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Flow limitation and dysanapsis in children and adolescents with exertional dyspnea

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ABSTRACT

The consequence of dysanapsis, quantitated by dysanapsis ratio (DR), on expiratory flow limitation (EFL) during exercise in pediatric subjects was examined. EFL occurred in 80 (56%) subjects from an enriched sample of children and adolescents tested during investigation of exertional dyspnea. DR was lower in subjects with *vs* without EFL during exercise: (0.055 ± 0.015 *vs* 0.067 ± 0.017, $p < 0.001$), and lower ratio correlated with greater extent of EFL ($r = -0.64$, $p < 0.001$). EFL was seen more often in boys: 67% *vs* 46% ($p = 0.01$), as girls had higher DR (0.063 ± 0.016 *vs* 0.056 ± 0.018, $p = 0.007$). Lower FEV_1 (95 ± 17 *vs* 102 ± 15%predicted, $p < 0.005$) and FEF_{50} (3.47 ± 1.28 *vs* 4.08 ± 1.20 L s^{-1}, $p = 0.002$) distinguished those with *vs* without EFL. Inspiratory capacity rose (IC) steadily, as work increased among those with EFL, whereas it fell to back resting levels after an initial rise in subjects without EFL. Low DR predicts EFL in pediatric subjects. Adjusting operating lung volume during exercise can mitigate EFL but this strategy may contribute to exertional dyspnea.

1. Introduction

Dysanapsis was the term coined Green et al. and Mead subsequently developed the dsyanapsis ratio (DR) to describe how this phenomenon explained variation in the maximum expiratory flow-volume curve (Green et al., 1974; Mead, 1980). This phenomenon was thought to be a physiological curiosity but translational science shows it is now clinically relevant and explains why airflow obstruction in the presence of a normal FEV_1 and FVC is potentially a normal variant (Thompson, 2017). In contradistinction, recent data demonstrating dysanapsis is related to symptoms (e.g. exertional dyspnea) and morbidity in overweight children (Forno et al., 2017) argues that dysanapsis is not necessarily normal. Dysanapsis is particularly relevant in pediatric subjects because of the rapid growth that occurs in childhood and adolescence. Lung growth may be isotropic or dysanaptic, i.e. whether airway caliber grows in proportion to lung parenchymal volume or not. There is evidence for both isotropic or dysanaptic growth, such that timing (De Troyer et al., 1978; Martin et al., 1988; Tepper et al., 1986) or sex (Hibbert et al., 1995; Hibbert et al., 1984; Martin et al., 1987; Merkus et al., 1993; Pagtakhan et al., 1984) may be more salient determinants of relative airway and parenchymal size. Women have smaller lungs (McClaran et al., 1998) and lower flow rates compared to height-matched men (Dominelli et al., 2011). Smaller airway caliber for a given lung volume, i.e. lower DR, is associated with increased likelihood and severity of (EFL) expiratory flow limitation (Smith et al., 2014) resulting in higher resistive work of breathing during exercise (Guenette et al., 2009). This could trigger one to breathe at higher operating lung volume as a means of compensation to avert EFL, i.e. dynamic hyperinflation (Babb, 2013; Dolmage et al., 2013).

The concept of ventilatory limitation to exercise, specifically expiratory flow limitation (EFL), in healthy individuals has gained traction in the past 20 years (Johnson et al., 1992, 1995, 1999). Similar observations were made in small samples of healthy children. Nourry et al. reported that most prepubescent children experience EFL during exercise (Nourry et al., 2005, 2006), and Swain et al. found it common in both prepubescent boys and girls during heavy exercise (Swain et al., 2010). This same group re-evaluated half their original cohort 5 years later and concluded that interval lung growth resulted in lower prevalence after puberty (Emerson et al., 2015; Smith et al., 2015).

Tidal flow-volume analysis during exercise testing was routinely performed in subjects evaluated clinically for exertional dyspnea. This method can track operating lung volume in addition to demonstrating flow limitation. Breathing at higher lung volume – operationalized as change in inspiratory capacity or its complement, expiratory reserve volume from rest – can moderate EFL (Babb, 2013; Dolmage et al., 2013). Data from exercise tests were audited to test the following hypotheses: [1] DR correlates with EFL during exercise; [2] EFL is associated with failure to raise end-expiratory lung volume.

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2. Methods

2.1. Subjects

Medical records of children and adolescents up to 18 years of age seen at Mayo Clinic from 2007 to 2014, who underwent maximal cardiopulmonary exercise tests with tidal flow-volume loop analysis as part of clinical evaluation for exertional dyspnea were abstracted. There was no documentation of active or sedentary lifestyle; nor was pubertal status assessed. Some underwent simultaneous trans-nasal flexible fiber-optic laryngoscopy, enabling us to exclude those with exercise-induced laryngeal obstruction. Subjects with congenital heart disease (known to affect lung growth) were also excluded. The cohort was comprised of subjects with known lung or airway disease (chiefly asthma) who still complained of exertional dyspnea despite aggressive therapy; subjects with disease in other systems with possible pulmonary involvement; and subjects evaluated for exertional dyspnea or chest pain in whom no cause was found and thus had no medical diagnosis. Patients with asthma had a history of compatible symptoms plus airway hyperreactivity or bronchodilator responsiveness, and were well-controlled when tested. Testing was conducted for clinical indications and informed consent was not required. Mayo Clinic Institutional Review Board approved the study.

2.2. Exercise testing

Patients reported for exercise with no specific instructions other than fast prior to the test. They continued their usual medications, but albuterol was withheld at least four hours. Subjects performed spirometry on the same MedGraphics system used for exercise (see below) according to ATS/ERS criteria (Miller et al., 2005) while seated on the cycle ergometer with the best effort so defined chosen as the maximum expiratory flow-volume envelope. Subjects next performed a maximal cardiopulmonary exercise test on an electronically-braked cycle ergometer. The James protocol (James, 1981) was used prior to 2008 but subsequent tests followed a Godfrey protocol (Godfrey, 1974) of 1-min incremental workloads with steps of 10–30 W min^{-1} in order to achieve test duration of 10 ± 2 min. Ventilation and gas exchange was measured breath-by-breath with subjects breathing through a mouthpiece and wearing nose clips using MedGraphics CPX/D that employs a Pitot tube to measure flow, electronically integrated to give minute volume. Exhaled gases concentrations were measured by mass spectrometry. Heart rate and oxygen saturation were continuously monitored by 12-lead ECG and pulse oximetry, respectively. Blood pressure was measured by auscultation every other subsequent work increment, alternating with inspiratory capacity maneuvers (see below). Patients were encouraged to exercise to voluntary exhaustion to achieve presumed maximal criteria (gas exchange ratio > 1.1, HR > 190 bpm).

2.3. EFL determination

MedGraphics Breeze software© measures EFL according to method described by Johnson et al. at Mayo Clinic (Johnson et al., 1995). In short, the degree of flow limitation was obtained by aligning a tidal exercise breath flow-volume loop within the maximum expiratory flow-volume envelope obtained at rest prior to the test. Alignment was accomplished by having subjects perform an inspiratory capacity (IC) from resting end-expiratory lung volume, assuming no change in total lung capacity with exercise. Resting maneuvers were rehearsed until subjects could perform them satisfactorily, defined by observing a plateau in the volume-time display. IC maneuvers were performed at rest, during a 3-min warm-up at the initial workload, then every other workload (alternating with blood pressure checks) up to respiratory compensation point. EFL was defined by tidal expiratory flow-volume loop overlapped or exceeded the maximum expiratory flow-volume envelope at least 10% of their tidal volume for 6 or more breaths. As these were clinically indicated tests, post-test spirometry was done at the physician's discretion. Ensemble averaging of repeated efforts before or after exercise to create a composite maximum expiratory flow-volume curve was not done; nor were partial expiratory maneuvers performed.

2.4. Dysanapsis ratio

DR was computed for each subject (Mead, 1980) estimating static elastic lung recoil pressure at 50% VC ($PstL_{50\%}$) from published normal values (Zapletal et al., 1976):

$$DR = FEF_{50}/FVC^{*}Pst(L)_{50\%}$$

FEF_{50} was measured during standard spirometry done within a few days of the exercise test on a Jaeger MasterScreen pulmonary function testing system, again adhering to ATS/ERS standards. Different testing equipment or days occurred because many subjects also underwent bronchial provocation challenges as part of our standard clinical investigation of exertional dyspnea. Median (IQR) time between FEF_{50} measurement and the exercise test was 0 (0–4) days. Most subjects performed a slow vital capacity maneuver during this process, which did not differ significantly from FVC, but otherwise there was no attempt to estimate degree of thoracic gas compression. Tracking changes in end-expiratory lung volume was done as follows. Subjects performed an IC maneuver on demand from a stable (≥5 breaths) baseline. Expiratory reserve volume (ERV) was calculated as VC–IC at rest. A plateau during the IC maneuver was sought, and the sum of ERV + IC during exercise was always within 10% of FVC at rest. Given the test protocol with individualized work increments, changes in ERV and IC during exercise were placed in bins to optimize sample size for statistical analysis: three bins – rest (all subjects), 10%-20% peak work capacity (N = 80), plus 60% ± 10% peak work capacity (N = 70); or two bins – rest coupled with subjects who had data at *both* 10%-20% and 60% ± 10% peak work capacity.

2.5. Statistics

Changes in operating lung volume from rest to exercise were explored using general linear modeling, controlling for DR. Comparisons between groups were tested for statistical significance using unpaired Student's *t*-test for continuous data, or χ^2 for proportions, as appropriate. Pearson's r was used to describe direction and magnitude of correlation between DR and EFL. Associations with EFL after adjusting for age and sex *and* DR were evaluated using multivariable linear regression models. Analyses were done using SAS version 9.3.

3. Results

The final subject population consisted of 85 subjects with exertional dyspnea without any underlying medical diagnosis, 40 with asthma, and 19 with miscellaneous conditions. The latter comprised individuals with respiratory disease (e.g. bronchiectasis), musculoskeletal disorders (e.g. pectus excavatum, scoliosis), supraventricular tachycardia, or systemic disorders (e.g. postural tachycardia syndrome) who complained of dyspnea or chest pain on exertion.

3.1. Dysanapsis ratio

There was no difference between DR computed using FVC *vs* slow vital capacity (0.061 ± 0.017 *vs* 0.061 ± 0.019) and thus all DR are based on FVC. Static elastic lung recoil pressure at 50% of VC was virtually identical in subjects with *vs* without expiratory flow limitation (16.0 cmH_2O). DR was lower in subjects with (0.055 ± 0.015) *vs* without (0.067 ± 0.017, $p < 0.001$) expiratory flow limitation, exhibiting an inverse correlation ($r = -0.64$, $p < 0.001$) between DR