Exercise-induced dyspnea in children and adolescents: if not asthma then what?

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Background: Exercise-induced dyspnea (EID) in children and adolescents is a common manifestation of asthma and is therefore commonly attributed to exercise-induced asthma (EIA) when present in otherwise healthy children.

Objective: To report the outcome of evaluations for EID when other symptoms and signs of asthma were absent or if there was no response to previous use of an inhaled β_2-agonist.

Methods: We reviewed the results of all exercise tests performed in otherwise healthy patients with EID during 1996 to 2003. Physiologic measures included preexercise and postexercise spirometry with the addition of oxygen uptake, carbon dioxide production, continuous oximetry, and electrocardiogram monitoring during most tests. EIA was diagnosed if symptoms were reproduced in association with a 15% or greater decrease in forced expiratory volume in 1 second from baseline. Endoscopy was performed if stridor and/or decreased maximal inspiratory flow were present. Criteria were established for restrictive abnormalities, physical conditioning, exercise-induced hyperventilation, and normal physiologic limitation.

Results: A total of 142 patients met our criteria for inclusion. EID had been present in these patients for a mean duration of 30.2 months (range, <1 to 192 months) before evaluation and had been previously attributed to asthma by the referring physician in 98 of them. Symptoms of EID were reproduced during exercise testing in 117 patients. EIA was identified as the cause of EID in only 11 of those 117. Seventy-four demonstrated only normal physiologic exercise limitation; 48 of these 74 had normal to high cardiovascular conditioning, and 26 had poor conditioning. Other diagnoses associated with reproduced EID included restrictive abnormalities in 15, vocal cord dysfunction in 13, laryngomalacia in 2 (1 of whom had unilateral vocal cord paralysis), primary hyperventilation in 1, and supraventricular tachycardia in 1.

Conclusion: The diagnosis of EIA should be questioned as the etiology of EID in children and adolescents who have no other clinical manifestations of asthma and who do not respond to pretreatment with a β_2-agonist. Exercise testing that reproduces symptoms while monitoring cardiac and respiratory physiology is then indicated to identify causes of EID other than EIA.

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INTRODUCTION

Exercise-induced asthma (EIA) has been the most commonly recognized cause of exercise-induced dyspnea (EID) in otherwise healthy children and adolescents.[1–4] Asthma produces dyspnea during exercise due to airway obstruction from bronchospasm. Typically, EIA is demonstrated by a significant decrease in baseline forced expiratory volume in 1 second (FEV_1) during or immediately after a standardized exercise test.[5,6] Bronchodilators and anti-inflammatory medications modify that response and, therefore, have been used clinically in prevention and treatment of EIA.[7]

However, EID in otherwise healthy children and adolescents may have causes other than asthma.[8] Several entities can produce EID through different pathophysiologic mechanisms. Vocal cord dysfunction and exercise-induced laryngomalacia can present with EID due to upper airway obstruction during exercise from paradoxical cord movement and collapse of the laryngeal structures, respectively.[9–12] Both conditions can mimic asthma and therefore require an appropriate diagnostic and therapeutic approach to avoid misdiagnosis and mismanagement. Exercise-induced hyperventilation has been described in patients with EID who demonstrated excessive reduction in end-tidal carbon dioxide on exercise testing without exercise-induced bronchospasm.[13] Additionally, some patients may experience dyspnea associated with normal physiologic limitation consistent with their level of conditioning and interpret that as abnormal dyspnea. In this retrospective examination of our experience, we report the previous diagnoses and treatment and eventual outcome of evaluations for patients referred to our pediatric pulmonary and allergy clinic for EID who had no clinically apparent cause or who had been treated for EIA without benefit.

METHODS

Patient Selection

Treadmill exercise test results were reviewed on all healthy individuals referred to our pediatric allergy and pulmonary clinic from 1996 to 2003 for EID without other symptoms and signs of asthma or with a previous diagnosis of EIA that failed to respond to an inhaled β_2-agonist. Patients with known chronic lung disease, cardiac diseases, or abnormal initial pulmonary function were excluded.

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Patient Evaluation

Following an initial detailed history, physical examination, and baseline pulmonary function, treadmill exercise was performed in all patients for at least 6 minutes after a warm-up period at a rate that maintained a heart rate consistent with 85% of aerobic capacity. Since these patients had continued to be symptomatic during exercise despite treatment, use of previous maintenance medications, if any, were not discontinued before the exercise test. Short-acting inhaled β_2-agonists such as albuterol were avoided during the previous 4 hours. Spirometry was performed on all patients before and at 2, 5, 15, and 20 minutes after exercise and again after administration of a bronchodilator aerosol. For most of the patients, physiologic monitoring during exercise included continuous electrocardiography, pulse oximetry, and breath-by-breath analysis of oxygen utilization and carbon dioxide production to evaluate for cardiovascular conditioning and gas-exchange abnormalities (Vmax Spectra; Sensormedics, Yorba Linda, CA). If the patient's typical symptoms of EID were not reproduced during the 6 minutes at the target heart rate in those patients who had the more extensive physiologic monitoring, the treadmill incline or speed was incrementally increased until the patient acknowledged that dyspnea consistent with that experienced previously had been reproduced. Flexible fiberoptic laryngoscopy was performed in patients who showed signs of upper airway obstruction (stridor and/or flattening of the inspiratory portion of the flow-volume loop) during exercise testing. Percent of predicted for previously published normal reference values was used for all parameters.[14–16]

Criteria for Diagnoses

We considered EIA the etiology for the EID if the treadmill exercise resulted in reproduction of symptoms in association with a decrease in FEV_1 of at least 15%.[5,6] We diagnosed upper airway obstruction if patients had reproduction of symptoms during exercise in association with stridor or a decrease in the ratio of the forced inspiratory flow to the forced expiratory flow at 50% of vital capacity (FIF_{50}/FEF_{50}) to 0.5 or less. Vocal cord dysfunction was identified as the cause of upper airway obstruction by visualizing paradoxical vocal cord movement with flexible fiberoptic laryngoscopy.[10] Exercise-induced laryngomalacia was diagnosed if laryngoscopy revealed dynamic collapse of the epiglottis and/or arytenoids.[11,12] Primary exercise-induced hyperventilation was based on a decrease of at least 20% from baseline of the end-tidal carbon dioxide at the time symptoms were reproduced with no other apparent cardiopulmonary abnormalities.[13]

We defined respiratory limitation from restrictive physiology as the etiology if symptoms were reproduced in association with a maximal tidal volume during exercise of less than 80% of predicted and/or the ratio of the maximum tidal volume to the vital capacity was less than 60%, with respiratory rate greater than 50/min and decreased respiratory reserve as determined by a maximal minute ventilation during exercise being greater than 80% of maximal voluntary ventilation at rest.[17]

If symptoms were reproduced with no cardiopulmonary abnormalities detected, we considered the etiology of the dyspnea to be physiologic exercise limitation due to reaching the maximum capacity of the cardiovascular system to deliver oxygen. We judged this to occur from below normal cardiovascular conditioning if maximum oxygen consumption ($\dot{V}O_2max$) was less than 80% of predicted at the time of symptom reproduction with the presence of at least 1 of the following indicators of poor conditioning: lower than normal anaerobic threshold, decreased oxygen pulse, an increase in the ratio of minute ventilation to oxygen consumption ($\dot{V}E/\dot{V}O_2$), and greater increase than normal in heart rate response to increasing workload. Normal level of conditioning was considered when $\dot{V}O_2max$ was between 80% and 120% of predicted with absence of all the listed indicators of poor conditioning. Above normal level of conditioning was considered when $\dot{V}O_2max$ was more than 120% with absence of all the listed indicators of poor conditioning. The etiology of EID could not be identified if symptoms were not reproduced during the treadmill exercise testing.

RESULTS

One hundred forty-two patients (mean age, 14 years; age range, 6–21 years; mostly preteens and teenagers) met our criteria for inclusion. The male-female ratio was 0.7:1. The duration of EID before our evaluation averaged 30.2 months (range, <1 to 192 months). Although all had EID, 41 (29%) reported dyspnea only with competitive athletic activity.

Ninety-eight (69%) of the patients had been previously diagnosed as having asthma by referring physicians. One hundred one (71%) had been treated before their referral with various asthma medications, including bronchodilators in 96, inhaled corticosteroids in 35, and systemic corticosteroids in 31. In 82 patients (58%), EID had resulted in at least 1 urgent medical care visit.

Symptoms were reproduced during exercise testing in the 117 patients (82% of the 142) who had complete physiologic monitoring and underwent increases in treadmill speed or incline if needed to reproduce symptoms. Only 11 patients (8%) had evidence of EIA as demonstrated by a significant decrease in FEV_1 in association with reproduction of their dyspnea. Eight of those 11 had been previously diagnosed as having asthma. EID did not occur in 25 patients (18%) who only had 6 minutes of treadmill exercise beyond the warm-up period without further attempts to reproduce their symptoms by further increasing rate and/or incline. None of those 25 patients had exercise-induced bronchospasm despite maintaining a heart rate consistent with 85% of aerobic capacity during the 6 minutes on the treadmill. Since symptoms were not reproduced and physiologic measures other than spirometry were not monitored in these 25 patients, the etiology of their EID was not identified.

Seventy-four patients (52%) had evidence only for normal physiologic limitations associated with reproduction of EID,

including 21 (15%) who met our defined criteria for above normal cardiovascular conditioning, 27 (19%) with cardiovascular conditioning within the defined normal range, and 26 (18%) with poor cardiovascular conditioning. Our criteria for restrictive physiology were met in 15 patients (11%) in association with reproduction of their EID; these patients had minor degrees of thoracic cage abnormalities (scoliosis and pectus deformities) that were not associated with baseline spirometry outside the normal range. Vocal cord dysfunction was identified in 13 patients (9%). Exercise-induced laryngomalacia was documented in 2 (1%), 1 of whom had a unilateral vocal cord paralysis that contributed to the laryngomalacia, which was symptomatic only during attempted athletic activities. Exercise-induced hyperventilation was observed in 1 patient. One patient, a highly competitive high school athlete with well above normal cardiovascular conditioning who had previously been treated for EIA, demonstrated supraventricular tachycardia in association with reproduction of his typical EID. His heart rate increased to more than 200/min and remained there for more than 20 minutes following completion of the exercise. It then suddenly reverted back to a normal sinus rhythm after approximately 20 minutes of rest. He never had dyspnea other than during vigorous exercise and was never aware of palpitations. His EID was subsequently resolved following ablation of an identified aberrant discharge focus.

DISCUSSION

Although asthma is the most common cause of EID in children and adolescents, this analysis of our experience indicates that other causes of EID should be considered when other symptoms and signs of asthma are absent or there is no benefit from pretreatment with an inhaled β_2-agonist. When EID is reproduced with treadmill exercise testing, other physiologic abnormalities associated with the dyspnea can be identified when cardiac and respiratory physiology are monitored.

Although many of the patients studied were taking medication that might suppress exercise-induced bronchospasm at the time of testing, the 117 who underwent the gas-exchange analysis with incremental increases on the treadmill beyond the initial 6 minutes had their typical symptoms reproduced. This confirmed the ineffectiveness of the medication in preventing the EID in these patients. Only 8% had exercise-induced bronchospasm associated with those symptoms. This low frequency of finding evidence for EIA in this population was consistent with our decision to only perform exercise testing when the history was otherwise atypical for or inconsistent with asthma, and there was consequently a diagnostic question.

The largest proportion of the study patients were not found to have any cardiopulmonary abnormalities, demonstrating only normal physiologic limitation associated with reproduction of symptoms. Some of these patients had below normal cardiovascular conditioning that appeared to be due to a sedentary lifestyle, whereas more were highly motivated athletes who had normal or above normal cardiovascular conditioning. Notably, we were able to reproduce EID even in those high school athletes with above normal cardiovascular conditioning by incrementally increasing the speed and/or incline of the treadmill sufficiently. Other patients exhibited various other causes for their dyspnea with exercise. These included vocal cord dysfunction, exercise-induced laryngomalacia, exercise-induced hyperventilation, restrictive physiology associated with minor skeletal abnormalities such as scoliosis and pectus deformities that apparently restricted chest wall mobility, and a cardiac arrhythmia that was only manifested during maximal exercise in a conditioned athlete.

Dyspnea is a complex psycho-physiologic sensation of an excessive increase in the perceived work of breathing that occurs in a variety of cardiopulmonary diseases. Increase in the work of breathing is produced by an increase in mechanical loading of the respiratory system, both resistive and elastic.[18,19] The sensation of dyspnea requires intact afferent and efferent pathways for the full perception of the neuromechanical dissociation between the respiratory effort attempted and the work actually accomplished.[20] The sensation is triggered or accentuated by a variety of receptors located in the chest wall, respiratory muscles, lung parenchyma, carotid body, and brainstem.[21] The sensation of dyspnea is stronger in patients with higher scores for anxiety and has been reported in patients with anxiety disorders with no cardiopulmonary disease.[22–26] These observations demonstrate the importance of cerebral cognition in this complex symptom.

Dyspnea during exercise in patients who otherwise have no obvious lung or heart disease is a symptom that warrants investigation to determine the etiology.[27] Exercise-induced bronchospasm as a manifestation of asthma is the most widely studied cause of EID. Its prevalence is very high, but because of poor correlation between the degree of airway obstruction and the sensation of dyspnea, exercise-induced bronchospasm is subject to being both unrecognized or overreported.[28–30] In the current report, where most patients were suspected by their primary care physicians to have EIA and were treated unsuccessfully for such, the absence of other symptoms consistent with asthma and a history that exercise-induced symptoms were not prevented with a bronchodilator established for us a diagnostic question that warranted further evaluation with exercise testing. Only a small proportion of these patients fulfilled the criteria for exercise-induced bronchospasm during reproduction of symptoms. This demonstrates and makes evident the importance of considering other causes of EID when other symptoms of asthma are not present, bronchodilators do not completely prevent or promptly relieve EID, and baseline pulmonary function is normal.

Vocal cord dysfunction has been recognized in healthy and athletic teenagers with EID who could be misdiagnosed as asthmatic.[31] In patients with vocal cord dysfunction, there is paradoxical movement of the vocal cords with adduction during inspiration that produces increased upper airway resistance. The consequent increased work of breathing causes

the sensation of dyspnea. Typically, these patients present with stridor that is sometimes mistaken for wheezing by patients and parents.[32] The diagnosis is based on demonstrating upper airway obstruction caused by paradoxical vocal cord movement as seen on endoscopy. Exercise-induced laryngomalacia also is associated with inspiratory stridor during exercise. Marked improvement of this entity can be seen after laryngoplastic surgical correction.[11,33] Direct visualization of the larynx and vocal cords is important to differentiate between vocal cord dysfunction and exercise-induced laryngomalacia as a cause of upper airway obstruction, since both conditions can produce stridor and a decrease in the FIF_{50}/FEF_{50}.

The diagnosis of exercise-induced hyperventilation was determined for one patient who had an inappropriate increase in ventilation as demonstrated by an increase in $\dot{V}_E/\dot{V}_{O_2}$ concomitant with low end-tidal carbon dioxide. Exercise-induced hyperventilation has been described in a group of mostly teenagers previously diagnosed as having EIA[13] and in adults with exercise-induced chest pain initially suspected to be of cardiac etiology.[34,35] In the patient with that diagnosis in this report, hyperventilation in association with dyspnea was noted early during the warm-up period of exercise testing. Even though a transient mild decrease in end-tidal carbon dioxide was commonly observed during initial exercise, this seems to be exaggerated in those with exercise-induced hyperventilation when associated with the sensation of dyspnea. This exaggerated hyperventilation may be due to anxiety associated with exercise.[36,37]

The observation of restrictive physiology in association with EID was unexpected, since baseline spirometry was within normal limits in the patients selected for inclusion in this report. However, these patients with generally minor chest wall abnormalities met the criteria for restrictive physiology by having a decreased maximal tidal volume during exercise, increased respiratory rate, and decreased respiratory reserve in association with their reproduced EID.[17] These data suggest that minor degrees of chest wall abnormalities insufficient to result in abnormal resting pulmonary function nonetheless can be associated with chest wall stiffness that causes exercise limitation with associated dyspnea when such individuals attempt to keep up with peers in athletic activity.

Exercise testing using gas-exchange analysis has been recognized as a valuable tool in detecting cardiovascular or pulmonary causes of exercise limitation.[38] Despite the wide variety of causes for EID found in this study, our data showed that EID in a large number of adolescents referred to a specialty clinic was not due to asthma or to any other cardiorespiratory abnormality but was instead associated only with normal physiologic limitation. More than half of our patients showed no defined pathophysiologic abnormality and demonstrated varying degrees of conditioning, ranging from those who were well-conditioned athletes to others who showed evidence consistent with poor cardiovascular conditioning. This latter group had no evidence for cardiovascular disease from the history and physical examination. Determination of the $\dot{V}_{O_2}$max, anaerobic threshold, oxygen pulse, $\dot{V}_E/\dot{V}_{O_2}$, and heart rate–work ratio enabled identification of the level of conditioning.[39]

This grouping according to cardiovascular conditioning in essentially healthy patients with EID indicates a spectrum for the level of activity and circumstances that trigger their dyspnea rather than differences in symptom mechanism. Patients in the poorly conditioned group tended to have a more sedentary lifestyle and complained of dyspnea when occasionally required to exercise at levels to which they were not accustomed, mostly during physical education classes or if they attempted competitive athletic activities without undergoing conditioning or training. Sensation of dyspnea in these patients was probably caused by the increased ventilatory equivalent at smaller work load (the increased $\dot{V}_E/\dot{V}_{O_2}$ ratio).[40] On the other hand, the well-conditioned group included some highly driven athletes who complain of dyspnea mostly in competitive settings. It appears that their dyspnea was a consequence of their increased ventilatory work due to maximal utilization of their ventilatory capacity with intense exercise. It is also possible that the sensation of dyspnea in these patients was induced or accentuated by anxiety during the competitive athletic activities.[41] These clinical differences required differences in treatment strategy. Our treatment approach for the first group focused on more involvement of the poorly conditioned patient in frequent and consistent aerobic activities, whereas for the second group the focus was on assurance, education, and attempts to obtain skillful athletic training.

The diagnosis of EIA has been associated with controversy. Various studies have used different criteria to define significant exercise-induced bronchospasm with 10% to 20% decreases in FEV_1 used in various studies.[42] In examining the relationship between a screening history for EID and exercise-induced bronchospasm in 256 adolescent athletes, 40% had a positive screening history.[43] When exercise testing was performed in these children with a negative screening history, 8% were identified as having exercise-induced bronchospasm based on a 10% or greater decrease in FEV_1. In contrast, only 13% of those with a positive screening history had exercise-induced bronchospasm defined by the same criteria. Since children without asthma can have decreases in FEV_1 during exercise by as much as 10%,[6] we chose 15% as the critical value for defining exercise-induced bronchospasm to minimize false-positive results. Furthermore, we only considered the 15% decrease in FEV_1 to be the explanation for the patient's EID if it was associated with reproduction of the patient's typical symptoms that were the basis for referral to our clinic.

A limitation of our study was its retrospective nature. This study was based on clinical assessments and was not a prospective study. Outcome subsequent to evaluation was not systematically obtained, and the benefit of the evaluation, diagnosis, and recommendations was not evaluated. However, those receiving ineffectual asthma treatment, many for an extended period, could be counseled to discontinue use of

those medications and presumably did. Furthermore, we anticipated that an explanation of the reason for the EID would be expected to decrease anxiety of the patient and family that had occurred as a consequence of those symptoms.

In considering the implications of our data, it is important to recognize the selective nature of the patients studied. These were patients generally referred to a specialty clinic and as such should not be considered to be representative of the population of children with EID in the community, where asthma is probably more likely to be a major contributor, However, the study by Hallstrand et al[43] in unselected adolescent athletes demonstrates an impressive disconnect between symptoms of EID and exercise-induced bronchospasm. The lower the FEV_1 decrease used to define exercise-induced bronchospasm, the more likely that clinically unimportant spirometric changes will be seen that are not actually the cause of the EID.

In conclusion, this study demonstrates the value of reproducing symptoms of EID on a treadmill with cardiac and respiratory physiologic monitoring when other symptoms or signs of asthma are absent and a bronchodilator aerosol does not provide complete blocking of EID. Persistent attempts to treat EID as asthma in such patients without documentation of exercise-indued bronchospasm actually associated with their dyspnea only subject the patient to frustration and unnecessary medication while delaying more specific treatment when indicated.

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