstruction and is characteristic of asthma. However, expiratory wheezing is neither sensitive nor specific for asthma (20) with a positive predictive value of 43% (34). Inspiratory wheezing classically is associated with extrathoracic upper airway obstruction such as postnasal drip syndrome, vocal cord dysfunction (VCD), tonsillar hypertrophy, and laryngeal and tracheal pathology but can occur with lower airway disorders. Stridor can be heard if the upper airway diameter is less than 5 mm (1).

Introduction

Asthma and wheezing may be more common in athletes than in the general population (32). The purpose of this article was to focus on a subset of athletes who develop wheezing and bronchoreactivity associated with upper and lower respiratory tract infections (RTI). This is otherwise known as wheezing after RTI (WARI). Information was compiled through a review of textbooks, UpToDate online, and articles identified through a PubMed literature search with the following keywords: adult acquired asthmatic syndromes, atypical pneumonia with wheezing, adult onset

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The Athlete with New Onset of Wheezing

In an athlete who has new-onset wheezing, determine whether there has been a recent upper or lower RTI. Consider and exclude common extrathoracic upper airway obstruction problems including postnasal drip syndrome, tonsillar hypertrophy, laryngeal pathology, anaphylaxis, and obesity (33). VCD is another common cause of extrathoracic upper airway obstruction routinely mistaken for asthma/bronchoconstriction. Hallmarks of VCD include failure to respond to bronchodilators in a patient who seems to have predominantly stridulous breath sounds as opposed to wheezing heard better over the lung fields. Diagnosis may require indirect laryngoscopy demonstrating abnormal vocal cord motion. Uncommon intrathoracic upper airway obstruction etiologies include tracheal stenosis, tracheomalacia, compressive tumors, and foreign body aspiration. Possible causes for lower airway obstructions include infection, asthma, chronic obstructive pulmonary disease, pulmonary edema, bronchiolitis, carcinoid syndrome, bronchiectasis, and pulmonary embolus.

The most common etiology of new-onset wheezing in sports medicine practice is exercise-induced bronchoconstriction (EIB). EIB affects 10% of the general population and up to 90% of those with a prior diagnosis of asthma (22). Asthma may be more prevalent in elite athletes (10.0%) than in the general population (6.9%) (32). However, studies use different diagnostic criteria, so the numbers reported may be misleading. Diagnoses of EIB and intrinsic asthma have been well documented in the literature, but less information documents how to identify whether the athlete has developed a new-onset wheezing syndrome related to a recent infection.

Wheezing Related to Infection

There is an association between RTI, subsequent wheezing, and reduced ventilatory function. Persistent wheezing can occur after atypical pneumonias and viral upper RTI (URI). Wheezing can be evanescent or persistent. Pulmonary function changes after pneumonia, and respiratory infections usually persist for weeks but can persist for decades.

Chlamydophila pneumoniae

C. pneumoniae most commonly occurs in people between the ages of 65 and 79 years but can cause pneumonia in all age groups. There are no reliable clinical features or laboratory abnormalities that distinguish infection with *C. pneumoniae* (7). Pharyngitis and sinusitis commonly occur with this type of pneumonia (13). *C. pneumoniae* infections were linked to reactive airway disease in children in the 1990s. Studies found *C. pneumoniae* in 11% of children with wheezing. In 75% of the children, clinical improvement of wheezing followed antibiotic treatment (9). Suttithawil *et al.* (40) examined 110 Thai military recruits during a *C. pneumoniae* outbreak. They failed to show bronchial hyperresponsiveness with methacholine challenge testing, and none of those tested developed physician-diagnosed asthma at 2 years of follow-up (40). Conversely, The study of Hahn and McDonald (14) of 163 adolescents and adults with an acute wheezing illness suggested that acute *C. pneumoniae* infections in nonasthmatic patients can result in chronic asthma. While not all studies are consistent,

published results do suggest that *C. pneumoniae* infections can lead to acquired reactive airway disease in all age groups.

Mycoplasma pneumoniae

M. pneumoniae is one of the most common causes of atypical pneumonia and characteristically strikes children, college students, and military recruits. Symptoms include cough, malaise, and pharyngitis. Symptoms usually are mild but may persist for 4 wk or more. There are several studies confirming the presence of wheezing following *M. pneumoniae* infections. Stempel and Boucher (39) concluded that viral and *Mycoplasma* infections can cause wheezing in children and adults. Wongtim and Mogmued (43) compared 12 healthy subjects with 12 patients at the 4th and 12th weeks after recovery from *M. pneumoniae*. Methacholine challenge testing showed a 20% fall in forced expiratory volume in 1 s (FEV1) from baseline at 4 wk in 67% of the infected patients. This constituted a positive test. Fifty percent of these patients were still positive on the second test at 12 wk. None of the 12 healthy subjects had any bronchial reactivity to the methacholine challenge at the 4th or 12th weeks (43). This would suggest WARI is common after and has a causal association with *M. pneumoniae*. Abnormal lung physiology can persist beyond 12 wk. Johnston *et al.* (19) followed 1,392 British children from birth in 1958 to age 34 to 35. One hundred ninety-three of these children had a history of pneumonia, and 215 had a history of whooping cough by the time they were 7 years old. At the age of 34 to 35, pre- and post-bronchodilator (albuterol) FEV1 and forced vital capacity (FVC) were measured. History of pneumonia was found to be associated with deficits in both FEV1 and FVC. There was, however, no change in the FEV1/FVC ratio. These deficits persisted after inhalation of albuterol. Shaheen *et al.* (37) also showed this in a study of 1,070 British children with a history of pneumonia before the age of 2. Statistically significant deficits in FEV1 and FVC were seen at 14 years. Perhaps, the strongest association of *M. pneumoniae* with new-onset wheezing is from a study of children hospitalized with asthma. Of 51 patients experiencing their first asthma attack, 50% had evidence of *M. pneumoniae* infection. Patients who had *M. pneumoniae* infections also were more likely to have asthma recurrence (4).

Viral Infection

Viral respiratory infections cause cough, sneezing, rhinorrhea, and sore throat in a heterogeneous fashion. Approximately 500 million episodes are reported yearly. An adult may have two to three episodes annually, while school-aged children may have an average of seven episodes per year (10). While respiratory syncytial virus commonly causes wheezing in infants younger than 2 years, this presentation is unusual in older children. Viral URI can cause wheezing and exacerbation in asthmatic patients; however, URI do not seem to cause a change in lung physiology in nonasthmatic, nonathletic adults. Weidner *et al.* (42) randomized 43 men and women aged 18 to 29 years to control and experimental URI groups. All experimental subjects were screened to exclude those with human rhinovirus 16 antibodies. All subjects underwent baseline

pulmonary function testing and a graded exercise test to fatigue. Experimental URI subjects were then inoculated with human rhinovirus 16 twice within 10 d of completing the baseline tests. On the day following the second inoculation, a repeat pulmonary function test and exercise tolerance test were conducted on both the control and the experimental URI subjects. There were no significant differences in pulmonary functional testing (PFT) or maximal-exercise performance between the control and the experimental URI groups (42).

A study of 19 nonasthmatic cross-country skiers and 22 nonathletic controls suggests that although nonasthmatic nonathletes do not seem to be susceptible to a viral-induced wheeze, athletes who require a high minute ventilation might have differing results. In this study, 12 skiers and 10 controls contracted acute RTI. Pulmonary function testing with methacholine challenge was performed before and at 1, 3, and 6 wk after onset of symptoms. Results showed a transient increase in bronchial responsiveness in the athlete group but not in the control group (16).

While wheezing has been shown to occur with *C. pneumoniae* and *M. pneumoniae* infections, wheezing is usually not a sign of pneumonia. In a study of 247 patients with wheezing who received a chest radiograph to assess for pneumonia, only 4.9% had radiographic pneumonia (26,28).

Diagnostic and Treatment Approaches

Diagnosis of postinfectious wheezing syndromes is based primarily on history. When symptoms are significant or diagnosis is in doubt, physicians should obtain standard PFT with and without bronchodilators. Exercise challenge testing with repeated PFT and/or serial peak expiratory flow rates (PEFR) measures may help identify athletes who have few symptoms at rest but develop chest tightness, shortness of breath, wheezing, or cough during sport. These test results often mimic those typically seen in asthmatic patients. The primary difference is that in almost all cases, PFT does return to normal within 12 wk, unless the infection has led to permanent pulmonary injury.

Treatment approaches are similar to those used for intrinsic asthma and exercise-induced bronchospasm. Physicians should aggressively control symptoms before participation so that athletes are exercising with PEFR above 80% of predicted levels. In addition to short-acting β -2 agonists used as a rescue medication, inhaled glucocorticoids can be used in patients with uncontrolled symptoms. If symptoms occur with most episodes of exercise, prophylactic inhaled β -2 agonists should be used 10 to 15 min prior to participation (3,30). Combination medicines have a long-acting β -2 agonist such as salmeterol plus a corticosteroid. These also may be used when exercise occurs intermittently throughout the day as with children (41), tournaments with multiple games, or events that have trials and finals. Clinicians should be aware that while long-acting β agonists can be used alone in EIB, there is some evidence that they may increase mortality when used alone in asthmatic patients (5,31). Chromones and antileukotriene agents also have evidence for use in EIB and asthmatic patients (23,35).

Antibiotics have a role in postinfectious wheezing cases suspected of following *C. pneumoniae* or *M. pneumoniae*

(6,23,45). Macrolides may be particularly efficacious in treating the inflammation associated with WARI. In addition to their antibacterial properties, they also have been shown to have anti-inflammatory effects (2). Community-acquired pneumonias may be treated empirically with azithromycin or doxycycline alone in the outpatient setting. Antibiotics also have shown efficacy in treating acute sinusitis. Empiric amoxicillin is the first-line agent for this illness, and azithromycin or doxycycline can be used in penicillin-allergic patients (8). The common cold and acute bronchitis should not be treated with antibiotics as they have not been shown to be beneficial.

Data regarding supplementation with anti-inflammatory ω -3 fatty acids are conflicting; however, some studies show promise with preventing EIB (27). Zinc has been shown to reduce rhinovirus replication *in vitro*, and subsequent studies have shown an improvement in the duration and severity of cold symptoms with supplementation (38). Ascorbic acid (vitamin C) did not improve symptoms of, or duration of, the common cold; however, it did cause a clinically significant reduction in the frequency when taken prophylactically (37). None of these have been studied specifically in the subset of athletes who have postinfectious wheezing syndromes.

There is evidence that physical activity itself can decrease the incidence of URI of all types (21,25). Conversely, the athlete and clinician should be aware that extremely intense exercise actually can increase the incidence of URI. A large study of 530 subjects showed that runners training 16 to 26 miles·wk⁻¹ greatly increased their chances (odds ratio = 3.5) of contracting URI compared with those who trained less than 9 miles·wk⁻¹ (15).

Return to Play

There is no consistent evidence regarding return to play in patients with a history of wheezing. Patients actively wheezing typically are unable to participate until symptoms are improved significantly. In athletes who still seem to have acute infection, consideration must be taken into whether they are contagious and could infect other participants. The degree of their acute illness might preclude them from safely exercising particularly if they have systemic symptoms or resting tachycardia. Premature return to physical activity may delay recovery and promote complications such as myocarditis (12,18). Athletes should be reassured that deconditioning does not occur until after 4 to 5 d of complete inactivity (24).

Pulmonary function testing and exercise challenge testing can be used to monitor patient recovery. Pulmonary function testing can include spirometry (measurement of FEV1 and FVC), diffusion capacity, and flow-volume loops. For most athletes, inexpensive spirometry adequately allows the physician to assess ability to play when this testing is coupled with an exercise challenge. The exercise challenge can be designed to test the specific ventilatory demands that the athlete would face in a given sport. In addition, medication regimens can be assessed to see if they are allowing the athlete to improve exercise testing performance adequately to return to their sport.

In athletes with milder cases, clinical follow-up can progress sequentially starting the athlete at low workloads

and progressing to maximal effort in practice prior to initiating competition. Since many of these syndromes resolve in 6 to 12 wk, physicians can use the severity of the given illness, the degree of pulmonary compromise, and the provocation of symptoms by training to judge how rapidly to allow return to sport. Field-side PEFr monitors traditionally have been used to assist with this and may be adequate to demonstrate good function in many patients.

WADA/NCAA Guidelines

β -2 agonists and inhaled glucocorticoids are commonly used medications with treating postinfectious wheezing syndromes. When prescribing β -2 agonists and other medications, the physician should be sure they are not restricted in competition. The NCAA and WADA prohibit the use of all β -2 agonists except albuterol and salmeterol. These are permitted by inhalation only. Albuterol is restricted to urine concentrations less than 1,000 ng·mL⁻¹. Other β -2 agonists such as formoterol are permitted only with TUE. Inhaled glucocorticoids are permitted without TUE; however, oral or intravenous routes require TUE. Other treatments for wheezing that are nonprohibited include leukotriene receptor antagonists, anticholinergics, chromones, theophyllines, and anti-immunoglobulin E agents. The validity of a TUE for an asthmatic athlete is 4 years with at least annual confirmation of the treatment regimen by a physician experienced in treating asthma in athletes. After 4 years, repeated pulmonary function tests must meet the agreed diagnostic criteria (44).

Conclusions

Postinfectious wheezing syndromes may complicate the ability of an athlete to return to sport. Confirming the diagnosis and degree of pulmonary compromise is a cornerstone to choosing a therapeutic strategy. Treatment typically follows the same guidelines used for asthma and EIB with the exception that antibiotics that treat atypical pneumonia — doxycycline and azithromycin — have a beneficial role in certain cases. Return to play requires close clinical monitoring or objective pulmonary challenge testing to ensure success for the athlete.

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