levels specific to epitope peptides of omega-5 gliadin or recombinant omega-5 gliadin might be useful as an *in vitro* diagnostic method (Fig E1).[E226,E227]

Oral challenge with gluten alone or along with aspirin and alcohol is a sensitive and specific test for the diagnosis of wheat-dependent EIAna. Exercise is not an essential trigger for the onset of symptoms in these patients.[E228]

FDEIAna can have a delayed onset for an unpredictable number of hours. Therefore it has been suggested that in such patients exercise should be avoided 4 to 6 hours after specific food ingestion. In patients with wheat gliadin–associated EIAna, a gluten-free diet is recommended.[E224,E229]

Susceptible patients might be advised to take an antihistamine before exercise and should carry self-injectable epinephrine, which is the primary treatment for anaphylaxis.[E229]

Summary Statement 15: Refer to appropriate specialists (eg, cardiologist or pulmonologist) to perform cardiopulmonary testing when breathlessness with exercise, with or without chest pain, might be caused by heart disease or other conditions in the absence of EIB. [Strength of Recommendation: Moderate; Evidence: C]

Although the incidence of cardiac-related dyspnea with exercise in young healthy patients is minimal, it remains an important differential in patients with EIB (Fig E1). Idiopathic pulmonary arterial hypertension can occur in both adults and children. Patients with primary pulmonary hypertension can demonstrate peripheral airway obstruction, poor oxygenation, and early physiologic aerobic limits restricting exertion and, in children, documentation of significant reversibility of lower airway obstruction.[E230-E232]

A case report documents how idiopathic pulmonary arterial hypertension can masquerade as asthma. Two adult nonsmokers presenting with wheezing, chronic cough, and irreversible obstructive lung disease were given a diagnosis of adult-onset severe refractory asthma but actually had dilation of the central pulmonary arteries, compressing the mainstream bronchi.[E233]

"Cardiac asthma" can be considered one presentation of cardiac dyspnea caused by cardiogenic pulmonary edema. The pathogenesis might be reflex bronchoconstriction as a manifestation of pulmonary venous hypertension. In distinguishing cardiac from pulmonary dyspnea, the most useful studies include B-natriuretic peptide measurement, echocardiography, and, if needed, a cardiopulmonary exercise test.[E198] Congestive heart failure can present with dyspnea on exertion. Hyperpnea with exercise can occur without lung function impairment. Ventilation-perfusion mismatch in exercise can be enhanced by increased treatment of heart failure.[E234]

Hypertrophic cardiomyopathy is well known to cause sudden death in young athletes, with an annual 1% mortality rate.[E235] Patients can have dyspnea and chest pain that improve with β-blockers.[E236]

Cardiac dysrhythmias can also cause dyspnea with exercise. Supraventricular tachycardia can cause EIB in children.[E199] Young adults with complete heart block can have shortness of breath, dyspnea on exertion, syncope, dizziness, or fatigue.[E237]

Vascular rings of the aorta are rare but can present as asthma. Spirometry in these patients reveals decreased peak expiratory flow and truncation of the expiratory flow-volume loop with normal FVC, FEV_1, and FEV_1/FVC ratio values. Chest radiographs are significant for a right aortic arch.[E238]

Pulmonary arteriovenous malformations and disorders with right-to-left shunts can cause exercise-induced dyspnea because of hypoxemia, without associated bronchoconstriction. Hereditary hemorrhagic telangiectasia, atrial septal defects, ventricular septal defects, and Osler-Rendu-Weber syndrome are among the primary causes. Cardiopulmonary exercise testing, as differentiated from pulmonary function testing for EIB, is an appropriate noninvasive tool to begin and guide the evaluation of these patients presenting with undiagnosed dyspnea.

The evaluation might require procedures, such as cardiac catheterization, to further delineate the right-to-left shunt.[E239,E240] Exertional dyspnea in symptomatic patients with COPD might be due to the combined deleterious effects of higher ventilatory demand and abnormal ventilatory dynamics but not temporally attributable to bronchoconstriction.[E241] Patients with COPD might have evidence of small-airway dysfunction with increased ventilatory requirements during exercise, likely on the basis of greater ventilation and perfusion abnormalities. These abnormalities also involve changes in end-expiratory lung volume and breathing patterns that are more shallow and rapid than in a comparatively healthy cohort.

Although there are reports of exertional gastroesophageal reflux in healthy subjects, most studies have demonstrated no significant correlations between GERD and EIB.[E242-E244]

Although acid reflux can be common in patients with EIB, many patients with exercise-related respiratory symptoms can receive a misdiagnosis of asthma when they truly have exercise-onset GERD (Fig E1).[E245] Some controversies exist in the treatment of GERD and EIB. One study demonstrated that symptoms of acid reflux related to running were relieved by a proton pump inhibitor, but the respiratory symptoms of EIB were not relieved by proton pump inhibitors.[E246] In contrast, other investigators have reported improvements in exercise-related breathing symptoms when patients were treated with proton pump inhibitors.[E245]

Impaired oxidative phosphorylation in working muscle disrupts the normal regulation of cardiac output and ventilation relative to muscle metabolic rate in exercise.[E247] Deficiencies of mitochondrial enzymes cause a number of severe neurologic syndromes in pediatric patients. Isolated myopathies secondary to enzymatic deficiency have been recognized in adults and might be more prevalent than reported previously (Fig E1).[E248,E249]

Summary Statement 16: Refer patients for psychological evaluation when the symptoms (eg, hyperventilation and anxiety disorders) are in the differential diagnosis of EIB. [Strength of Recommendation: Weak; Evidence: D]

Psychological factors can obfuscate the diagnosis in patients with apparent exercise intolerance. Such scenarios, such as subjects, particularly young women, complaining of shortness of breath while running without having stridor, wheezing, or relief with trial bronchodilators, are not uncommon but might be vexing to patients, their parents, and their physicians.

Although VCD and exercise-induced hyperventilation can have functional triggers, differentiating EIB requires subjective and objective assessment.[E250] Mental stress might be one trigger factor in which hyperventilation is seen in patients with asthma-like symptoms with negative asthma test results.[E251] If objective testing does not reveal any bronchoconstriction or other physiologic explanations, then a psychological cause should be considered and addressed with the patient, which might involve a recommendation for psychological consultation (Fig E1).