Published in final edited form as:

Respir Physiol Neurobiol. 2018 June ; 252-253: 58–63. doi:10.1016/j.resp.2018.03.013.

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 , $p < .001$), and lower ratio correlated with greater extent of EFL ($r = -.64$, $p < .001$). EFL was seen more often in boys: 67% vs 46% ($p = .01$), as girls had higher DR (0.063 ± 0.016 vs 0.056 ± 0.018 , $p = .007$). Lower FEV₁ (95 ± 17 vs 102 ± 15 %predicted, $p < 0.005$) and FEF₅₀ (3.47 ± 1.28 vs 4.08 ± 1.20 L·sec⁻¹, $p = .002$) 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 to EFL in pediatric subjects. Adjusting operating lung volume during exercise can mitigate EFL but this strategy may contribute to exertional dyspnea.

Keywords

dysanapsis; ventilation; exercise; flow limitation

Introduction

Dysanapsis was the term coined Green et al. and Mead subsequently developed the dysanapsis 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 FEV₁ 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.

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Conflict of interest statement: No financial disclosures to report.

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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; Johnson et al., 1995; Johnson et al., 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.

Methods

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.

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-minute incremental workloads with steps of 10 to 30 watts·min⁻¹ in order to achieve test duration of 10±2 minutes. 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).

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-minute 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.

Dysanapsis Ratio

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

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

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.

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.

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.

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 cmH₂O). DR was lower in subjects with (0.055 ± 0.015) *vs* without (0.067 ± 0.017 , $p < .001$) expiratory flow limitation, exhibiting an inverse correlation ($r = -.64$, $p < .001$) between

DR and percentage of exercise tidal volume over which tidal expiratory flow-volume loop overlapped or exceeded the maximum expiratory flow-volume envelope (Figure 1). In other words, lower DR was associated with greater degree of expiratory flow limitation. Expiratory flow limitation also showed increasing prevalence among subjects as DR fell (Figure 2). Lower spirometric indices of airflow obstruction distinguished subjects with vs without expiratory flow limitation (Tables 1 and 2), but differences were subtle when sexes were analyzed together.

Effect of Age and Sex

There was no correlation between age and presence/absence or degree of expiratory flow limitation in these cross-sectional data. Ages of boys and girls with expiratory flow limitation were similar (14.6 ± 2.9 vs 14.4 ± 2.6 years, $p=0.6$). Sex specific determinants of DR and expiratory flow limitation are shown in Table 2, which data confirm that lower indices of airflow are most apparent in girls with flow limitation but less obvious in boys. Girls had lower FVC than boys (3.76 ± 0.84 vs 4.23 ± 1.40 L, $p=.009$) but similar FEV1 ($p=0.12$), and FEF₅₀ ($p=.98$). Lung elastic recoil pressure was marginally lower in girls, 15.9 ± 8 vs 16.3 ± 1.3 cm H₂O ($p=.04$), but upstream conductance ($G_{us}=FEF_{50}/P_{s(L)_{50\%}}$) was similar between sexes: 0.23 ± 0.06 vs 0.23 ± 0.09 Lsec⁻¹cmH₂O⁻¹ ($p=.60$). Overall, girls had a higher DR than boys: 0.063 ± 0.016 vs 0.056 ± 0.018 ($p=.007$) and were less likely to have expiratory flow limitation with exercise: seen in 46% of girls vs 67% of boys (χ^2 , $p=.010$). The same trend of greater expiratory flow limitation with lower DR was observed in both girls ($r=-0.57$) and boys ($r=-.67$).

Effect of Diagnosis

Expiratory flow limitation during exercise was equally prevalent (χ^2 , $p=0.31$) in each diagnostic group (asthma, exertional dyspnea, or miscellaneous). Subjects with asthma were younger than those without: 13.0 ± 3.1 vs 15.1 ± 2.3 years ($p<.001$); but there was no difference in sex distribution (χ^2 , $p=.46$). Spirometric indices in patients with asthma showed mild obstruction despite being clinically stable (Table 1b). As a result, their DR was lower than that of subjects without asthma: 0.054 ± 0.019 vs 0.063 ± 0.016 ($p=.005$). Expiratory flow limitation occurred overall in 60% of asthmatics. The male predominance among subjects with expiratory flow limitation described above was driven by subjects *without* asthma: nearly half (48%) of whom were boys, compared with only 22% boys among those without expiratory flow limitation ($p=0.003$). In contrast among asthmatics, 42% of those with, vs 41% of those without, expiratory flow limitation were boys ($p=0.94$).

Exercise Ventilation

Approximately one-third of subjects had peak $\dot{V}O_2$ values $<10\%$ *ile* (~ 36.8 ml kg⁻¹min⁻¹ in males, ~ 30.8 ml kg⁻¹min⁻¹ in females) (27). Subjects with EFL had higher peak $\dot{V}O_2$ compared to those without EFL (Table 3), whether expressed as percent predicted or L·min⁻¹ ($p=.01$, data not shown). They achieved higher minute volume at peak exercise via higher frequency (Table 3), similar tidal volume in liters ($p=.12$) though it comprised a slightly higher proportion of FVC: $43 \pm 7\%$ vs $40 \pm 8\%$ ($p=.008$).

Among the majority ($N=85$) with exertional dyspnea but *without* an underlying or specific diagnosis, we found similar relationships between age (no difference between those with *vs* without expiratory flow limitation), sex (nearly twice percentage of boys as girls exhibited EFL), and DR as a predictor of expiratory flow limitation, to the entire study sample. There was a similar inverse relationship between expiratory flow limitation and DR ($r=-0.62$). Multivariate analysis adjusting for age and sex yielded similar conclusions: subjects with lower indices of airflow or upstream conductance, or those who exerted themselves more, were more likely to exhibit flow limitation (Table 3). The latter group achieved higher peak minute volume primarily by breathing faster – i.e. increasing expiratory flow.

Higher expiratory flow rates were possible by manipulation of operating lung volume during incremental exercise. Most subjects dipped into expiratory reserve volume, reducing end-expiratory lung volume, as an initial step to boost tidal volume with onset of exercise. Breathing pattern subsequently changed between those with *vs* without expiratory flow limitation. Those who *maintained* a lower end-expiratory lung volume as work progressively rose were more likely to develop expiratory flow limitation. Subjects whose expiratory reserve volume rose (i.e. inspiratory capacity declined) from rest to light (10%-20% peak) or moderate (50%-70% peak) exercise were less likely to become flow-limited ($p=0.22$ or $.014$, respectively) when controlling for DR. Subjects who raised end-expiratory lung volume as exercise intensity rose maintained tidal flow-volume loops within their maximum expiratory flow-volume envelope.

Discussion

Dysanapsis

Green et al. (Green et al., 1974) postulated that intra-individual differences in maximum expiratory flow rates were due to differences in airway calibre and geometry (diameter *vs* length) and suggested that disharmony between lung size and airway size was a normal variant. The ATS/ERS lung function interpretation statement arbitrarily defined dysanapsis as airflow obstruction (FEV_1/FVC lower limit of normal) in the presence of FEV_1 100% predicted normal (Pellegrino et al., 2005). The concept of “airway obstruction”, i.e. (FEV_1/FVC lower limit of normal) in the presence of a normal FEV_1 , was at odds with what Mead et al. posited, begging the question whether dysanapsis truly is a normal variant? Greater recognition of an association between dysanapsis and EFL in children (Nourry et al., 2006), adolescents (Emerson et al., 2015), and adults (Smith et al., 2014) with sex differences (Dominelli et al., 2011) has revived interest. The present data demonstrating EFL as a function of dysanapsis in a large, cross-sectional study of children and adolescents provide a strong rationale to suggest that what was once thought to be a physiologic curiosity is indeed clinically relevant.

Deconstructing Dysanapsis

Indeed, these findings suggest that children and adolescents who present with exertional dyspnea often exhibit EFL during exercise. Among these subjects tested to elucidate its cause, higher DR was associated with both reduced likelihood and severity of EFL regardless of underlying diagnosis. The mechanism in females is physiologic, i.e. undersized

plumbing in simplistic terms, reflected in DR; whereas the mechanism in males is less clear. It may be related to the relative impact of parenchymal growth on radial traction of airway walls (increasing diameter) vs lengthening of airways (increasing resistance); but these data provide no clues to said mechanism(s). This complexity appears subtly in Figure 2, where frequency distribution of DR among EFL subjects had longer tail toward higher DR values despite lower mean DR; and vice versa for non-EFL subjects who had higher mean DR but longer leftward tail toward lower DR values.

Findings from the present study in pediatric subjects differ somewhat from a report in an equally large number of adults (Smith et al., 2014) but the common observation was existence of a continuum rather than threshold effect for DR as a predictor of EFL. Similarities end there but this is much more likely due to different study subjects rather than methodologic issues. The same group tested a small sample of children, permitting some comparison (Smith et al., 2015). Dysanapsis ratios reported in the present study were similar to the few pediatric subjects originally reported by Mead (Mead, 1980) whereas Smith et al. used a different set of reference equations for $P_{sL_{50\%}}$ to compute DR, resulting in their DR values at least double those obtained herein (Smith et al., 2014). The prevalence of EFL decreased in a smaller cohort tested ~5 years apart pre- and post- puberty (Emerson et al., 2015) but more boys than girls (as in the present study) manifested EFL after puberty. They also observed differences in operating lung volume during exercise but reported growth-related changes which differed between sexes. They offered as explanation that older subjects breathed at higher relative lung volumes during exercise as a strategy to avoid flow limitation, utilizing higher flow rates available with a leftward shift of the tidal flow-volume loop within the maximal flow volume envelope, not unlike present findings.

Transient Growth-related Phenomenon?

Subjects in our study underwent testing during a period of significant growth of their respiratory system and the manner in which such growth progresses is central to our discussion. In a longitudinal study of pediatric subjects, Hibbert et al. (Hibbert et al., 1995) showed that lung volumes were greater in boys than in girls, but maximum expiratory flows were higher in girls than in boys during childhood (absolute and normalized for TLC). Boys caught up and ultimately had higher TLC-normalized flows than girls by 18.5 years of age. This implied that girls have wider or shorter airways (higher DR) in childhood than boys but by adulthood boys had larger airways relative to lung size than girls. Although the present study was cross-sectional, one may presume that girls were programmed to relatively less airway growth than boys, eventually assuming proportionality observed in adult females (McClaran et al., 1998). This explains the finding that indices of airflow (FEV_1/FVC , FEF_{50}) were markers for EFL and dysanapsis in girls. Similarly, one cannot say whether subjects who demonstrated EFL would continue to do so into adulthood, although the lone study examining this question found otherwise (Smith et al., 2015). It is therefore conceivable that the phenomenon may be part of the growth process. Ergo, recognition of the phenomenon has therapeutic and prognostic relevance.

Factors Modifying EFL

Operating lung volume influenced occurrence of EFL with exercise. FVC did not differ between subjects with vs without EFL, but subjects who developed EFL showed slightly but significantly larger exercise tidal volume (Table 3). Subjects whose inspiratory capacity declined with increasing work were less likely to become flow-limited even after accounting for DR. This implies a strategic contradiction: lower end-inspiratory lung volume implies breathing closer to total lung capacity – the flatter part of the pressure-volume curve for the respiratory system. Yet subjects who did so were less likely to manifest EFL during exercise. One may speculate that such a strategy masks, but does not necessarily sever, the link between exertional dyspnea and expiratory flow limitation. Any given individual must choose between breathing in the range where the system is least compliant, which raises elastic work of breathing; or breathing within the most compliant, linear portion of the pressure-volume curve but at the cost of greater resistive work of breathing as one skirts expiratory flow limitation.

Higher mean peak $\dot{V}O_2$ was found in subjects with EFL (table 3); whereas previous work showed conflicting results regarding EFL and peak $\dot{V}O_2$. Specifically, Nourry et al. in separate papers noted no difference in EFL between trained and untrained children (Nourry et al., 2005) but subsequently observed higher peak $\dot{V}O_2$ in subjects without EFL (Nourry et al., 2006). Swain et al. found no correlation between EFL and peak $\dot{V}O_2$ (Swain et al., 2010) but all these studies were conducted in pre-pubertal children. Our study population spanned the entire testable age range through childhood and adolescence which likely weighted our findings, as they are more consistent with studies in adults (Dempsey et al., 2008). Moreover, results of multivariate analysis, specifically those who achieved higher peak $\dot{V}O_2$ doing so primarily by increasing expiratory flow rate, is compatible with true ventilatory limitation to exercise: effort compels an individual to exceed their maximum flow-volume envelope with tidal breaths at peak work.

Critique of Methods

It is becoming clear that traditional attribution of ventilatory limitation to exercise, specifically ratio of peak exercise ventilation to MVV, is no longer tenable (Agostoni et al., 2011; Klas and Dempsey, 1989) which has prompted development of alternative means to address this. Two newer methods are negative expiratory pressure and tidal flow-volume loops (Dominelli and Sheel, 2012). Pitfalls in the latter method were recently reviewed by Guenette et al. (Guenette et al., 2013) which must be addressed before touting significance of findings in this report. First, no attempt was made to have them do so during near-maximal exercise, meaning that placement of tidal breaths at peak exercise was based on IC maneuvers done at sub-maximal work. That said, subjects were routinely coached on performing IC breaths before commencing exercise, and if there was any doubt about accuracy or technical acceptability of the IC, it was repeated the very next workload. Most tests were supervised by the author, who routinely sought 4-5 tidal breaths with stable end-expiratory lung volume, and who also watched volume time plots during IC maneuver to ensure a short plateau (implying total lung capacity reached) was achieved at end-inhalation. Secondly, only a single – the best acceptable by standard criteria – maximum expiratory flow-volume curve was used in positioning tidal exercise loops with the maximum

expiratory flow-volume envelope; rather than obtaining both *pre-* and *post-* test maximum expiratory flow-volume curves, or having subjects perform partial as well as maximal FVC maneuvers. All these factors could substantially affect determination of expiratory flow limitation in one direction or another. For these reasons, a conservative definition of EFL was chosen. Slow VC was also measured, and regardless of what comparisons one chooses (sex, EFL, or asthma, groupings) differences between SVC and FVC were all trivial (<5%). Any bias should be neutralized given the large number of subjects, as said shortcomings could have positively *or* negatively influenced assessment of EFL.

Although exertional dyspnea was the reason for exercise testing, dyspnea ratings were not sought due to concern for validity of Borg scales in pediatrics (Pianosì et al., 2014; Pianosi et al., 2015). Finally, level of habitual activity was not gauged nor were subjects grouped according to training status. While this may have affected perceived dyspnea or breathing pattern, studies that reported these variables showed conflicting results (Nourry et al., 2005; Swain et al., 2010).

Conclusion

This is the largest descriptive study of EFL in pediatric subjects and shows that (i) many who report exertional dyspnea have ventilatory limitation to exercise; (ii) lower FEV₁/FVC and FEF₅₀ in girls predict EFL during exercise; (iii) whereas in boys it appears to be more than simply a plumbing problem, but likely to manifest in those who push their respiratory pump to its limits during exercise. The hypotheses are confirmed by the correlation between DR and both prevalence and severity of expiratory flow limitation during exercise. Furthermore, shifting end-expiratory lung volume influences development of expiratory flow limitation during exercise. The present study alludes a novel paradigm of exertional dyspnea in pediatric subjects using data obtained *from* pediatric subjects and provides clues to explanation(s) elucidating vague concepts of “restrictive” physiology (Abu-Hasan et al., 2005) or “physiologic” dyspnea (Mahut et al., 2014) used in previous reports that described results of maximal exercise tests in healthy pediatric subjects who reported shortness of breath. It was no surprise that low DR was found among well-controlled asthmatics too, but confirms that some asthmatics will experience flow limitation during exercise (Johnson et al., 1995) despite normal spirometry and aggressive pharmacotherapy. Findings add to growing evidence that dysanapsis has clinical implications.

Acknowledgments

The author thanks Katherine S King for her statistical support, and Alicia Woodward for her assistance with data extraction.

This work was supported financially by the Mayo Clinic CTSA through grant number UL1 TR000135 from the National Center for Advancing Translational Sciences (NCATS), a component of the National Institutes of Health (NIH), via a Departments of Pediatric and Adolescent Medicine Small Grant Award.

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Highlights

- Dysanaptic lung growth occurs during childhood
- This phenomenon predicts expiratory flow limitation during exercise in adults
- Higher DR protects against development of EFL during exercise in a dose-dependent manner among children and adolescents evaluated for exertional dyspnea
- Consequent adjustment of breathing pattern may contribute to this symptom

Figure 1. Scatterplot ($r=-.64$, $p<.001$) of percentage of exercise tidal volume which overlapped maximum expiratory flow-volume envelope, vs dysanapsis ratio.

Figure 2.

Histogram showing numbers of subjects with, and relative prevalence of, expiratory flow limitation as function of DR. Although DR values for the entire population appear normally distributed, mean, SD, and skewness, were 0.067, 0.017, and -0.093 , respectively, in non-EFL subjects; vs 0.055, 0.015, 0.092, respectively, in EFL subjects. Negative skewness in non-EFL subjects, indicates a longer leftward tail. By contrast, the EFL subjects had a longer rightward tail in their distribution.

Table 1

- a. Characteristics, split according to presence of EFL.
- b. Characteristics, split according to asthma diagnosis.

	No EFL	EFL	No asthma	Asthma
M:F (%male)	17:47 (26)	38:42 (47)	39:65 (38)	24:16 (60)
Age (years)	14.6±2.6	14.4±2.8	15.1±2.3	13.0±3.1 [*]
Height (cm)	164±12.1	164±13.8	167±10.6	159±16.5 [*]
Weight (kg)	59.0±14.5	60.7±17.2	60.4±13.4	58.6±21.4
BMI (kg/m ²)	21.6±4.0	22.2±4.5	21.6±3.7	22.7±5.5
FVC (L)	3.91±1.04	3.95±1.17	102±15	105±17
FEV ₁ (L)	3.34±0.84	3.18±0.93	100±16	95±17
FEV ₁ /FVC	0.86±0.06	0.81±0.08 [§]	0.85±0.06	0.78±0.09 [§]
FEF ₅₀ (L·sec ⁻¹)	4.08±1.20	3.47±1.28 [¶]	78±22	58±22 [*]

Mean±SD. EFL=expiratory flow-limited.

[¶] $p=0.02$.

[§] $p<0.001$ EFL compared with No-EFL.

^{*} $p<0.001$ asthma compared with no asthma.

Table 2

Sex differences in determinants of EFL (mean±SD).

	Boys		Girls		<i>p</i>
	No EFL	EFL	No EFL	EFL	
FVC (%pred)	102±17	100±16	104±14	104±17	.94
FEV ₁ (%pred)	100±17	93±18	103±14	97±16	.037
FEV ₁ /FVC	0.84±.07	0.79±.09	0.87±.06	0.82±.07	<.001
FEF ₅₀ (L·sec ⁻¹)	3.98±1.63	3.65±1.53	4.12±1.02	3.31±1.01	<.001
DR	.062±.018	.053±.017	.07	.068±.017	.057±.014
Gus	.243±.088	.221±.086	.36	.257±.062	.208±.058

Gus = upstream conductance (L·sec⁻¹·cmH₂O⁻¹), *p*-values for unpaired Student's *t*.

Table 3

Results of logistic regression model adjusting for age and sex. Lower 5 rows' data are peak exercise values.

Independent variable	No EFL	EFL	p-value
FVC (L)	3.91 ± 1.04	3.95 ± 1.17	.71
FVC (%pred)	104 ± 14.8	102 ± 16.6	.76
FEV₁ (L)	3.34 ± 0.84	3.18 ± 0.93	.042
FEV₁ (%pred)	102 ± 14.8	95 ± 16.7	.011
FEV₁/FVC	0.86 ± 0.06	0.81 ± 0.08	<.001
FEF₅₀ (L·sec⁻¹)	4.08 ± 1.20	3.47 ± 1.28	<.001
FEF₅₀ (%pred)	81 ± 23	65 ± 22	<.001
DR	0.067 ± 0.017	0.055 ± 0.015	<.001
Gus	0.25 ± 0.07	0.21 ± 0.07	<.001
peakVO₂ (ml·kg⁻¹·min⁻¹)	34.7 ± 6.8	38.1 ± 8.4	.044
HR (b·min⁻¹)	185±13	186±10	.45
RR (breaths·min⁻¹)	50 ± 12	54 ± 9	.028
V_T/FVC (%)	40±8	43±7	.006
peakVE (L·min⁻¹)	75.4 ± 23.2	91.1 ± 30.4	<.001