SPECIAL ISSUE ARTICLE

Exercise-Induced Dyspnea in Children and Adolescents: Differential Diagnosis

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ABSTRACT

Exercise-induced dyspnea in children and adolescents can occur for many reasons. Although asthma is the common cause, failure to prevent exercise-induced asthma by pretreatment with a bronchodilator, such as albuterol, indicates that other etiologies should be considered. Other causes of exercise-induced dyspnea include exercise-induced vocal cord dysfunction, exercise-induced laryngomalacia, exercise-induced hyperventilation, chest wall restrictive abnormalities, cardiac causes, and normal physiologic limitation. When exercise-induced dyspnea is not from asthma, cardiopulmonary exercise testing with reproduction of the patient's dyspnea is the means to identify the other causes. Cardiopulmonary exercise testing monitors oxygen use, carbon-dioxide production, end-tidal pCO_2 (partial pressure of carbon dioxide), and electrocardiogram. Additional components to testing are measurement of blood pH and pCO_2 when symptoms are reproduced, and selective flexible laryngoscopy when upper airway obstruction is observed to specifically identify vocal cord dysfunction or laryngomalacia. This approach is a highly effective means to identify exercise-induced dyspnea that is not caused by asthma. **[*Pediatr Ann*. 2019;48(3):e121-e127.]**

Dyspnea is defined as the perception of shortness of breath, difficult or labored breathing. Exercise-induced dyspnea (EID) is dyspnea that occurs or worsens with physical activity. As more children and adolescents are choosing to exercise regularly, often for an athletic activity, EID is becoming an increasingly common reason to see a physician. The frequency of EID was examined by Johansson et al.[1] in a large survey of Swedish children age 12 and 13 years. They reported that 14% of the children had experienced shortness of breath with exercise in the previous 12 months. Although a history of asthma was reported in 14.6% of those children, only 5.4% of those with asthma had a history of EID. No history of asthma was reported in 61% of those with EID.[1] Exercise-induced bronchospasm can be demonstrated in most children with active asthma.[2] However, EID may result from reasons other than asthma and can be mistaken for asthma.[3] This review describes the causes of EID and provides guidance for the clinician to identify and treat the problem in the individual patient.

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CAUSES OF EXERCISE-INDUCED DYSPNEA

Exercise-Induced Bronchospasm and Exercise-Induced Asthma

Exercise-induced bronchospasm (EIB) involves the transient narrowing of the airways during or after exercise. It is a pathophysiological response that can be measured using lung function testing. Exercise-induced asthma (EIA), on the other hand, is a clinical diagnosis based on demonstration of EIB in association with EID. Generally, the patient will have experienced other symptoms of asthma. The mechanism of EIB involves airway dehydration from increased ventilation resulting in mediator release.[4]

The presence of EIB can be suppressed with warm, humidified air. Consequently, EIB is likely to be less when swimming in warm water. Preceding exercise with an inhaled bronchodilator such as albuterol (salbutamol) can prevent EIB and EIA. EIB can sometimes be seen in the absence of

associated dyspnea or in the absence of other symptoms consistent with asthma.[5] If dyspnea does not occur in association with EIB, then another cause for EID may be present.

Estimates of the global prevalence of EIB in children and adolescents have been attempted,[6] but are confounded by different methodologies, such as free running versus treadmill testing, differences in the environmental temperature and humidity, and differences in the definition of EIB based on the percent decrease in FEV_1 (forced expiratory volume-one second; decreases of 10%-15% have been used in various studies). EIB in the absence of asthma has been described in elite athletes and in healthy college athletes.[7] There is evidence that the prevalence of EIB in athletes is overestimated. Price et al.[8] examined asymptomatic athletes using eucapnic voluntary hyperpnoea, which is a provocative indirect stimulus test used to diagnose EIB. Mild bronchospasm that met diagnostic criteria for EIB was common in that population of asymptomatic athletes, especially when a 10% decrease in FEV_1 was used to define EIB. The use of 10% increases sensitivity but decreases specificity by including the upper range of normal responses. They concluded that there is a spectrum of mild airway reactivity to exercise in that population, which should not be regarded as pathologic unless the fall in FEV_1 was substantially greater and associated with symptoms.[8]

A typical pattern of EIA includes initial transient bronchodilation followed by bronchoconstriction that peaks within about 5 minutes after cessation of exercise and lasts about 30 minutes in the absence of treatment (**Figure 1**). Symptoms include shortness of breath, cough, and chest tightness in association with the decrease in pulmonary function. Some people with asthma develop severe acute bronchospasm and hypoxemia during exercise (**Figure 2**).

The mechanism of EIB in athletes appears to be different when it is not associated with other clinical manifestations of asthma.[4] Rather than being associated with the intrinsic airway reactivity of asthma, EIB in athletes is suggested to be from the irritant effect of repeated episodes of certain high-level sports, especially when performed in noxious environments.[9] Examples include swimmers exposed to chlorine derivatives used to disinfect swimming pools and hockey players exposed to emissions from ice-resurfacing machines.

Treatment of symptomatic EIB is relatively simple, as a beta-2-agonist such as albuterol, given prior to exercise reliably prevents EIB. In the occasional patient in whom a long-acting beta-2-agonist is associated with down-regulation of the beta-2 receptor, albuterol may not prevent EIB.[10] Treatment with asthma maintenance therapy, such as inhaled corticosteroids and montelukast, can also effectively decrease EIB. However, treatment of EIB with these medications would be more appropriate in patients with other manifestations of persistent asthma.

Exercise-Induced Vocal Cord Dysfunction

Vocal cord dysfunction (VCD) refers to abnormal functioning of the vocal cords. There are different phenotypes of this disorder.[11] It can occur spontaneously and unpredictably, but it is the exercise-induced VCD (EIVCD) phenotype that is addressed in this review. There are two physiologic patterns of VCD. The most common that is seen with EIVCD is paradoxical vocal cord movement. The normal movement of vocal cords is abduction with inspiration so that the vocal cords move out of the way allowing air to pass unobstructed, and then relax on expiration. Paradoxical movement occurs when the vocal cords adduct on inspiration. This vocal cord adduction creates obstruction to air flow that is shown on a spirometric tracing as a flattening of the inspiratory portion of the flow-volume loop (**Figure 3A**). Stridor on inspiration and the feeling that the patient cannot get enough air are the most common presenting symptoms. If the patient also has asthma, the dyspnea and inspiratory stridor associated with VCD may be confused with the dyspnea and expiratory wheezing of the patient's underlying asthma.[12] Less common but more serious upper airway obstruction occurs when the vocal cords stay in adduction during both inspiration and expiration. This results in blunting of both the inspiratory and expiratory portions of the flow-volume loop (**Figure 3B**). (See Weinberger and Doshi[13] for supplemental videos demonstrating both physiologic types of VCD.)

Prevention of EIVCD has been successful by pretreating with an anticholinergic aerosol, ipratropium bromide, which is available as a metered-dose inhaler. The vocal cords' adductors and abductors derive motor innervation from superior laryngeal and recurrent laryngeal nerves, both of which are branches of the vagus nerve. Vagal nerve stimulators, used for patients with intractable seizures, have been shown to cause VCD as a complication.[14] Those reports provide a rationale for the use of an anticholinergic inhibitor aerosol as VCD prevention. Although data from a controlled clinical trial are not available, six patients in one report described complete blocking of their EIVCD by pretreatment with ipratropium bromide.[11] One other single case report has also described efficacy of ip-

ratropium for EIVCD.[15] Speech therapy has been described in detail as a means for preventing EIVCD, but neither controlled clinical trials nor specific case outcomes are available.[16]

Exercise-Induced Laryngomalacia

Laryngomalacia is the term used to describe collapse of supraglottic structures, mainly the arytenoids and/or the epiglottis, during inspiration causing upper airway obstruction. Laryngomalacia is a common disorder affecting infants and the most common cause of the inspiratory sound known as stridor. Some infants with congenital laryngomalacia have been seen to later have exercise-induced laryngomalacia (EIL) as adolescents when they begin vigorous athletic activity.[17] EIL causes symptoms and physiologic abnormalities like EIVCD but is much less common. Both cause upper airway obstruction with inspiratory stridor. EIL and EIVCD cause similar spirometric abnormalities when symptomatic (**Figure 3A**). Flexible laryngoscopy is the only reliable means of distinguishing whether vocal cord closure or invaginating laryngeal structures are obstructing the inspiratory airflow. Some have chosen to lump EIL and EIVCD with the term exercise-induced laryngeal obstruction.[18] Because the physiology, anatomy, and treatment of EIL and EIVCD are different, the specific disorder, EIL or EIVCD, should be identified.

Treatment of EIL is supraglottoplasty. The abnormality and the successful outcome of the corrective procedure are described and illustrated in several publications.[19]

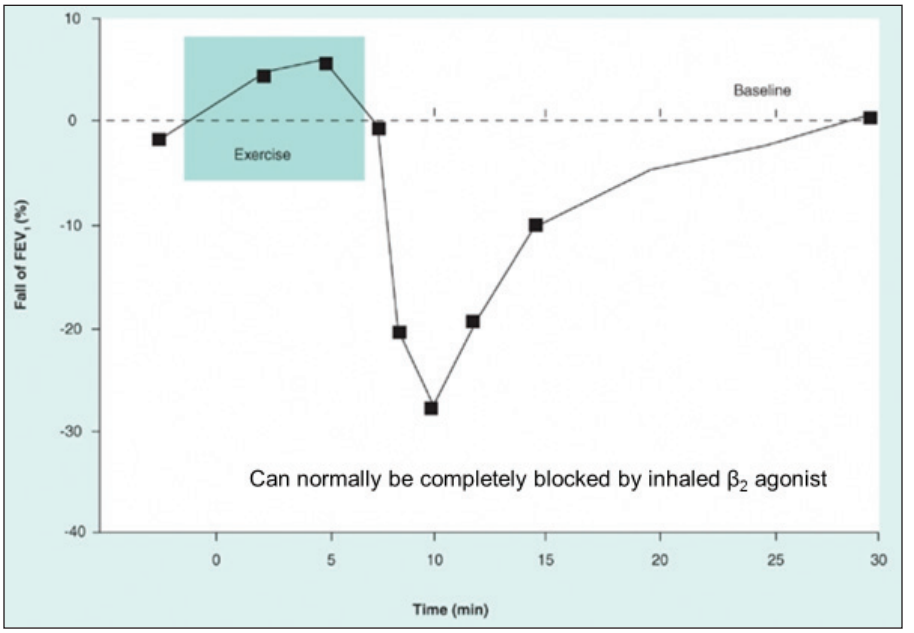

Figure 1. Typical time course of pulmonary function from exercise-induced asthma. The one-second forced expiratory volume (FEV_1) is used as the measure in this example.

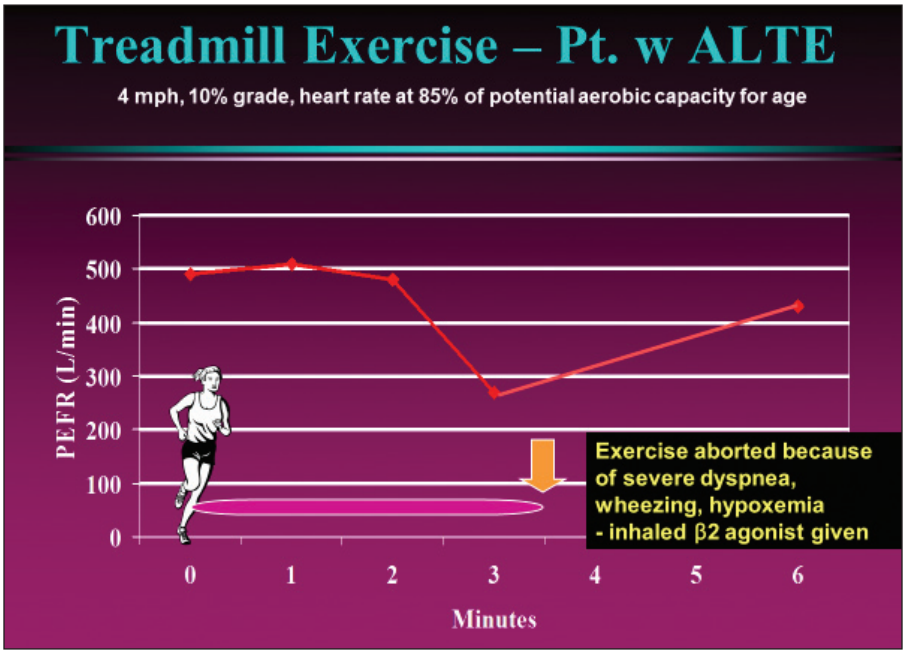

Figure 2. A 15-year-old girl with a history of repeated exertion-induced, severe acute life-threatening episodes from asthma was given a treadmill exercise test. The test was performed at 4 mph with a 10% grade, and heart rate reaching a value consistent with 85% of maximal aerobic capacity for age. The peak expiratory flow rate (PEFR) was used to monitor her pulmonary function.

Restrictive Physiological Abnormalities

Vigorous exercise depends on the increase in ventilation, which is achieved by increasing tidal volume and respiratory rate. Therefore, any disease process that limits chest expansion can limit exercise capacity. Pectus abnormalities and scoliosis, even if not affecting normal activities, may influence maximal exercise by causing restrictive physiology.[20] Abu-Hasan et al.[3] defined respiratory limitation from restrictive

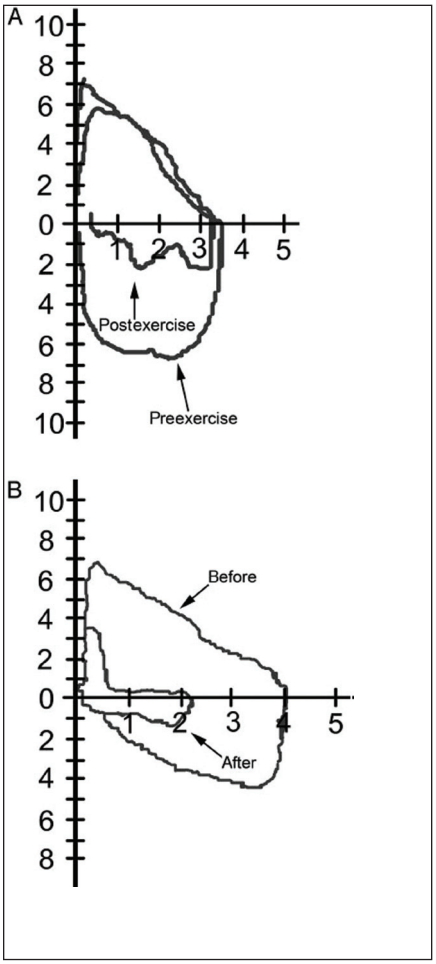

Figure 3. (A) Flow-volume loop in a 15-year-old. girl with exercise-induced vocal cord dysfunction. The paradoxical adduction during inspiration after exercise results in the low post-exercise inspiratory flow shown. (B) Flow-volume loops from another 15-year-old girl with a history of repeated episodes of sudden-onset severe dyspnea. In this case, where adduction persists during both inspiration and expiration, the inspiratory and expiratory flows are both compromised.

physiology as the etiology for EID if symptoms were reproduced during cardiopulmonary stress testing in association with a low maximal tidal volume during exercise and increased respiratory rate. The patient essentially compensates for the lower maximal tidal volume during exercise by increasing respiratory rate, a less efficient means of maximizing ventilation. The result is a limitation of maximal voluntary ventilation during exercise.

In our evaluation of 120 sequential children and adolescents seen for EID and evaluated with cardiopulmonary exercise testing, our criteria for restrictive physiology were met in 15 patients (11% of the 120).[3] These patients often had minor degrees of thoracic cage abnormalities (scoliosis and pectus deformities) that were not associated with a decrease in forced vital capacity or total lung capacity at rest. In severe cases of pectus excavatum, exercise limitation can be due to low cardiac stroke volume and decreased cardiac output rather than decreased minute ventilation. Pulmonary function, chest dynamics, and exercise have been examined after the Nuss method of surgical repair for severe pectus excavatum. Although that procedure results in little change in either spirometric measures or dynamic chest wall motion, significant increase in exercise tolerance has been described. There is evidence that the improvement in exercise after pectus repair is related to improved cardiac function.[21]

Another group of patients with EID due to restrictive physiology are those with obesity. EID in obese children and adolescents may result from increased restrictive loading of the chest wall and abdomen, resulting in exercise limitation associated with decreased lung volumes and decreased peak work rate during exercise. EID from obesity is sometimes misdiagnosed as being from asthma.[22]

Exercise-Induced Hyperventilation

Exercise-induced hyperventilation (EIH) was first reported in some patients who were initially diagnosed with EIA but experienced chest discomfort associated with hyperventilation in the absence of bronchospasm or hypoxemia on exercise testing (**Figure 4**).[23] Hyperventilation is identified by increased ventilation accompanied by a decrease in pCO_2 (partial pressure of carbon dioxide) in the absence of bronchospasm (no significant decrease in any measure of expiratory flow rate) and not explainable as compensation for metabolic acidosis that results from lactic acid generated with sustained vigorous exercise. A decrease in end-tidal CO_2 early in the exercise that is associated with chest discomfort without wheezing is typical of EIH. Dizziness, a feeling of being light-headed, and/or tingling in fingers or toes may be present. Anxiety may be related to EIH. Interestingly, similar chest discomfort with decreased pCO_2 has been reproduced in adults who have been exercise tested because of concern for angina but had no accompanying abnormality on electrocardiogram (ECG) testing.[24] Moreover, their symptoms could be reproduced with voluntary hyperventilation sufficient to lower their pCO_2.[25] Thus, chest discomfort during exercise in a child causes concern that asthma is the cause, whereas the same symptoms in an adult causes concern that there is cardiac disease. In both cases, inappropriate hyperventilation can be the cause.

EIH is a result of increased minute ventilation early in exercise. Excess CO_2 production and decreasing end-tidal CO_2 will be seen during cardiopulmonary exercise testing. Diagnosis of EIH is made by monitoring end-tidal CO_2 and obtaining a blood gas to measure pH and pCO_2 when symptoms are reproduced. An elevated pH and low pCO_2 at the time of dyspnea confirm the diagnosis.

Treatment of EIH consists of explanation, reassurance, and counseling.

Cardiac Causes of EID

Although most instances of cardiac disease will have been previously identified prior to seeing a physician for EID, exercise-induced supraventricular tachycardia may be quiescent until a vigorous exercise stress. We saw this

during cardiopulmonary exercise testing in an adolescent athlete whose sole complaint was EID that prevented him from completing a quarter during basketball games.[3] He experienced no palpitations or other symptoms associated with the dyspnea. When his EID was reproduced on a treadmill, it was associated with a sudden increase of heart rate to greater than 200 beats per minute. Return to normal values occurred suddenly after 20 minutes of rest. The associated ECG reading was ventricular tachycardia. Radio frequency catheter ablation subsequently eliminated the disorder.

Pathological conditions that decrease cardiac output will result in exercise limitation.[26] In children, most exercise limitation from cardiac causes is due to congenital heart disease where structural heart defects result in decreased cardiac output and/or hypoxemia. Cyanotic congenital heart disease cause more significant exercise limitations than noncyanotic heart disease.[27] This is likely due to the associated gas exchange abnormality from shunting and compromised cardiac output.[28] In addition to congenital heart diseases, cardiomyopathies in children are also associated with severe exercise limitation due to depressed cardiac function.[29] Exercise limitation due to vascular abnormalities, especially atherosclerosis, are common in adults but rarely present in children.

Cardiac causes of exercise limitation in otherwise healthy-appearing people are suspected when symptoms of chest pain, chest tightness, presyncope, syncope, and heart palpitation are present in association with EID. Cardiac abnormalities are usually detected and characterized by ECG, cardiac echocardiography, and cardiac catheterization. The value of cardiopulmonary stress test in these patients is mainly to quantify the extent to which cardiac or respiratory disease is limiting exercise.[30]

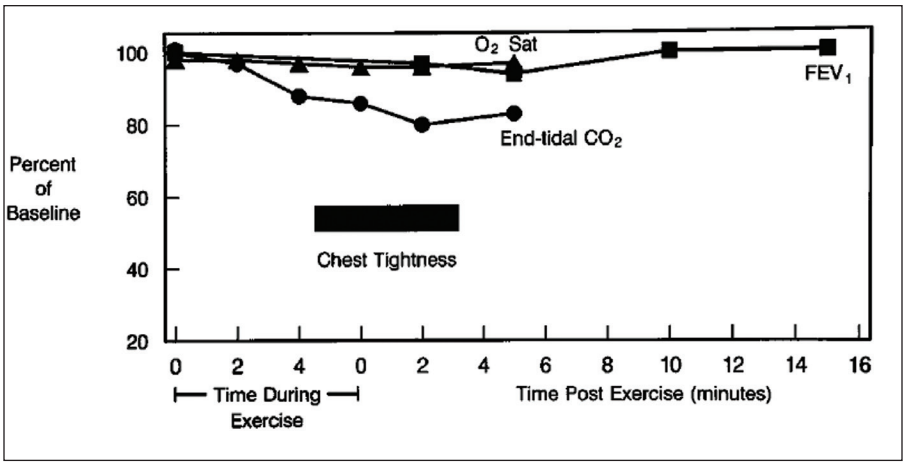

Figure 4. Illustration of exercise-induced hyperventilation in a teenage girl athlete. This figure describes measurements of pulse oximetry, expiratory flow rate (one-second forced expiratory volume [FEV_1]), and her end-tidal carbon dioxide (CO_2, which correlates with arterial partial pressure of carbon dioxide). Chest tightness begins early, about 4 minutes into the exercise, in association with the decreasing end-tidal CO_2. O_2 Sat, oxygen saturation.

Normal Physiologic Limitation Causing EID

In people without EID, peak exercise is determined mainly by reaching maximum cardiac output. Increasing exercise intensity is dependent on the increase of oxygen supply to the exercising muscles up to the point when cardiac output is not sufficient for their increasing demand. At that point, which is called anaerobic threshold, any further exercise activity is achieved by switching from oxygen-dependent metabolism (aerobic metabolism) to oxygen-independent metabolism (anaerobic metabolism). Continued exercise beyond anaerobic threshold causes accumulation of lactic acid.

Although the various causes of EID discussed above need to be considered, the most common cause of EID in children and adolescents referred to a specialist for evaluation is normal physiologic limitation.[3] This commonly occurs in a highly motivated adolescent or preadolescent who exceeds the anaerobic threshold sufficiently during exercise that lactic acid production results in metabolic acidosis, after which compensatory respiratory alkalosis by increasing respiration occurs. Respiratory drive eventually reaches maximum output, and yet the acidosis is creating increased respiratory drive. The patient then perceives that they are not getting enough air, which is technically correct; they cannot physically get more air, as their ability to respond to the further respiratory drive is limited by their maximal ventilatory capacity. This is identified in these children during cardiopulmonary exercise testing. When symptoms are reproduced, no airway obstruction is observed, and the blood pH is acidotic. Essentially, the patient then has reached the maximum capacity of the cardiovascular system to deliver oxygen, and yet the low pH from the lactic acidosis is creating further respiratory drive beyond the ability to deliver. This could occur in a patient with normal, subnormal, or above-normal cardiovascular conditioning.[3]

The treatment for EID caused by normal physiologic limitation in the

TABLE 1.

History Taking for Exercise-Induced dyspnea

- Duration
  - How long
- Sports or activities
  - Competitive or recreational
- Symptoms
  - Shortness of breath, chest tightness, cough, wheezing, or stridor
  - Inspiratory, expiratory, or both?
  - Dizziness/syncope
  - Tingling in arms/legs
- Timing
  - Gradual vs dramatic onset
  - During or after exercise and duration
- Modifying factors
  - Seasonal
  - Outdoor vs. indoor
- Family history
  - Asthma
  - Allergies
  - Serious heart disease
- Psychosocial history
  - Academic performance and anxiety
  - Response to bronchodilators (if already tried)

absence of any anatomic or physiologic etiology is reassurance and counseling. Providing an age-appropriate explanation of exercise physiology is likely to enable the patient to understand the cause of their EID and permits counseling and education in conditioning and pacing during vigorous athletic activities.

EVALUATION OF THE PATIENT WITH EID

The evaluation for patients with EID begins with a detailed history (**Table 1**), physical examination, and spirometry. Patients with an abnormal examination and/or spirometry should be further evaluated for the relevant finding. In patients with evidence of underlying asthma and/or symptoms suggestive of EIB, a trial of short-acting bronchodilator inhaler (SABA) such as albuterol taken before exercise is reasonable before pursuing any further testing. Prevention of EID by pretreatment with albuterol provides evidence of EIB and a presumption of EIA if other symptoms suggestive of asthma are present. If there is minimal or no improvement from a trial of a SABA or symptoms had been atypical, alternative diagnoses should be considered and cardiopulmonary exercise testing (CPET) is needed to identify other causes of EID.[5]

CPET is the most effective means for arriving at a diagnosis once EIA cannot be demonstrated by blocking the EID with a SABA. For most cases, a treadmill is used because it usually more closely approximates the activity causing EID in the patient. CPET is a noninvasive test that provides a global assessment of the integrative exercise responses of pulmonary, cardiovascular, hematopoietic, neuropsychological, and skeletal muscle systems. Patients with atypical symptoms of EID and especially nonresponders to bronchodilators are candidates for CPET that results in reproduction of the patient's EID. In addition to spirometry before and after exercise to assess EIB, metabolic, respiratory, and cardiac parameters are continuously recorded during exercise in CPET. This permits a continuous visualization of air flow to identify upper or lower airway obstruction, oxygen utilization, carbon dioxide production, and heart rate. From these parameters, maximal oxygen utilization, which reflects the degree of cardiovascular conditioning, can be determined. Suppression of inspiratory flow identified during CPET warrants prompt examination of the upper airway with a flexible laryngoscope while the patient is still symptomatic to identify if the upper airway obstruction is from the more common EIVCD or the less common EIL. A blood gas (usually a finger stick for capillary blood is sufficient) while reproduced symptoms are present enables examination of pH and pCO_2. A high pH and low pCO_2 identifies EIH. The more commonly observed low pH identifies metabolic acidosis from muscle lactate production. The associated low pCO_2 demonstrates the extent to which respiratory effort was attempting to compensate for the metabolic acidosis by increasing ventilation.

The extent of the data generated requires that the physician be experienced in interpreting and explaining the results of the test. It is useful for the physician interpreting the results of the CPET to have observed the test in order to assess the patient's effort and response. Finally, the results need to be translated to a level appropriate for the patient and family.

SUMMARY

EID can occur for many reasons in children and adolescents. Although asthma is the most common cause, EIA is readily diagnosed by demonstrating elimination of EID and EIB when exercise is preceded by a beta-2 adrenergic agent such as albuterol, commonly referred to as a SABA. In the absence of prevention of EID with a SABA, other diagnoses including EIVCD, EIL, EIH, chest wall restrictive abnormalities, cardiac causes, and normal physiologic limitation need to be considered. When EIA is not confirmed by consistent prevention with a SABA, a CPET is essential to identify the other causes of EID.

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