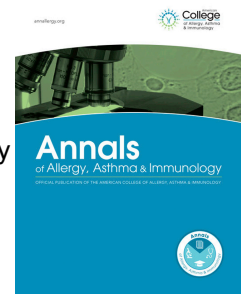


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Cardiopulmonary Exercise Testing for Pediatric Exercise Induced Dyspnea Especially in Patients who Failed Asthma Treatment

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Conflict of Interest

There are no potential conflicts of interest to report that knowingly existed or otherwise before and during the process of this research study.

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Keywords- Asthma; Exercise-induced dyspnea; Exercise-induced bronchospasm; Exercise testing; Vocal cord dysfunction; Shortness of breath

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Abbreviations

CPET- Cardiopulmonary Exercise Testing

EIB- Exercise-Induced Bronchospasm

EID- Exercise Induced Dyspnea

EIH- Exercise-Induced Hyperventilation

VCD- Vocal Cord Dysfunction

Exercise-induced bronchospasm (EIB) is the most common suspected diagnosis for exercise induced dyspnea (EID) in pediatric patients with or without asthma.^{1, 2} Previous studies show that EIB is present in just 8%-19% of otherwise healthy children with EID^{1,2,3}. In fact, a majority of these patients have one or more problems other than EIB limiting exercise. Cardiopulmonary Exercise Testing (CPET) can identify clinical entities that mimic EIB. Multiple parameters are continuously recorded during CPET providing a global assessment of pulmonary, cardiovascular, neuropsychological, and skeletal muscle systems.⁴ In this retrospective study, we investigated the clinical utility of CPET in evaluating pediatric patients with EID referred to our tertiary center over the last 6 years (2012-2018).

The data were collected retrospectively from all the CPET administered on a treadmill to pediatric subjects for EID in the last 6 years at a tertiary center's clinical exercise physiology laboratory. Patients with chronic conditions e.g. cystic fibrosis, neuromuscular weakness, significant cardiac condition etc. were excluded. Patients with an asthma diagnosis were not excluded. Each patient performed the CPET on a treadmill as per American Thoracic Society (ATS) guidelines.⁴ Spirometry was done at 0, 5, 10, and 15 minutes following exercise to assess for EIB. A drop of 10% or more in forced expiratory volume in one second (FEV₁) post exercise was taken as a positive test for EIB. Vocal cord dysfunction (VCD) was diagnosed based on clinical history, pre and post CPET spirometry (i.e. blunting of inspiratory loop) and symptoms during the study (i.e. stridor). Exercise induced hyperventilation (EIH) was diagnosed based on excessive respiratory rate and/or an abnormal drop in CO₂ during exercise with a consistent history.⁵

133 (96 Females, 37 Males, age range 7-20 years, 14.4±2.5 years; Mean±SD) out of 216 CPET studies met the criteria. 78% (104/133) were referred by the pulmonologist from the institution

whereas 22 % (29/133) were referred from outside providers. Majority of patients (77 %) had previously tried bronchodilator for their symptoms prior to the test with only 13% reporting as good symptomatic improvement. Mean baseline spirometry was normal (FEV_1 (% predicted) 97.4 ± 12.8 ; FEV_1 / FVC 85.0 ± 6.3 %). CPET results showed VCD as the most common cause of exercise limitation (36/133; 28 females) followed closely by physiological limitation (33/133; 23 females). EIH was responsible for exercise limitation in 10% (13/133; 12 females) of patients and similar number of patients (14/133; 11 females) was limited because of deconditioning. Obesity, pulmonary limitation, cardiac limitation, and anxiety were other causes of exercise intolerance (Figure 1). EIB was the limiting cause of exercise only in 10% (13/133; 6 females) of patients (Figure 1). There was evidence of a relationship between EIH and female sex (p value <0.01) with an odds ratio of 6.3 (95% CI = 1.8 – 22.1).

EID is an increasingly common reason to see a physician. Pediatric EID although commonly attributed to EIB, can have many causes.⁶ Many studies of pediatric patients referred for consultation for EID showed EIB in only 8-19%, in line with our findings.^{1, 2, 3} While the majority of our patients had been prescribed bronchodilators for suspected EIB, only 10% showed EIB on CPET results. This highlights that self-reported exercise-induced symptoms are poor predictors of EIB. Therefore, other causes of EID should be considered especially in patients with no significant clinical response to bronchodilators.

VCD is characterized by paradoxical closure of vocal cords during inspiration causing stridor and dyspnea. In our study, VCD was the most common primary cause of EID (27%). In 294 pediatric patients with EID, Hseu et al also found VCD as the most frequent cause (30%) of exercise intolerance.⁷ The incidence tends to be higher in female athletes.⁸ We did not see any dependence between sex and VCD in our cohort. The documentation of excessive respiratory

rate and/or an abnormal drop in CO₂ during exercise with a consistent history is often diagnostic of EIH.⁵ In a study done in pediatric patients with atypical or refractory asthma, 1/3rd of these patients demonstrate EIH.⁹ It is speculated that abnormal ventilatory homeostasis during exercise could be the underlying reason.⁹ We saw evidence of EIH in 10% of our patients and it was approximately 6 times more common in females. Progesterone combines with estrogen to increase ventilation by action both centrally and on the carotid body which explains the higher prevalence in females.¹⁰

Physiological limitation, often a diagnosis of exclusion, is related to an excessive sensation of the perceived work of breathing with increased ventilation. In a study done by Abu-Hasan, et al. on 142 children and adolescents with EID, the most common cause was a normal physiological limitation (52%).¹ Physiological limitation as a cause of EID was the second most frequent cause in our study group. Seear et al showed that 23 % of those previously diagnosed with EIB were considered “unfit” (deconditioned) based on CPET In contrast to 10 % in this study.² Deconditioned subjects accumulate lactate at a lower level of exercise with resultant increased metabolic acidosis and ventilation.⁴ 11 % of our patients had obesity as the primary contributor to EID due to excessive metabolic requirement and ventilatory limitation.⁴ Pulmonary limitation is a rare cause of EID in apparently well individuals. 11% of patients in the series published by Abu-Hasan, et al. had chest wall restriction (due to mild pectus deformity or scoliosis) as a cause of EID.¹ In our cohort, 5 % showed abnormal cardiac or pulmonary limitation which included mainly patients with chest wall abnormalities (pectus excavatum, scoliosis).

In conclusion, CPET was helpful in assessing pediatric EID patients who failed to improve after routine interventions. EIB was present in few patients and the majority of the patients had other causes of EID. Based on these results, we were able to provide specific recommendations to our

70 patients. CPET, although expensive and more complex, should be considered in pediatric EID

71 patients especially in patients with absence of significant response to asthma treatment.

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Figure Legend

Figure 1: Pie chart showing different causes of EID in our study patients (n=133) as uncovered by CPET

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