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Pitfalls in Expiratory Flow Limitation Assessment at Peak Exercise in Children: Role of Thoracic Gas Compression

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Abstract

Purpose: Thoracic gas compression and exercise-induced bronchodilation can influence the assessment of expiratory flow limitation (EFL) during cardiopulmonary exercise tests. The purpose of this study was to examine the effect of thoracic gas compression and exercise-induced bronchodilation on assessment of EFL in children with and without obesity.

Methods: Forty children (10.7±1.0 years; 27 obese; 15 with EFL) completed pulmonary function tests and incremental exercise tests. Inspiratory capacity maneuvers were performed during the incremental exercise test for placement of tidal flow volume loops within the maximal expiratory flow volume (MEFV) loops and EFL was calculated as the overlap between the tidal and MEFV loops. MEFV loops were plotted with volume measured at the lung using plethysmography (MEFVp), volume measured at the mouth using spirometry concurrent with measurements in the plethysmograph (MEFVm) as well as from spirometry before (MEFVpre) and after (MEFVpost) the incremental exercise test. Only the MEFVp loops were corrected for thoracic gas compression.

Results: Not correcting for thoracic gas compression resulted in incorrect diagnosis of EFL in 23% of children at peak exercise. EFL was 26±15% V_T higher for MEFVm compared with MEFVp (p<0.001), with no differences between children with and without obesity (p=0.833). The difference in EFL estimation using MEFVpre (37±30% V_T) and MEFVpost (31±26% V_T) did not reach statistical significance (p=0.346).

Conclusions: Not correcting the MEFV loops for thoracic gas compression leads to overdiagnosis and overestimation of EFL. Since most commercially available metabolic measurement systems do not correct for thoracic gas compression during spirometry, there may be significant overdiagnosis of expiratory flow limitation in cardiopulmonary exercise testing.

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Conflict of Interest:

Authors declare no conflict of interest. The results of this study are presented clearly, honestly, and without fabrication, falsification, or inappropriate data manipulation. The results of the present study do not constitute endorsement by ACSM.

Therefore, clinicians must exercise caution while interpreting expiratory flow limitation when the MEFV loop is derived through spirometry.

Keywords

pediatric; gas compression; bronchodilation; flow volume curve; ventilatory constraint; breathing mechanics

Introduction:

Fry et. al first noted in 1954 in emphysematous patients that, regardless of the effort exerted by the individual, patients were unable to exceed a certain expiratory flow rate at a given lung volume (1). Based on this observation, expiratory flow limitation (EFL) occurs when tidal expiratory flow reaches maximal expiratory flow and compensatory respiratory muscle effort is unable to increase expiratory flow, thus imposing a mechanical ventilatory constraint (2, 3). During exercise, greater ventilatory requirements can exacerbate EFL, especially in individuals with reduced expiratory flow reserve and those breathing at low lung volumes such as individuals with obesity (4, 5). In addition, when complete expiration is curtailed too early, end-expiratory lung volume (EELV) starts to increase leading to dynamic hyperinflation (4). Since EFL and dynamic hyperinflation can provoke dyspnea, respiratory muscle fatigue, and exercise intolerance (5, 6), they have become important assessments in routine cardiopulmonary exercise testing.

EFL is calculated as the percent overlap between the tidal exercise flow volume and maximal expiratory flow volume (MEFV) loops (7). The MEFV loop is most commonly constructed from expiratory volume measured at the mouth (MEFVm). However, MEFVm loops do not correct for gas compression artifact (8), which is the reduction in lung volume due to pressures applied by static elastic recoil, airway resistance, and increasing expiratory effort (8, 9). As a result, MEFVm loops can underestimate mid flow rates (8) and overestimate EFL (10). Gas compression artifact can be corrected by measuring MEFV loops with a volume displacement plethysmograph (MEFVp) where volumes are measured at the lung instead of at the mouth (8, 10, 11).

Although the link between overestimated EFL with MEFVm has been shown in healthy adults (10–12), it has never before been investigated in children, who experience a high prevalence of EFL (13). In addition, children have lower lung volumes, less elastic recoil (14), and exert less maximum expiratory pressure (15) compared with adults, potentially leading to less thoracic gas compression. Children also have a higher ventilatory demand when compared with adults (16), which increases the risk of EFL. Furthermore, in children with obesity, the mechanical load imposed by adipose tissue exerts an unfavorable burden on the respiratory system leading to low functional residual capacity at rest (17, 18). During exercise, increased metabolic demands combined with expiratory muscle recruitment to increase tidal volume could further lower end-expiratory lung volume and increase the risk of EFL in children with obesity (17, 18). Finally, since EFL is a routinely reported as an indicator of ventilatory constraint during cardiopulmonary exercise testing studies in healthy

and diseased children (13, 18–21), it is critical to estimate the effect of thoracic gas compression on the assessment of EFL in children with and without obesity.

Another factor that can affect the assessment of EFL during exercise is the phenomenon of exercise-induced bronchodilation. Bronchodilation increases forced expiratory flow at 25–75% of forced vital capacity (FEF_{25-75}) in prepubescent children without obesity (13) and may be as important as thoracic gas compression in the assessment of EFL (12). Post-exercise MEFV (MEFV_{post}) measurements can account for exercise-induced bronchodilation. However, it is unclear whether assessment of EFL is affected by bronchodilation in children with and without obesity.

The first purpose of this study was to compare EFL measured at peak exercise from tidal exercise flow volume loops plotted within MEFV_m (i.e., not corrected for gas compression artifact) with MEFV_p (i.e., corrected for gas compression artifact) in children with and without obesity. We hypothesized that MEFV_m would overestimate EFL at peak exercise compared with MEFV_p in children with and without obesity. The second purpose of this study was to compare EFL from MEFV measurements taken pre- and post-exercise in children with and without obesity. We hypothesized that MEFV_{pre}, which does not account for bronchodilation induced by exercise, will overestimate EFL compared with MEFV_{post} in those children with and without obesity who experience bronchodilation. As is typical for most exercise stations, the MEFV_{pre} and MEFV_{post} measurements were not corrected for thoracic gas compression. These data were part of a larger study designed to examine the respiratory effects of obesity in children.

Methods:

The child's parent or guardian provided written, informed consent, and all children provided written assent. The protocol was approved by the UT Southwestern Institutional Review Board (approval #052012–076). Participants were 8 – 12 years old with no history of cardiovascular, metabolic or renal disease. BMI percentile was calculated for each participant using age and sex-specific BMI tables from the Centers for Disease and Control and Prevention (22); obesity was classified as BMI ≥ 95th percentile and without obesity was classified as BMI between the 16 and 84th percentile. Participants completed a Tanner pubertal stage self-assessment (23) and those Tanner stage 4 or higher were excluded. Participants that showed evidence of pulmonary disease (forced expiratory volume in 1 s [FEV₁], FVC, or total lung capacity (TLC) < 80% predicted) or bronchodilator response (increase in FEV₁ ≥ 12% with a minimum volume improvement of 200 mL after 360 mcg of albuterol) were excluded.

Pulmonary Function

Standard spirometry and lung volume determinations were performed according to the guidelines of the American Thoracic Society (24). Predicted values for spirometry and lung volumes were based on the norms from NHANES (25) and Goldman and Becklake (26), respectively. Maximal flow-volume loops (MEFV_m and MEFV_p) were measured in a pressure-corrected volume-displacement body plethysmograph to correct for thoracic gas compression (SensorMedics model 6200, Yorba Linda, CA). Volume (mouth and lung) and

flow (mouth) were exported as text files and graphed using Spike 2 software (Cambridge Electronic Design Limited, Cambridge, England) for overlays with exercise tidal flow volume loops. Volume of gas compressed was assessed by measuring the difference in volume at peak expiratory flow between MEFVm and MEFVp (Figure 1). Percent difference in isovolume FEF₅₀ (isoFEF₅₀) between MEFVm and MEFVp was assessed at 50% of FVC from the MEFVp loop (Figure 1).

Incremental Exercise Test

The incremental exercise test was performed on a cycle ergometer. The initial work rate was 20W and work rate was increased by 15W or 10W increments every minute until volitional exhaustion, with no differences between the two increments for eliciting $\dot{V}O_{2\text{peak}}$ as described previously (27). The protocol included a verification test at 105% of peak work rate as described previously (27). Participants breathed through a mouthpiece connected to a Hans Rudolph valve (Model 2700). Total body O₂ uptake ($\dot{V}O_2$), carbon dioxide production ($\dot{V}CO_2$), and minute ventilation ($\dot{V}_E$) were measured using the Douglas bag technique where expired gases were collected in polyurethane bags. Gas fractions were analyzed by a mass spectrometer (Marquette Electronics, model 1100) and ventilatory volume was measured with a 200L Tissot spirometer.

Expiratory and inspiratory flows were measured at rest and continuously during exercise to obtain tidal volume (V_T), breathing frequency, and exercise tidal flow-volume. Inspiratory flow was measured using a pneumotachograph (Hans Rudolph, Model 4813) and expiratory flows were measured using a heated pneumotachograph (Hans Rudolph, model 3850A). Flow signals were combined into a single bidirectional flow signal (Validyne Buffer Amplifier, model BA112) and digitally integrated to yield volume. Data were collected using the Spike 2 data acquisition and analysis package. Inspiratory capacity (IC) maneuvers were performed at rest and during the last 20 s of each exercise increment by having participants inhale maximally to TLC or a little sooner if the child appeared to be struggling to maintain cadence at the peak exercise stage. Participants performed multiple IC maneuvers during the pulmonary function test and before starting the incremental exercise test. Firm encouragement was provided during each IC maneuver.

MEFV loops were also obtained pre-exercise (i.e., MEFVpre) and within 5 min of terminating exercise (MEFVpost; Mean $\pm$ SD: 2.35 $\pm$ 1.20 min; 95% confidence interval: 1.89 – 2.82 min) while the subjects were seated on the cycle ergometer with the same data acquisition system as the one used during exercise. Since this system also measured volume at the mouth, the MEFVpre and post loops were not corrected for thoracic gas compression. Comparisons of the MEFVm and MEFVpre loops were completed to assess any differences between the SensorMedics system and the custom data acquisition system used for exercise testing, respectively. We report no significant differences in EFL estimation between MEFVm and MEFVpre methods ($P=0.705$), suggesting that the two systems offer similar estimates of EFL.

Data processing

Each file was processed in Spike 2 for drift correction and plotting of MEFV and tidal flow volume loops. First, BTPS correction was applied to the ATPS flow signal to derive BTPS volume and flow. Drift correction was completed by selecting ranges of breaths from start to finish and interpolating between two known volumes (i.e., two consecutive IC's). Each range was usually 60 – 90 s long. If the peak stage IC was the only remaining IC, the file was reprocessed to include the peak stage and the stage prior for the drift correction. If either of the IC's did not reach TLC as noted by inspiratory or expiratory drift, a user-defined drift correction was completed using the best IC. Breaths were marked next using a volume change of 0.1L, minimum interval of 0.2s, and transitions were marked at zero flow. Breath by breath analyses was completed and a report was generated with respiratory parameters including tidal volume, peak flow, IC (i.e., volume from end of each breath to TLC), and duty cycle for each breath in the range. 8 – 12 breaths that were preceding the IC at peak exercise were selected and respiratory parameters were averaged for these breaths. A typical breath was selected and plotted based on duty cycle, V_T , peak flow, extrapolated $\dot{V}_E$, and IC being the most similar to the average of the 8 – 12 breaths. End-expiratory lung volume (EELV) was calculated as TLC – IC.

Expiratory flow limitation

The typical breath was plotted within the MEFV loops and EFL was calculated for each participant and method. EFL was defined as the percentage of V_T (% V_T) where tidal expiratory flow at peak exercise impinged on maximal expiratory flow (7) as shown in Figure 1. Four MEFV loops were compared with typical peak exercise tidal flow volume loops:

1. MEFVp: lung volume obtained from plethysmography; corrected for thoracic gas compression.
2. MEFVm: mouth volume obtained concurrently during plethysmography; not corrected for thoracic gas compression.
3. MEFVpre: mouth volume obtained before the incremental exercise test; not corrected for thoracic gas compression.
4. MEFVpost: mouth volume obtained within 5min of ending the incremental exercise test; not corrected for thoracic gas compression.

The flow volume loop overlay in Spike 2 contained all four MEFV loops (i.e., MEFVm, p, pre, and post) along with the peak exercise tidal flow volume loop. Each MEFV loop was displayed with the peak exercise tidal flow volume loop for assessment of EFL by each method. The traditionally definitive overlay technique for measuring EFL used in this study (28) is very common in most cardiopulmonary exercise testing laboratories (29). It produces reliable and qualitatively similar estimates of expiratory flow limitation when compared with maximal effective pleural pressure (30) and the negative expiratory pressure (31, 32) techniques at high exercise intensities.

Exercise-related bronchodilation

Percent difference in isoFEF₅₀ between MEFV_{pre} and MEFV_{post} was assessed at 50% of FVC from the MEFV_{pre} loop. Percent change in FEV₁ was also calculated between MEFV_{pre} and MEFV_{post}. No children experienced bronchoconstriction (i.e., decrease in FEV₁ of greater than 10%) and one child experienced bronchodilation (i.e., increase in FEV₁ of greater than 12%) after the incremental exercise test (33, 34).

Statistical analysis

All values are expressed as mean $\pm$ SD unless otherwise specified. Data were checked for normality using the Shapiro Wilk test; data were normally distributed. Differences in variables between children with vs. without EFL as well as with vs. without obesity were assessed with a two-way ANOVA. A general linear model with repeated measures was used to detect differences in EFL (% V_T) by method (MEFV_p, MEFV_m, MEFV_{pre}, and MEFV_{post}) and group (with and without obesity), and to examine a group $\times$ method interaction. Posthoc differences by method were determined after applying a Bonferroni correction. Bland-Altman plots were used to examine the agreement between the methods for measurement of EFL (35). Pearson correlations were used to examine associations between variables. Chi square tests were used to detect frequency differences in categorical variables. A P value of 0.05, two tailed, was considered significant. SPSS 20 (IBM, Armonk, NY) was used for analyses.

Based on published data in adults (12), a sample size of 9 individuals would allow detection of a significant difference in EFL estimation between methods that correct vs. don't correct for thoracic gas compression with a power of 0.82 and type 1 error of 0.05 (two dependent samples t-test). Based on published data in adults (12), a sample size of 7 individuals would allow detection of a significant difference in EFL estimation between pre and post-exercise MEFV loops that were not corrected for thoracic gas compression with a power of 0.86 and type 1 error of 0.05 (two dependent samples t-test). A total sample of 11 individuals would allow detection of a significant group $\times$ method interaction with a power of 0.80 and type 1 error of 0.05 for a moderate effect size (Cohen's $f = 0.25$) and assuming strong correlation between repeated measures ($r = 0.79$) based on published data in adults (12).

Results:

Forty children were included in the analyses after exclusions (Figure 2), 13 without obesity and 27 with obesity. After correcting the MEFV loop for thoracic gas compression (i.e., MEFV_p), 15 children experienced EFL at peak exercise (true positives) and 25 children experienced no EFL (Table 1). FEF₂₅₋₇₅ and FEV₁/FVC were lower in children with EFL compared with those without EFL (Table 1). There were no statistically significant differences in the age, BMI z-score, and other pulmonary function variables between participants with and without EFL (Table 1). Children with obesity had a lower functional residual capacity as a % of total lung capacity when compared with children without obesity (Table 1). $\dot{V}_E$ and V_T were higher in those children without obesity who experienced EFL when compared with those children without obesity who did not experience EFL (Table 1).

Effect of thoracic gas compression on EFL estimation

There were no significant differences between children without and with obesity in volume of thoracic gas compression (237 ± 108 vs. 248 ± 111 mL, respectively; $P = 0.949$) or difference in isoFEF₅₀ between MEFVm and MEFVp (without obesity: 12.1 ± 6.4 , with obesity: 14.3 ± 6.4 ; $P = 0.260$). There were no significant differences between children without and with obesity from pre to post exercise in isoFEF₅₀ (-2.8 ± 21.1 vs. 1.9 ± 10.6 %; $P = 0.700$) and FEV₁ (-0.08 ± 4.5 vs. 0.35 ± 4.7 %; $P = 0.724$). Table 1 also shows that there were no differences in thoracic gas compression or bronchodilation from pre to post exercise between children with vs. without EFL and no obesity $\times$ EFL status interaction.

We did not detect statistical differences for the volume of gas compressed between MEFVm and MEFVp between children who were false positives (N=9) and children who were true positives (N=15; 293 ± 94 mL and 263 ± 131 mL, respectively; $P = 0.572$). We also did not detect statistical differences in isoFEF₅₀ between MEFVm and MEFVp between children who were false positives vs. true positives (16.9 ± 4.8 and 14.2 ± 7.4 %, respectively; $P = 0.332$). However, the difference in EFL between the MEFVm and MEFVp methods was associated with volume of gas compression ($r = 0.407$; $P = 0.049$; N=24).

There were no statistical differences in the magnitude of EFL between children with and without obesity at peak exercise (Table 1). Table 2 shows individual data for EFL estimation by each method. There was no significant main effect of group (i.e., with vs. without obesity) and no significant group $\times$ method (i.e., MEFVp, m, pre, and post) interaction in EFL estimation. 60% (N=24) of children experienced EFL (i.e., tidal flow-volume overlap with MEFV loop at peak exercise) as measured by MEFVm and 37% (N=15) as measured by MEFVp, showing that 23% of children were falsely diagnosed with EFL using MEFVm.

Posthoc differences between the four methods of EFL estimation were assessed and reported in Figure 3. MEFVm, which does not correct for thoracic gas compression, overestimated the degree of EFL by $26 \pm 15\%$ V_T when compared with MEFVp, which does correct for thoracic gas compression ($P < 0.001$). Figure 3A shows average and individual data for differences between MEFVm and MEFVp for true positives (N=15) and Figure 3B shows data only from MEFVm for false positives (N=9; MEFVp = 0 in these cases). Differences between MEFVp and MEFVpre (pre-exercise; not corrected for thoracic gas compression; $20 \pm 25\%$ V_T) did not reach statistical significance ($P = 0.215$; Figure 3C).

Effect of exercise-induced bronchodilation on EFL estimation

Complete data for MEFVpre and MEFVpost were available in 29 children (Figure 2). 17 of 29 children experienced EFL in either MEFVpre or MEFVpost overlays. MEFVpre and MEFVpost methods did not differ statistically in their measurement of EFL ($P = 0.280$; Figure 3D). The difference in isoFEF₅₀ between MEFVpre and MEFVpost was inversely and moderately correlated with the difference in EFL between these two methods ($r = -0.494$; $P = 0.044$; N = 17).

Bland-Altman analysis

Bland-Altman analysis showed an overestimation bias and wide limits of agreement for assessment of EFL with MEFV_m compared with MEFV_p with no proportional bias (Figure 4A). Figures 3B and 4B show that, when MEFV loops are not corrected for thoracic gas compression, most false positives occur below an EFL threshold of 40% V_T . Only one false positive case had an EFL estimation above 40% V_T . Similarly, MEFV_{pre} and MEFV_{post}, which were both not corrected for thoracic gas compression, demonstrated an overestimation bias compared with MEFV_p for assessment of EFL (Figure 4C and 4D); overestimation error from MEFV_{pre} was higher than MEFV_{post} likely due to bronchodilation after exercise in some participants.

Discussion:

To the best of our knowledge, this is the first study to show that EFL can be significantly overestimated when the MEFV loop is not corrected for thoracic gas compression in children with and without obesity. EFL is a mechanical ventilatory constraint, potentially associated with dynamic hyperinflation, dyspnea, and exercise tolerance (36). Since EFL has been the focus of numerous studies in children (13, 18–21), accurate assessment of EFL is critical during cardiopulmonary exercise testing. Although it has been long established that thoracic gas compression can affect the measurement of EFL in children and young adults (11), previous studies examining EFL in children have not corrected for thoracic gas compression (13, 18–21). We show that EFL can be overestimated by $\approx 26\%$ in children, when the MEFV loop is not corrected for thoracic gas compression. This magnitude of overestimation can significantly affect the interpretation of clinical exercise tests. Furthermore, we showed that the change in EFL from pre to post exercise was inversely associated with change in isoFEF₅₀, suggesting that exercise-induced bronchodilation may also play a role in the determination of EFL in children.

Thoracic gas compression

Coates et. al (11) investigated the difference in thoracic gas compression on mid flows in children and young adults with and without airflow obstruction. The largest errors in FEF₅₀ between MEFV loops not corrected vs. corrected for gas compression artifact were noted in individuals who were able to generate the highest pleural pressures and had the lowest FEF₅₀ (i.e., those with airflow limitation) (11). The authors suggested that MEFV_m could offer valid volume related flow rates only in individuals with no significant airflow limitation. In the current study, isoFEF₅₀ was 14% higher after correction for gas compression artifact in children without airflow limitation. As a result, EFL was overestimated by $\approx 26\% V_T$ and misdiagnosed in 23% of children when MEFV_m loops were utilized. In addition, there was a moderate association between the overestimation of EFL by MEFV_m compared with EFL by MEFV_p and the volume of gas compression observed during the MEFV maneuver.

The effect of thoracic gas compression on EFL was greater in children (i.e., $26\% V_T$ difference between MEFV_m and MEFV_p methods) than previously demonstrated in adults (i.e., $19\% V_T$) (12). The study in adults (12) attempted to correct for thoracic gas

compression by using graded effort loops. This method is performed by having participants complete maximal expirations at different volumes from total lung capacity to residual volume. The current study utilized a volume displacement plethysmograph, which directly corrects for thoracic gas compression and thus offers a more accurate assessment for the effect of thoracic gas compression on EFL. The largest difference in the current study was seen in one child who showed a 60% overestimation of EFL by MEFVm (65%) when compared with MEFVp (5%).

There is no consensus regarding a specific threshold for “significant” EFL during pediatric cardiopulmonary exercise testing. In adults, Johnson et al defined EFL as “significant” when overlap between tidal flow-volume and MEFV loops was 40 – 50% V_T , while also suggesting correction for thoracic gas compression (37). In children, Swain et al (13) and Pianosi and Smith (21) have used a “threshold” of 5% V_T overlap between tidal flow-volume and MEFV loops for defining EFL without correcting for thoracic gas compression. The current study, which did not use a specific EFL threshold but rather dichotomized presence or absence of EFL and reported the magnitude of EFL as % V_T for each method, showed that the average overestimation of EFL using MEFVm was $\approx 26\% V_T$. These data suggest that a threshold of 5% V_T is certainly too low when using MEFVm loops and could lead to overdiagnoses of ventilatory limitations. We also show that false positives occurred at an EFL of less than 40% V_T in all but one case. Therefore, in a clinical setting, an EFL of greater than 40% could be a more conservative and appropriate threshold rather than 5% V_T when it is not possible to correct the MEFV loop for thoracic gas compression. It should be noted that this proposed threshold is based on exercise tidal volume loop overlap with the resting MEFVm loop. Therefore, this threshold may not apply for children who experience significant exercise-induced bronchodilation, which could theoretically affect both thoracic gas compression and the magnitude of EFL assessed using post-exercise compression corrected or uncorrected MEFV loops.

Exercise-related Bronchodilation

In adults, Guenette et al. (12) reported a difference in EFL of 23% V_T between MEFVpre and MEFVpost methods, with both methods not corrected for thoracic gas compression. MEFVpost loops were completed approximately 1 – 2 min after the incremental exercise test in Guenette et al (12). When graded effort MEFV loops were used in an attempt to correct for thoracic gas compression, they determined that the overestimation of EFL was 28% V_T (12). Although there was no significant decrease in EFL (% V_T) from MEFVpre to MEFVpost in the current study, the decrease in EFL (% V_T) from MEFVpre to MEFVpost was correlated with the increase in isoFEF₅₀, suggesting that exercise-induced bronchodilation can influence the measurement and interpretation of EFL in children.

The time course of exercise-induced bronchodilation in non-asthmatic children who exhibit low bronchial lability (38) is unclear. Previous studies have reported improvements in mid flows (i.e., FEF₅₀) during (39) or immediately after (30) an incremental exercise test in non-asthmatic adults. In contrast, Johnson et al (40) reported no change in MEFV loops from pre-exercise to immediately and 5 min after exercise in non-asthmatic adults. MEFVpost loops in the current study were completed 2.35 ± 1.20 min after volitional exhaustion during

the incremental exercise test, with 80% of MEFVpost loops completed within 3 min of ending the test. In some cases, the need for repeated efforts increased the time between ending the test and acquiring an MEFVpost loop. We cannot exclude the possibility that our timing of MEFVpost loops could have missed bronchodilation that resolved very rapidly with the cessation of exercise. Furthermore, exercise-induced bronchoconstriction could occur anytime from 2 – 30 min post exercise in children (34). Our ability to detect exercise-induced bronchoconstriction, if any, was also limited, but this should not affect the measurement of EFL *during exercise*. Future studies are needed to clarify the time course of exercise-induced bronchodilation or bronchoconstriction and the optimal timing, number, and feasibility of post-exercise MEFV loops in non-asthmatic children with and without obesity.

EFL and Obesity

EFL has been reported in 55 – 90% of pre-pubescent children without obesity (13, 20). Mendelson et al reported EFL in 50% of children with obesity at peak exercise compared with no prevalence of EFL in children without obesity (17). In the current study, 44% of children with obesity experienced EFL at peak exercise compared with 23% of children without obesity, with no statistical differences observed in the magnitude of EFL (% V_T) between children with and without obesity. Previous studies in children (13, 17, 20) did not correct for thoracic gas compression, which could have led to overestimation of EFL. In addition, changes in lung size (41) and ventilatory responses to exercise (42) with growth and development could explain differences in EFL noted between children of different ages.

Methodological considerations

Most commercially available pulmonary and metabolic measurement systems do not plot MEFV loops with volumes measured at the lung (i.e., MEFVp). In addition, even when a plethysmograph is available and it is able to plot MEFV loops with volumes measured at the lung, there are often limited options for overlaying these MEFVp loops with exercise tidal flow volume loops for accurate EFL assessment. The current study is novel because of the ability to measure volumes at the lung and to overlay MEFV loops from the plethysmograph with flow-volume loops before, during, and after exercise. Although MEFVm and MEFVpre measurements were completed on two different systems, they offered fairly similar “over” estimates of EFL. In clinical settings where spirometry is easily available for MEFV loops pre- and post-exercise, considering the influence of thoracic gas compression on EFL assessment during interpretation of mechanical ventilatory constraints is recommended.

Limitations

The study was limited by its sample size (N=40), specifically in the sample of children who experienced “true” EFL (N=15). Our small sample size was, in part, due to the exclusion of 32 children from the initial sample because they had taken 360µg of albuterol prior to the incremental exercise test. To eliminate confounding in the measurement of EFL due to the increase in mid-flow rates after albuterol, all children who were given albuterol prior to the incremental exercise test were excluded from the study.

Previous reports showed no significant change in TLC with exercise in adults (43–45) and therefore, in the current study, we placed tidal volume loops within MEFV loops based on changes in IC during peak exercise. However, whether TLC changes significantly during exercise in children with and without obesity remains unknown and should be studied.

Although we were unable to explore sex differences due to the sample size, we did find that the volume of thoracic gas compression was greater in boys compared with girls (296 ± 99 vs. 191 ± 91 mL, $P = 0.001$). This could be attributable to higher expiratory pressures that boys are able to generate (predicted maximal expiratory pressure boys: 96 ± 4 vs. girls: 74 ± 7 mmHg; $P < 0.001$). We did not find differences in isoFEF₅₀ between MEFV_m and MEFV_p loops between boys and girls ($P = 0.979$). Thus, sex differences in estimation of EFL using compression corrected vs. uncorrected MEFV loops need to be explored further in children. Despite these limitations, the results from this study could be useful for assessment and interpretation of EFL during routine cardiopulmonary exercise testing in 8 – 12-year-old children with and without obesity.

Conclusions

EFL is significantly overestimated and misdiagnosed when thoracic gas compression is not corrected for in children. There are moderate associations between the volume of thoracic gas compression as well as the increase in mid-flows with exercise-induced bronchodilation and the overestimation of EFL. If pre-exercise MEFV loops are utilized for assessment of EFL during routine cardiopulmonary exercise testing and the MEFV loops cannot be corrected for thoracic gas compression, $EFL > 40\% V_T$ may be used as a reasonable clinical threshold for “true” EFL in children, assuming that there is no significant exercise-induced bronchodilation. Since correction for thoracic gas compression and exercise-induced bronchodilation would be ideal in cardiopulmonary exercise tests, clinical interpretation of EFL assessments without these corrections should be made with caution in children.

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Figure 1:

Maximal expiratory flow volume (MEFV) loops with volume assessed at the lung with a plethysmograph MEFVp (dashed line), volume assessed at the mouth with spirometry MEFVm (solid line), and peak exercise tidal flow volume loop (dotted line) for a single participant. Illustrations of assessment of thoracic gas compression, difference in isovolume forced expiratory flow at 50% of forced vital capacity (isoFEF₅₀), and expiratory flow limitation (EFL) are provided.

Figure 2:

Participant flowchart. PFT: pulmonary function test, INCR: incremental exercise test, MEFV: maximal expiratory flow volume loop, MEFVm: volume measured at the mouth, MEFVp: volume measured with a volume displacement plethysmograph, MEFVpre: pre-exercise, MEFVpost: post-exercise.

Figure 3:

Differences in expiratory flow limitation (EFL) assessed using (A) Maximal expiratory flow volume (MEFV) loops with volume assessed at the lung with a plethysmograph MEFVp and volume assessed at the mouth with spirometry MEFVm for "true positives", (B) MEFVm for "false positives" (i.e., zero EFL for MEFVp), (C) MEFVp and pre-exercise MEFVpre, and (D) MEFVpre and post-exercise MEFVpost. Plus sign represents mean, top and bottom of box represent interquartile range, error bars represent minimum to maximum, and individual data are plotted as symbols. *indicates statistical difference $p < 0.05$.

Figure 4:

Bland Altman plots with different symbols for children correctly diagnosed (true positives) and misdiagnosed (false positive): (A) comparing expiratory flow limitation (EFL) assessed using maximal expiratory flow volume (MEFV) loops with volume assessed at the lung with a plethysmograph MEFVp and volume assessed at the mouth with spirometry MEFVm, (B) MEFVm plotted on the X axis to demonstrate individual data from false positive cases that could help detect an EFL threshold above which an EFL diagnosis can be made with confidence if correction for thoracic gas compression is not possible. (C) comparing EFL assessed using MEFVp and pre-exercise MEFVpre, and (D) comparing EFL assessed using MEFVp and pre-exercise MEFVpost. Difference between methods plotted on the Y axis and average of methods plotted on the X axis.

Table 1:

Participant characteristics presented for children with and without obesity as well as with and without expiratory flow limitation (EFL). EFL status was based on overlap between peak exercise tidal volume loop and maximal expiratory flow volume loop measured by the plethysmograph (MEFVp).

	Without Obesity			With Obesity		P Value		
	Without EFL (N=10)	With EFL (N=3)	Without EFL (N=15)	With EFL (N=12)	Obesity Status	EFL Status	Interaction	
Boys/Girls (N)								
Tanner Stage (1, 2, 3; N)	4/6	3/0	7/8	8/4	0.071	0.919		
Age (year)								
	2/6/2	0/1/2	3/6/6	3/4/5	0.603	0.600		
Height (cm)								
	10.5 ± 0.7	11.3 ± 1.4	10.5 ± 1	10.7 ± 1.2	0.220	0.447		0.436
Weight (kg)								
	142.0 ± 6.1	153.9 ± 8.9	146.5 ± 6.8	148.0 ± 8.2	0.813	0.021		0.067
BMI (kg·m⁻²)								
	34.4 ± 2.8	42.4 ± 7.6	58.6 ± 14.7	64.9 ± 19.2	<0.001	0.195		0.876
BMI % of the 95thile								
	17.1 ± 1.0	17.8 ± 1.2	26.9 ± 4.5	29.1 ± 6.0	<0.001	0.396		0.663
BMI z-score								
	74 ± 6	76 ± 3	117 ± 17	126 ± 22	<0.001	0.404		0.586
Pulmonary Function								
	-0.02 ± 0.59	0.15 ± 0.28	2.02 ± 0.45	2.19 ± 0.35	<0.001	0.320		0.999
FVC (L)								
	2.52 ± 0.39	3.05 ± 0.73	2.73 ± 0.52	2.89 ± 0.66	0.915	0.109		0.391
FVC (% Predicted)								
	104 ± 10	102 ± 2	107 ± 8	109 ± 12	0.190	0.951		0.575
FEV₁ (L)								
	2.22 ± 0.32	2.45 ± 0.62	2.33 ± 0.47	2.34 ± 0.53	0.999	0.520		0.545
FEV₁ (% Predicted)								
	104 ± 8	95 ± 7	106 ± 10	101 ± 12	0.355	0.105		0.557
FEV₁/FVC								
	89 ± 5	80 ± 3	87 ± 4	81 ± 3	0.683	<0.001		0.398
FEF₂₅₋₇₅ (L/s)								
	2.72 ± 0.57	2.28 ± 0.7	2.73 ± 0.64	2.30 ± 0.58	0.957	0.070		0.989
FEF₂₅₋₇₅ (% Predicted)								
	107 ± 21	82 ± 16	107 ± 22	86 ± 17	0.778	0.005		0.821
TLC (L)								
	3.11 ± 0.48	3.69 ± 0.72	3.35 ± 0.59	3.68 ± 0.86	0.642	0.084		0.621
TLC (% Predicted)								
	95 ± 8	96 ± 5	97 ± 8	104 ± 15	0.161	0.278		0.467
IC (L)								
	1.68 ± 0.41	1.91 ± 0.42	2.13 ± 0.53	2.21 ± 0.58	0.067	0.435		0.716
FRC (% TLC)								
	46 ± 8	48 ± 7	37 ± 8	40 ± 7	0.005	0.423		0.861
Maximal Exercise Test								
V_E (L/min)								
	54.7 ± 10.8	78.5 ± 9.9	58.5 ± 9.5	60.6 ± 14.7	0.122	0.006		0.020
f_R (bpm)								
	58 ± 12	60 ± 15	61 ± 15	58 ± 12	0.901	0.902		0.681
V_T (L)								
	0.96 ± 0.17	1.37 ± 0.39	1.01 ± 0.25	1.05 ± 0.20	0.132	0.013		0.042
V_T (%FVC)								
	38 ± 6	45 ± 4	37 ± 5	37 ± 4	0.018	0.098		0.108

	Without Obesity			With Obesity		P Value		
	Without EFL (N=10)	With EFL (N=3)	Without EFL (N=15)	With EFL (N=12)	Obesity Status	EFL Status	Interaction	
IC (L)	1.61 ± 0.3	2.03 ± 0.67	1.86 ± 0.38	2.08 ± 0.53	0.376	0.061	0.526	
EELV (%TLC)	48 ± 4	46 ± 9	45 ± 4	44 ± 5	0.110	0.349	0.660	
EFL (%V_T)	0 ± 0	30.5 ± 22.6	0 ± 0	33.8 ± 25.0	0.771			
<i>Thoracic gas compression (MEFV_p vs. MEFV_m)</i>								
Volume difference at peak flow (mL)	223 ± 102	281 ± 140	241 ± 91	259 ± 135	0.949	0.377	0.642	
isoFEF₅₀ difference (%)	12.7 ± 5.5	10.3 ± 10.2	13.6 ± 6.3	15.1 ± 6.7	0.260	0.875	0.445	
<i>Pre to Post exercise *</i>								
isoFEF₅₀ (%)	-9.5 ± 24.7	8.2 ± 6.0	2.8 ± 11.5	0.5 ± 9.5	0.700	0.205	0.102	
FEV₁ (%)	0.72 ± 3.71	-1.40 ± 6.28	0.20 ± 4.41	0.59 ± 5.42	0.724	0.677	0.547	

BMI: body mass index, FVC: forced vital capacity, FEV₁: forced expiratory volume in 1s, isoFEF: isovolume forced expiratory flow, V_E: minute ventilation, fB: breathing frequency, V_T: tidal volume, MEFV_p: maximal expiratory flow volume curve where volume was measured at the lung with a plethysmograph, MEFV_m: MEFV curve where volume was measured at the mouth with a spirometer.

* n=5 (without obesity and without EFL),
n=3 (without obesity and with EFL), n=13 (with obesity and without EFL), n=8 (with obesity and with EFL)

Table 2:

Individual data showing expiratory flow limitation measurements as a percent of tidal volume calculated from four different maximal expiratory flow volume (MEFV) loops with peak exercise tidal flow volume loop overlays. The four MEFV loops were: m = volume at the mouth during the pulmonary function test, p = volume at the lung using a plethysmograph during the pulmonary function test, pre = volume at the mouth before starting the incremental exercise test, and post = volume at the mouth after completing the incremental exercise test.

Subject	Group	Sex	MEFVm	MEFVp	MEFVpre*	MEFVpost*
1	Nonobese	F	0	0	-	-
2	Nonobese	F	0	0	0	0
3	Nonobese	F	0	0	0	0
4	Nonobese	F	0	0	-	18.6
5	Nonobese	F	0	0	0	-
6	Nonobese	F	0	0	0	0
7	Nonobese	M	0	0	12.3	1.1
8	Nonobese	M	0	0	-	-
9	Nonobese	M	12.8	0	0	0
10	Nonobese	M	24.8	0	50.5	-
11	Nonobese	M	59.7	47.7	37.4	0.0
12	Nonobese	M	62.2	38.8	57.0	55.1
13	Nonobese	M	65.2	4.9	64.8	20.0
14	Obese	F	0	0	0	-
15	Obese	F	0	0	4.2	23.1
16	Obese	F	0	0	0	0
17	Obese	F	0	0	0	0
18	Obese	F	25.5	5.5	8.1	7.2
19	Obese	F	30.8	0	22.9	26.1
20	Obese	F	31.2	0	0	0
21	Obese	F	51.5	34.5	0	33.0
22	Obese	F	53.0	0	0	0
23	Obese	F	58.1	32.7	53.2	50.0
24	Obese	F	85.5	72.7	83.5	82.5
25	Obese	M	0	0	0.5	0
26	Obese	M	0	0	0	0
27	Obese	M	0	0	0	2.8
28	Obese	M	0	0	0	0
29	Obese	M	5.2	0	0	0
30	Obese	M	17.6	8.1	-	-
31	Obese	M	26.1	16.7	20.6	26.2
32	Obese	M	33.8	0	60.3	40.6
33	Obese	M	34.4	0	0	-
34	Obese	M	37.3	15.8	49.9	-

Subject	Group	Sex	MEFVm	MEFVp	MEFVpre [*]	MEFVpost [*]
35	Obese	M	38.1	0	0	0
36	Obese	M	52.1	22.7	42.1	54.2
37	Obese	M	72.7	16.3	81.0	35.5
38	Obese	M	73.1	55.4	75.3	80.6
39	Obese	M	75.6	43.1	-	-
40	Obese	M	88.5	81.7	-	88.3

F = female, M = male;

^{*} six pre and nine post MEFV loops were excluded because of poor effort and are denoted by “-”