

CME review article

Exercise-Induced Respiratory Symptoms: An Epidemic Among Adolescents

Stephen A. Tilles, MD*

Objective: To review the most important causes of exercise-induced respiratory symptoms in adolescents.

Data Sources: Published English-language medical literature.

Study Selection: Primary literature and consensus publications relevant to the objective.

Results: The diagnosis and treatment of exercise-induced asthma are well characterized. Other syndromes, such as exercise-induced vocal cord dysfunction, exercise-induced paradoxical arytenoid motion, and exercise-induced hyperventilation, are relatively common but so far are described primarily in uncontrolled case reports.

Conclusion: Controlled studies are necessary to define efficient diagnostic and treatment algorithms for young patients experiencing respiratory symptoms during exercise who do not respond to asthma treatment.

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INTRODUCTION

Whether an octogenarian walking a mile or more on a regular basis, a 45-year-old executive religiously sweating out 45-minute elliptical machine workouts several times a week, or a 13-year-old involved in year-round soccer practices and games, an increasing number of us are choosing to exercise regularly. Although the benefits of exercise are undeniable, symptoms associated with exercise are an increasingly common reason for seeing a physician. Adolescents are a particularly challenging patient population, in part because of the rapid physical and emotional development that takes place during this stage of life. This review uses a sequential case report to help illustrate a discussion of the important causes of exercise-induced respiratory symptoms in adolescents, including exercise-induced asthma, vocal cord dysfunction (VCD), paradoxical arytenoid motion, hyperventilation syndrome, and cardiac disease. We reviewed the published En-

glish-language medical literature, and retrieved information from the primary literature and consensus publications relevant to the objective.

SUMMARY OF INITIAL PRESENTATION TO ASTHMA SPECIALIST

A 13-year-old female competitive soccer player presented with an 8-month history of dyspnea and chest tightness during exercise. Symptoms only occur while running and begin about 10 minutes after the start of games or practices. She describes the chest tightness as localized to her mid sternal area. She is not able to recall whether the symptoms are more prominent during inhalation or exhalation. Symptoms typically resolve within 5 minutes without treatment when she stops exercising. She denies ever having syncope or dizziness during or after exercise. Symptoms were not prevented by twice-daily fluticasone and salmeterol, 250 μ g/50 μ g, once-daily montelukast, 10 mg, and prophylactic inhaled albuterol. Her history is notable for acne and mild eczema. She has no history of croup or laryngomalacia as a young child, allergic rhinitis, hypertension, or congenital heart problems. Family history is notable for the absence of atopy, sudden death before the age of 50 years, or unusual heart problems. Social history includes having supportive parents, and there is no history of anxiety, depression, or major psychological

Affiliations: * Department of Medicine, University of Washington School of Medicine, and ASTHMA Inc, Seattle, Washington.

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trauma. She has a 3.5-grade point average. The results of physical examination were normal, including a height of 52 in and a weight of 111 lb. Baseline spirometry results were normal (Figure 1). An inhalant skin testing panel (including dust mites, animal dander, molds, and pollens) was performed and the results were negative.

EXERCISE-INDUCED BRONCHOSPASM

Exercise-induced bronchospasm (EIB) involves airway narrowing during and/or following exercise, resulting in respiratory symptoms, such as dyspnea, chest tightness, cough, or wheezing.¹ The EIB response is well characterized and includes a reproducible pattern of physiologic changes that depends on both the intensity and duration of exercise. Early studies in children^{2,3} showed that exercise lasting up to 4 minutes failed to elicit an EIB response, whereas exercise continued for 8, 12, or 16 minutes elicited what has become accepted as a classic response. The classic EIB response involves symptoms correlating with acute intrathoracic airflow obstruction that is greatest approximately 10 to 15 minutes after the start of exercise and persists before gradually returning to baseline 30 to 60 minutes later. The timing of this response is independent of the duration of exercise as long as the patient performs intense exercise for at least 5 to 8 minutes.²

The EIB response also involves a relative refractory period in most patients.³ Exercise repeated sooner than 60 minutes after an initial EIB response generally results in bronchospasm that is both of smaller magnitude and shorter duration than the initial response. This has led some physicians to recommend careful pre-event warm-up routines for athletes when EIB is refractory to conventional prophylactic medication. The goal is to warm up intensely enough that an EIB response occurs well before the event start, allowing the refractory period to protect against performance impairing EIB that might otherwise occur during the event.

When evaluating an adolescent who describes exercise-induced dyspnea, it is important to consider the expected

prevalence of EIB. Although EIB is a common condition, its prevalence depends on the population being studied and the methods used to detect it. For example, the prevalence of EIB is greater than 90% in patients with persistent asthma, 30% to 70% in elite athletes,⁴ and 5% to 20% in the general population.¹

The reason why so many elite athletes develop EIB is not entirely clear, but there is increasing evidence that EIB in this population is a chronic inflammatory condition that is analogous to occupational asthma. For example, Helenius et al⁵ performed histamine challenge and induced sputum examination on 29 unselected members of the Finnish National Swim Team. At the time of the study, these swimmers had been training intensely for an average of 9 years. Compared with healthy controls, the swimmers had significantly greater bronchial hyperresponsiveness and sputum eosinophilia.

The prevalence of EIB among adolescent elite athletes has not been studied extensively, but a recent study comparing adolescent elite swimmers with both adolescent asthmatic patients and unselected adolescents found that the elite swimmers as a group had methacholine bronchial hyperresponsiveness that was similar to the unselected adolescent controls and lower than the adolescents with mild asthma.⁶ Therefore, in contrast to adult elite athletes, the prevalence of EIB in adolescent athletes may not be unusually high.

Expected physical examination findings in EIB patients vary depending on whether the patient is symptomatic. At rest without symptoms, EIB patients often have normal physical examination results. Findings suggestive of asthma are more often present while the patient is symptomatic and include hyperexpansion of the chest, prolonged expiratory phase, and wheezing. Because asthma is more likely in patients with rhinitis and/or atopic dermatitis, additional relevant findings include nasal turbinate edema, nasal polyposis, rhinorrhea, or eczema.⁷

What diagnostic tests are appropriate when EIB is suspected? As with all patients suspected of having asthma, spirometry should be performed, including, if intrathoracic obstruction is present, a postbronchodilator measurement. Because most adolescents with asthma are atopic, negative results on inhalant allergen skin tests or in vitro specific IgE tests would decrease the probability of having asthma, although allergy testing can not confirm or exclude the diagnosis of asthma. Patients with previously diagnosed asthma have a high pretest probability of having EIB and therefore do not require additional diagnostic testing unless they have failed EIB treatment. However, the National Heart, Lung, and Blood Institute's Guidelines for the Diagnosis and Management of Asthma⁸ point out that using history alone has been shown to both overdiagnose and underdiagnose EIB. Reasonable diagnostic testing options to confirm EIB include exercise challenge on a treadmill, free running exercise challenge, or provocation by an exercise surrogate, such as eucapnic voluntary hyperventilation (EVH). When performing formal

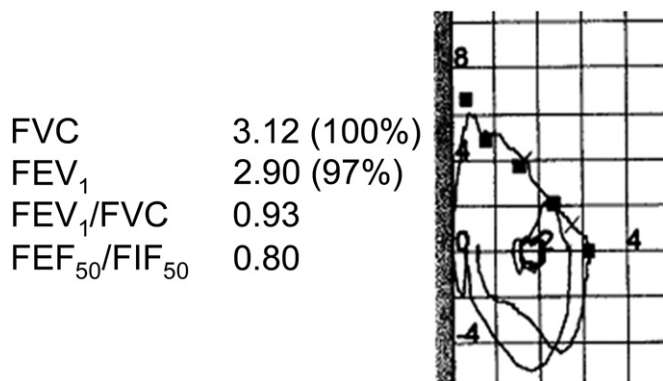


Figure 1. Spirometry data, including flow volume loops. Forced vital capacity (FVC), forced expiratory volume in 1 second (FEV_1), ratio of FEV_1 to FVC (FEV_1/FVC), and ratio of expiratory flow at 50% FVC to inspiratory flow at 50% FVC (FEF_{50}/FIF_{50}) were all within normal limits.

diagnostic EIB treadmill provocations, the American Thoracic Society recommends continuing the exercise for 6 to 8 minutes, including maintaining a heart rate of 80% to 90% of the patient's predicted maximum for 4 to 6 minutes.⁸ A postexercise decrease in the forced expiratory volume in 1 second (FEV₁) of 10% is abnormal, and a decrease in FEV₁ of 15% is diagnostic of EIB.⁸

EVH reproduces hyperventilation experienced during exercise and is a particularly sensitive method for demonstrating EIB.¹ EVH protocols involve breathing at 85% maximum voluntary ventilation rate for 6 minutes while controlling the concentration of inhaled carbon dioxide. Temperature is also varied in some protocols. Unfortunately, EVH testing requires special equipment and is physically demanding such that some adults and children are unable to complete the test.¹ Therefore, EVH testing is not widely available and is usually reserved for cases where objective documentation of EIB is a high priority, such as in an Olympic athlete who needs clearance to be able to use albuterol before exercising in a competition. Inhaled mannitol provocation is another exercise surrogate with a validated protocol.⁹ Unlike EVH testing, mannitol challenge testing is convenient and not physically demanding, although to date inhaled mannitol bronchoprovocation is not approved in the United States.

EIB treatment options include both situational prophylactic strategies and using an everyday controller medication to control underlying asthmatic inflammation. An effective pre-exercise regimen for many patients includes using 2 puffs of a short-acting inhaled β -agonist, such as albuterol, 15 minutes before exercise. This approach typically results in protection against EIB for 2 to 3 hours.⁷ The use of a long-acting inhaled β -agonist protects against EIB for up to 12 hours,¹⁰ although with continuous use the duration of protection afforded by a long-acting β -agonist decreases because of tolerance.¹¹ Other preexercise prophylactic options include inhaled sodium cromolyn¹² (15 minutes before exercise) and oral leukotriene modifiers¹³ (at least 2 hours before exercise). In patients with persistent asthma, reducing underlying asthmatic inflammation using an inhaled corticosteroid reduces bronchial hyperresponsiveness and the severity of EIB symptoms.¹⁴

INITIAL IMPRESSION OF ASTHMA SPECIALIST

In our case, the nature of the patient's symptoms (eg, dyspnea, chest tightness) and their relation to exercise (onset 10 minutes after the start of exercise) are consistent with EIB. Her normal spirometry in clinic is consistent with EIB because many patients with EIB (and other phenotypes of mild asthma) have normal baseline spirometry results while asymptomatic. Although as an adolescent her risk of asthma may not be unusually high, based on her history alone the probability of her having EIB was significantly greater than the 5% to 20% prevalence in the general population. With this information, it was appropriate to empirically treat for EIB, although because she had no prior history of asthma, it would also have been reasonable to proceed with a provoc-

ative challenge. The use of a short-acting inhaled β -agonist (albuterol) 15 minutes before exercise, plus the continuous use of both montelukast (an oral leukotriene antagonist) and the combination of a moderate-dose inhaled corticosteroid (fluticasone propionate, 250 μ g) and long-acting inhaled β -agonist (salmeterol, 50 μ g) constituted an aggressive EIB regimen. The failure of the patient's symptoms to respond to this treatment suggests that EIB was not the primary cause of her symptoms; therefore, other possibilities should be considered.

VOCAL CORD DYSFUNCTION

VCD is a disorder that involves respiratory symptoms due to paradoxical motion of the larynx while breathing.¹⁵ In its classic form, VCD involves the total adduction of the anterior two-thirds of the vocal cords during inspiration, resulting in a small posterior airway referred to as a "posterior chink."¹⁵ First described in adult patients in 1982¹⁶ and later in adolescents in 1995,¹⁷ VCD should be considered in any patient with difficult-to-treat asthma and in athletes in whom exercise-induced symptoms fail to respond to asthma treatment.⁸ Most VCD patients are female, but many male VCD patients have also been described. Exercise is an especially common trigger of VCD symptoms among adolescent patients.¹⁷ Unfortunately, much of the literature describing VCD consists of descriptive case series without controls, and therefore our understanding of VCD is not based on true evidenced-based investigation. Nevertheless, VCD is well known to asthma specialists as a common masquerader of asthma and is prominently featured in the National Heart, Lung, and Blood Institute's Guidelines for the Diagnosis and Management of Asthma.⁸

Although the pathophysiologic features of VCD are unknown, there appear to be several VCD phenotypes, including VCD as a primary psychiatric disorder,^{16,18–23} irritant-induced VCD,²⁴ exercise-induced VCD,^{17,25} VCD due to laryngopharyngeal acid reflux,^{24–26} VCD due to postnasal drip,²⁷ and VCD associated with chronic cough.^{28,29} Patients with VCD often exhibit features of more than 1 phenotype. Most reported cases of VCD in adolescents involve exercise as a trigger of symptoms,^{17,25} and laryngopharyngeal reflux has been suggested as a frequent associated condition in adolescents with VCD.^{20,25} In addition, some patients have both clinical asthma and VCD.¹⁷ The role of psychopathological conditions in adolescent VCD is not well studied, but in 1 case series¹⁷ most patients had either Axis I or Axis II diagnoses from the *Diagnostic and Statistical Manual of Mental Disorders*, including most prominently anxiety and depressive disorders, and all of the patients were straight A students.

The primary treatment for VCD is speech therapy focusing on relaxed breathing techniques.^{15,16} In some cases biofeedback may also be helpful. In a retrospective, uncontrolled survey performed 6 months after completing speech therapy for exercise-induced VCD, 19 of 20 female athletes diagnosed as having exercise-induced VCD re-

ported control of their symptoms.³⁰ If a potential exacerbating condition, such as acid reflux and/or psychiatric impairment, is present, concurrent treatment of these is appropriate, although there are no controlled studies demonstrating an improvement in VCD symptoms after treating reflux, anxiety, or depression.

EXERCISE-INDUCED PARADOXICAL ARYTENOID MOTION

Exercise-induced paradoxical arytenoid motion (EPAM) has been most often reported in the otolaryngology literature, whereas VCD has been most often reported in the asthma literature. Also referred to as exercise-induced laryngomalacia or exercise-induced laryngeal prolapse, the typical EPAM patient is adolescent and female.^{31–34} Symptoms with EPAM include dyspnea, throat tightness, stridor, and/or chest tightness. EPAM in adolescents has also been reported in association with acid reflux.³³ The primary treatment of EPAM, as with VCD, is speech therapy.³¹ In 1 case series,³³ refractory patients underwent supraglottoplasty (removal of part of the arytenoid tissue), resulting in clinical cure.

When 10 healthy asymptomatic adolescent and young adult volunteers underwent exercise challenge with simultaneous videotaped laryngoscopy, 1 was found to have paradoxical arytenoid motion.³⁵ Another study compared 4 female athletes reporting a history of exercise-induced stridor with 12 healthy controls using videotaped laryngoscopy during treadmill exercise challenge.³⁶ During moderate exercise, all 4 of the cases exhibited paradoxical arytenoid motion without abnormal vocal cord motion. None of the controls had paradoxical laryngeal motion during moderate exercise. However, during peak exercise, all 4 of the cases had paradoxical motion of both the arytenoids and vocal cords. Of the 6 controls who underwent maximal exercise challenge, 2 had paradoxical arytenoid motion without paradoxical vocal cord motion. Although no broad conclusions can be drawn from these data, there appears to be considerable overlap between exercise-induced VCD and EPAM in adolescents, and documenting the presence of paradoxical motion of the vocal cords may be a more specific and less sensitive symptom correlate than documenting paradoxical arytenoid motion. Therefore, reproducing respiratory symptoms that correspond with modest paradoxical arytenoid motion provides objective support for the diagnosis of EPAM but does not exclude VCD or other diagnoses. Comparative studies are needed to explore whether exercise-induced VCD and EPAM are in fact distinct syndromes with separate risk factors, comorbidities, treatments, and prognoses.

ALLERGY-ASTHMA SPECIALIST WORKUP AND RESULTS

Baseline laryngoscopy results were normal. Free-running exercise challenge reproduced symptoms of inspiratory upper chest tightness (Figure 2). Subsequent laryngoscopy during symptoms revealed consistent inspiratory paradoxical arytenoid motion with normal arytenoid positioning during exha-

Time	Exercise	Pulse	Symptoms
0		75	None
1.5 min	Jogging (warmup)	170	None
3.5 min	Six 30-meter sprints at three-fourths effort	180	None
7 min	3 sets sprinting lines (30 seconds each)	200	"6/10" inspiratory upper chest tightness

Figure 2. Free-running exercise challenge protocol and data for the case patient. Exercise was performed outdoors on a sidewalk. Pulse was taken before the challenge and recorded after each stage of the challenge was completed. The patient was asked to describe her symptoms and estimate her discomfort on a scale of 10.

lation (Figure 3). There was no paradoxical vocal cord motion (Figures 3 and 4). Postexercise spirometry results were normal without either bronchospasm or signs of extrathoracic airflow obstruction (Figure 5). Symptoms resolved with rest in less than 5 minutes.

ASTHMA SPECIALIST'S IMPRESSIONS AFTER INITIAL WORKUP

In this patient's case the exercise challenge successfully reproduced her symptoms. Although she had previously not recalled whether her symptoms were more prominent during inhalation or exhalation, in the midst of experiencing symptoms during the challenge she was able to specifically describe the discomfort as occurring during inhalation. The paradoxical arytenoid motion occurred during inhalation only and correlated with the patient's reported upper chest tightness and dyspnea. This suggests that EPAM explains the patient's symptoms. The absence of bronchospasm during a challenge with a heart rate of at least 85% of her predicted maximum for more than 5 minutes suggests that she does not have EIB.

ADDITIONAL HISTORY

On 2 occasions, within minutes after cessation of exercise, her exercise-induced chest tightness and dyspnea symptoms were accompanied by acute anxiety with paresthesias of her extremities followed by cramping of her hands that involved apparent tetany. Paramedics were called, but symptoms resolved without treatment on both occasions.

EXERCISE-INDUCED HYPERVENTILATION

Hyperventilation syndrome occurs when minute ventilation exceeds metabolic demands, resulting in respiratory alkalosis.

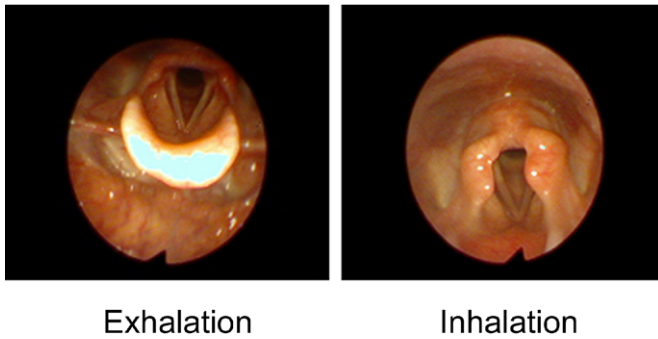


Figure 3. Laryngoscopy photographs of the patient taken during symptoms immediately after exercise challenge, showing the change in positioning of the arytenoids during inhalation and exhalation. This paradoxical arytenoid motion occurred with every breath during symptoms.

This may result in symptoms of dyspnea, chest tightness, light-headedness, and paresthesias. In extreme cases, the respiratory alkalosis involves a reduction of free serum calcium, resulting in carpopedal spasm.³⁷ Hyperventilation often occurs in the context of acute anxiety, and anxiety is presumed to be involved in exercise-induced hyperventilation masquerading as asthma.^{38,39} There is no criterion standard for establishing the diagnosis of hyperventilation,³⁸ although documenting an abnormal decrease in either arterial or end tidal P_{CO_2} supports the diagnosis. In 1 study,³⁹ 11 of 32 patients between the ages of 8 and 18 years referred for atypical or refractory exercise-induced asthma were found to have significantly elevated end tidal P_{CO_2} after exercise challenge. Appropriate treatment for exercise-induced hyperventilation may include psychotherapy, relaxed breathing techniques, and/or anxiolytic pharmacotherapy.³⁷

EXERCISE-INDUCED SYMPTOMS AND CARDIAC DISEASE IN ADOLESCENTS

Although cardiac abnormalities presenting in adolescence during exercise are rare, fatal cardiac events during exercise occasionally occur in young athletes. Hypertrophic cardiomyopathy (HCM) is the principal cause of sudden cardiac death in young athletes.⁴⁰ Other cardiac diseases to consider in adolescents with exercise-induced symptoms include arrhythmias (such as long QT syndrome and supraventricular tachycardia), premature atherosclerosis, valvular heart disease, and other congenital heart problems, such as anomalous coronary artery anatomy.

A normal baseline electrocardiogram (ECG) result effectively excludes HCM.⁴¹ This has led to considerable debate regarding whether all athletes should have a baseline ECG, and to date there is no such program in the United States. In Italy, exercise-associated sudden deaths due to HCM decreased after initiating a systematic national preparticipation screening program that includes obtaining a baseline 12-lead ECG in all competitive athletes. However, a recent comparison of comparable registries in the United States and Italy

failed to identify a difference in the rate of exercise-associated sudden death in young athletes.⁴²

What should an asthma specialist do to reduce the chance of missing an important but rare cardiac problem in an adolescent reporting respiratory symptoms during exercise? As with many other unexpected rare diagnoses, the most practical way to screen is with a thorough history. For example, symptoms such as syncope, palpitations, and/or irregular heart beat are less likely to occur with the more common causes of exercise-induced respiratory symptoms and raise suspicion of a cardiac cause. A personal history of hypertension or congenital heart disease would also increase the risk of an ongoing cardiac problem. Finally, it is also important to query about a family history of known congenital heart disease, sudden death before the age of 50 years, long QT syndrome, Marfan syndrome, or HCM.⁴³ Physical examination is another important way for the physician to obtain information regarding possible cardiac disease. Relevant findings include tachycardia, irregular heart rhythm, cyanosis, peripheral edema, jugulovenous distension, sustained precordial pulse, and heart murmurs.

Obtaining a baseline ECG is reasonable to consider in an adolescent athlete with exercise-induced chest discomfort, especially after unsuccessful empirical treatment for more common diagnoses, such as EIB and VCD or EPAM. Alternatively, or if concerns persist, then consultation with a cardiologist for echocardiography and/or cardiac exercise challenge testing would be appropriate.

ASTHMA SPECIALIST IMPRESSIONS AFTER ADDITIONAL HISTORY

Because her symptom history included acute anxiety, paresthesias, and apparent carpopedal spasm, the patient appears to have had acute hyperventilation after exercise on at least 2 occasions. It is also possible that her primary symptoms of exercise-induced dyspnea and chest tightness were due to exercise-induced hyperventilation, although paradoxical laryngeal motion is not an expected finding with hyperventilation. Monitoring either arterial or end tidal P_{CO_2} during exercise might help answer this question.

1. Vocal cords
2. False vocal cords
3. Arytenoids
4. Interarytenoid space
5. Epiglottis

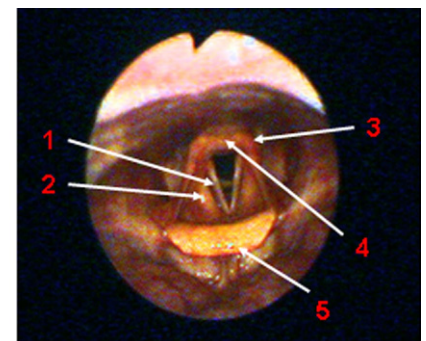


Figure 4. Photograph during flexible fiberoptic laryngoscopy revealing normal laryngeal anatomy in an asymptomatic patient.

	Baseline	Immediately after exercise	10 minutes after exercise
FVC	3.12 (100%)	3.03 (97%)	2.86 (91%)
FEV ₁	2.90 (97%)	2.91 (98%)	2.73 (92%)
FEV ₁ /FVC	0.93	0.96	0.96
FEF ₅₀ /FIF ₅₀	0.80	1.48	1.00



Figure 5. Spirometry and flow volume loops at baseline, immediately after exercise challenge, and 10 minutes after completion of the exercise challenge. No significant changes were found in forced expiratory volume in 1 second (FEV₁), forced vital capacity (FVC), or FEV₁/FVC ratio. The ratio of expiratory flow at 50% FVC to inspiratory flow at 50% FVC (FEF₅₀/FIF₅₀) increased to more than 1.0 immediately after exercise. This finding is consistent with extrathoracic airflow obstruction, although there was no obvious truncation of the inspiratory portion of the flow volume loop compared with his baseline loop. This underscores the difficulty relying on flow volume loops alone to confirm paradoxical laryngeal motion.

The patient's symptoms involved chest tightness as opposed to throat tightness. This, combined with the lack of response to EIB treatment, preserves the unlikely possibility that underlying cardiac disease may be contributing to her symptoms. However, with confirmed paradoxical laryngeal motion during exercise-induced symptoms without any risk factors for cardiac disease, it is not clear that additional cardiac workup is necessary before initiating treatment for EPAM and hyperventilation.

TREATMENT PLAN AND OUTCOME

After discussing the diagnostic test results and additional testing and treatment options with the patient and her parents, we agreed to have her seen by a speech pathologist with expertise teaching relaxed breathing using behavioral modification techniques. This is the primary treatment for VCD and EPAM and is also a reasonable treatment for hyperventilation. We also agreed that if her symptoms did not improve with this treatment within 1 month we would consider additional diagnostic testing and/or treatment possibilities, including cardiology consultation. After completing 5 sessions of speech therapy treatment for 6 weeks, she was able to exercise without symptoms.

CONCLUSIONS

Respiratory symptoms during exercise occur commonly in adolescents. As with patients of other ages, EIB is frequently the cause of these symptoms. The EIB response is well characterized, accurate diagnostic testing is available, and there are a variety of effective ways to treat EIB. When the history does not suggest EIB or when symptoms do not respond to EIB treatment, it is important to consider diag-

noses involving paradoxical laryngeal motion, such as exercise-induced VCD and/or EPAM. These diagnoses may be closely related to each other, appear to be more common in adolescents, and are often associated with concomitant acid reflux. Psychopathological conditions may also contribute to symptoms, although this has not been evaluated systematically. Exercise-induced hyperventilation should also be considered in adolescents with exercise-induced dyspnea, especially if the symptoms include light-headedness or paresthesias. Finally, given the potential ominous consequences of exercise-induced symptoms due to undiagnosed cardiac disease, it is important to obtain a thorough screening history to identify increased risk of cardiac disease. Further cardiac workup should be considered if there is a high index of suspicion or if symptoms persist despite initial treatment of a more common diagnosis.

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Requests for reprints should be addressed to:

Stephen A. Tilles, MD
 ASTHMA Inc
 4540 Sand Point Way NE
 Suite 100
 Seattle, WA 98105
 E-mail: stilles@nwasthma.com