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TITLE

Lung Mechanical Properties Distinguish Children with Asthma with Normal and Diminished Lung Function

RUNNING TITLE

Lung Mechanical Properties in Pediatric Asthma

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ABSTRACT

Background: Children with asthma, even those with severe persistent disease, can have forced expiratory volume in 1 second (FEV₁) values $\geq 100\%$ of predicted, while others have diminished FEV₁.

Objective: We sought to characterize the lung mechanical properties underlying these two asthma phenotypes and the mechanisms explaining the paradox of severe asthmatic children, whom when clinically stable can have an FEV₁ $> 100\%$ of predicted, but during an acute bronchospastic episode can experience a life-threatening asthma event.

Methods: Lung mechanics were evaluated in three groups of children: asthmatics with FEV₁ $\geq 100\%$ (HFEV₁; n=13), asthmatics with FEV₁ $\leq 80\%$ (LFEV₁; n=14), and non-asthmatic controls (n=10). A linear mixed model was used to examine the relationship between volume and static transpulmonary pressures obtained at total lung capacity (TLC); actual TLC % predicted and flow; and static transpulmonary pressure and flow.

Results: HFEV₁ asthmatics had larger airways (FEV₁ z-scores 1.12 vs. -2.37; $p < 0.05$), greater lung volumes (mean % predicted TLC 134.8 vs. 109.6%; $p < 0.05$) and lower airway resistance (mean % predicted Raw 101.9 vs. 199.9%; $p < 0.05$) compared to the LFEV₁ group. Moreover, HFEV₁ asthmatics had significantly reduced elastic recoil pressure (pressure-volume curve shifted upward and to the left) and higher lung compliance (0.21 vs. 0.09 L/cm H₂O; $p < 0.05$) compared to the LFEV₁ group. The pressure-flow curves revealed the LFEV₁ group to have significantly increased resistance to flow in the upstream segment of the airways at all lung volumes studied compared to HFEV₁.

Conclusion and Clinical Relevance: HFEV₁ asthmatic children display distinct lung mechanical properties compared to their LFEV₁ asthmatic peers. With loss of elastic recoil pressure, the HFEV₁ group could generate normal FEV₁ due to proportionally enlarged airways and reduced airway resistance, while airflow limitation in the LFEV₁ is due to increased airway resistance. Loss of elastic recoil and interdependence during acute bronchoconstriction episodes may predispose the HFEV₁ group to catastrophic reductions in airflow.

KEYWORDS

ABBREVIATIONS

FVC: Forced vital capacity

FEV₁: Forced expiratory volume at 1 second

FEV₁/FVC: Ratio of the forced expiratory volume at 1 second to the forced vital capacity

FEF₂₅₋₇₅: Forced expiratory flow between 25% and 75% of vital capacity

FRC: Functional residual capacity

GLI: Global Lung Function Initiative

HFEV₁ Group: Asthmatic children with baseline FEV₁ values >100%

LF_{FEV₁} Group: Asthmatic children with baseline FEV₁ values <80%

PV curve: Pressure to Volume curve

Raw: airway resistance measured at FRC

RV: Residual volume

R_{us}: Upstream resistance

SGaw: specific airway conductance

TLC: total lung capacity

1. INTRODUCTION

It is now recognized that many children with persistent asthma have forced expiratory volume in 1 second (FEV₁) values well within the normal range (1-6). In earlier studies, 28-49% of asthmatic children had FEV₁ > 100% of predicted (1-3). In contrast, only 14.8% of 12,844 adults studied had FEV₁ values of > 100% of predicted, and their mean FEV₁ was 75.6% of predicted (2). Bacharier et al. reported mean FEV₁ values of 97%, 101%, and 94% of predicted in those with mild, moderate, and severe persistent asthma, respectively, suggesting that even children with severe asthma could have normal FEV₁ values when clinically stable (3). Recent studies in children with severe asthma have confirmed these original observations. The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens (TENOR) study found that 66% of children aged 6-12 with severe or difficult to control asthma had normal FEV₁ values ($\geq 80\%$), compared to only 41% of adults (4). Among children participating in the cluster analysis of the Severe Asthma Research Program (SARP) (5), those grouped in clusters 1 and 2 had normal lung function with mean FEV₁ values of > 90% of predicted, while those in clusters 3 and 4 had mild or advanced airflow limitation and mean FEV₁ of 84% and 75% of predicted, respectively (5). Similarly, in a recent extensive cohort of uncontrolled severe asthmatics diagnosed by the ERS/ATS 2014 criteria, children had a mean FEV₁ of 85% of predicted whereas adults had a mean FEV₁ of 59% of predicted (6).

Taken together, these studies highlight important differences in lung function between children and adults and emphasize the relative lack of correlation in children between asthma severity and FEV₁. Further, these studies identify what appears to be a distinct phenotype of persistent asthma in children that is characterized by FEV₁ values of at least 100% of predicted. The findings of high FEV₁ values even in some children with severe asthma suggest that they can maintain “normal” airflow despite severe persistent disease. This is of significant clinical interest as these patients are at greater risk of being under-treated when compared to severe asthmatic children with diminished FEV₁ values (7). Indeed, at our institution, we observed a subgroup of children with severe asthma and FEV₁ values of > 100% of predicted (and normal FEV₁/FVC ratios), who had histories of severe exacerbations, some that had required intubation and mechanical ventilation.

Little is known about the mechanisms underlying this phenotype of childhood asthma characterized by normal lung function. As a result, we sought to characterize the lung mechanical

properties in this group of patients compared to asthmatic children with diminished FEV₁ values, and to identify the physiological mechanisms that could explain the paradox of severe asthmatic children, whom when clinically stable can have an FEV₁ >100% of predicted, but during an acute bronchospastic episode can experience a life-threatening asthma event.

2. METHODS

2.1 Study Population

Thirty-seven children (8-18 years of age) participated in this study. Ten healthy children without a diagnosis or history of asthma served as the control group (Control), while the remaining 27 were children with stable asthma having one of two distinct phenotypes based on baseline FEV₁ % of predicted values. Children were eligible for participation in the study if they had a baseline FEV₁ while clinically stable of $\leq 80\%$ of predicted (LFEV₁ group), or an FEV₁ value of $\geq 100\%$ of predicted (HFEV₁ group). The asthmatic children had to have a physician diagnosis of asthma and were required to have had either a positive methacholine challenge (PC₂₀ of ≤ 8 mg/ml) or documented beta-agonist reversibility ($\geq 12\%$ improvement in FEV₁ following inhalation of 200 mcg of albuterol). All subjects were studied during a symptom-free interval. The participants were enrolled from February 2003 to December 2009. Asthmatics were recruited from the Day Program Unit and the outpatient clinic at the National Jewish Health (Denver, USA), while normal controls were recruited from the community. Subjects were excluded if there was a history of chronic lung disease, viral infection within four weeks of enrollment, or an acute exacerbation of asthma within four weeks of entry. The children with asthma also completed a screening questionnaire designed to determine asthma severity based on NHLBI guidelines and medication usage (8). The study was approved by the National Jewish Health Institutional Review Board with written consent and assent obtained from each subject prior to enrollment.

2.2 Procedures

Lung function studies including flow-volume relationships, lung volume, airway resistance, and specific conductance were performed using a volume displacement, pressure compensated plethysmograph (Jaeger MasterScreen Body, Erich Jaeger Inc, Germany) by trained technicians with expertise in performing pediatric lung function measurements. Baseline and post-bronchodilator measurements for the lung function studies were obtained.

The volume-pressure relationship of the lungs was determined while the subject was seated in the body plethysmograph. Each subject performed a minimum of 3 acceptable, repeatable maneuvers of maximum inspiratory efforts followed by passive exhalation. The maximum expiratory flow was measured by having the subject inhale to total lung capacity (TLC), and forcibly exhale for ≥ 6 seconds until the patient reached his/her residual volume (RV) (9). Static transpulmonary pressures (esophagus-mouth differential pressures in cm H₂O) were determined while flow was interrupted by a solenoid-operated shutter at differing lung volumes during a slow maximal expiration from total lung capacity (TLC). Esophageal pressure was recorded from a 10 cm latex balloon on the end of a small polyethylene catheter that was positioned in the mid-esophagus below the tracheal bifurcation and connected to a differential strain gauge (10). A constant volume history was assured by having the subject inspire to TLC three times prior to the measurement of the volume-pressure relationship. Pressure-Volume (PV) data points from several efforts were generated and all the points were plotted on one graph. Static and quasi-static pressure-volume curves were evaluated by an exponential fit to the equation $V = A - B \cdot e^{(-K \cdot P)}$, where V is absolute lung volume from transmural flow, (a TGV maneuver was performed with this test), A is the volume when the pressure is infinite, B is the volume at zero recoil pressure, K depicts the overall compliance of the lungs, and P is transpulmonary pressure. K, the shape constant (unit/cm H₂O, %) was measured using the exponential expression of the PV curve first described by Salazar and Knowles (11) and later modified by Colbatch and Nikov (12) and compliance (L/cm H₂O) were also recorded, with predicted values based on Zapletal et al. (13). Pressure-flow curves were generated by integrating the information from maximum expiratory flow-volume curves measured in the plethysmograph and the transpulmonary pressures at equivalent volumes. Iso-volume flow rates were calculated by having each subject perform 3 forced maximal expiratory maneuvers. Flow was interpolated from the generated flow-volume curve where flow was measured at 30, 45, 60, 75 and 90% of the patient's TLC. Lung compliance was calculated from

simultaneous volume and intra-esophageal pressure changes at points of zero flow from 60 to 70% of each patient's TLC (13). The upstream resistance (R_{us}) was determined to estimate disease in airways distal (upstream) to the equal pressure point and it was calculated using the same volume source as the PV curve, transmural flow, by measuring transpulmonary pressure at a low flow rate (rate <0.5 liters/sec) (14).

The primary lung volume used for these analyses was TLC expressed as a % of predicted values (based on sex, race, height) (9). The data were expressed as % of predicted using the NHANES III reference values (15). To validate measurements of airflow limitation and reduce age and ethnicity bias, spirometric values were also analyzed and expressed in z-scores and percentiles based on the Global Lung Function Initiative (GLI) 2012 (16,17). Calculation of airway resistance (R_{aw}) and specific airway conductance (SG_{aw}) was based on equations adapted from Zapletal et al (18).

2.3 Statistical analyses

The characteristics of each group were summarized using descriptive statistics and compared across the groups using analysis of variance (ANOVA) for continuous measures and Fisher's exact test for categorical measures. When overall ANOVA tests were significant, pairwise comparisons were made using Tukey's HSD method. A linear mixed model was run to examine the relationship between TLC% of predicted values and static transpulmonary pressures obtained at defined cutoffs (60, 75, 90, and 100%) of the subject's TLC. To account for the repeated measures within each subject, a spatial power covariance structure was used. The predictors of interest in the linear mixed models were group (HFEV₁, LFEV₁ or Control), categorical % of patients' TLC (60, 75, 95 or 100%), TLC% of predicted values, corresponding two-way interactions (group*TLC%, group*categorical % of patient's TLC, TLC%*categorical % of patients' TLC) and the three-way interaction (group*TLC%*categorical TLC%). The outcome of interest was static transpulmonary pressure. Insignificant interaction terms were not removed from the model in order to allow for model flexibility. Similar linear mixed models were run for actual TLC% of predicted and flow, and static

transpulmonary pressure and flow. Flow was natural log-transformed in the models. All models allowed for random intercepts by subject. Analyses were carried out at the 0.05 significance level, and all hypothesis tests were two-tailed. Analyses were conducted with SAS version 9.3, and plots were generated with R version 3.0.2.

3. RESULTS

HFEV₁, LFEV₁, and Control groups were similar with respect to age, sex, race, and height, although both asthmatic groups tended to be younger and shorter than the Control group (**Table 1**). Both groups of asthmatics were on a high inhaled corticosteroid (ICS) dose based on the NHLBI guidelines (8), with the LFEV₁ asthmatics being on significantly higher dose than the HFEV₁. However, duration and prevalence of severe asthma (69 vs. 78%, respectively), as defined by the NHLBI guidelines (8), were not significantly different between the 2 asthmatic groups (**Table 1**).

3.1 Pulmonary function

By definition, the HFEV₁ group had significantly higher mean % predicted FEV₁ than the LFEV₁ group, but not compared to Controls (111.8% vs. 68.1% vs. 100.5%, respectively) (**Table 2**). Because the percentage of predicted retains age bias and the age range in this study was wide (8 to 18 years), the FEV₁ values were expressed as z-scores, GLI % predicted, and GLI percentile values (15,16). FEV₁ z-scores, GLI % predicted, and GLI percentile values were highest for the HFEV₁ and lowest for the LFEV₁ group. Pairwise comparisons in these values showed all significant differences between groups (**Table 2**).

FEV₁/FVC ratio (%) and z-scores were lowest for the LFEV₁ group and highest for the Control group. Pairwise comparisons in FEV₁/FVC z-scores were also significantly different between groups. The FEF₂₅₋₇₅ and FEF₂₅₋₇₅/FVC ratio, which are surrogate measures of dysanapsis, were significantly higher in the HFEV₁ compared to the LFEV₁ group, but not different from that of the Control group (**Table 2**). Not only did children with LFEV₁ demonstrate lower FEV₁ (p<0.0001) and FEV₁/FVC ratio (p<0.0001) compared to the Control group, but they also had lower FEF₂₅₋₇₅% % predicted (p<0.0001) and FEF₂₅₋₇₅/FVC ratio (p=0.0002). Following albuterol administration, only the LFEV₁ group had significant improvements in their FEV₁, FEV₁/FVC and FEF₂₅₋₇₅ values (**Table 1**).

Regarding lung volume measurements, the HFEV₁ group had greater % predicted FVC and TLC values, and a lower RV/TLC ratio compared to the LFEV₁ group. Compared to the Control group, the HFEV₁ group had higher % predicted FVC, TLC, FRC, and RV values, and RV/TLC ratio.

The LFEV₁ group had higher FRC/TLC, RV % predicted, and RV/TLC compared to the Control group (**Table 2**).

3.2 Pressure-volume relationships

The HFEV₁ group had lower static elastic recoil pressure (Pst), higher compliance (a measure of lung distensibility) and specific compliance than either LFEV₁ and Control groups (**Table 3**). In addition, the HFEV₁ group had a lower Raw, Rus and coefficient of retraction, and a higher SGaw compared to the LFEV₁ only; while there were no differences in SGaw and Rus between the HFEV₁ and Control groups. In fact, the LFEV₁ group had the lowest SGaw and the highest Rus values among the 3 groups (**Table 3**).

On visual inspection, the PV curve for the HFEV₁ group was displaced upward and to the left compared to both the LFEV₁ and Control groups (**Figure 1**). In addition, maximal recoil pressure was lower in the HFEV₁ vs. LFEV₁ and Control groups. In contrast, the shape of the PV curve in the LFEV₁ asthma group was similar to that of the Controls. The three-way interaction between groups, TLC volumes, and TLC % predicted was significant ($p=0.0001$ from Type 3 test, linear mixed model). Children in the HFEV₁ demonstrated lower transpulmonary pressure at any given lung volume compared to children in the LFEV₁ and Control groups (**Figure 1**). The HFEV₁ group had a smaller drop in static transpulmonary pressure per change in TLC compared to either the LFEV₁ or Control groups.

A plot of the static transpulmonary pressure of the three groups normalized to the individuals' TLC to enable the evaluation of elastic recoil pressure at comparable fractional lung volumes is presented in the **e-Figure 1**. At any given lung volume, the HFEV₁ group had lower lung pressures compared to both the LFEV₁ and Controls.

The K constant, which is a numerical description of both the shape and position of the PV curve, was greater in both absolute and % predicted values for the HFEV₁ compared to the LFEV₁ or the Control groups; while there were no differences in K or K% predicted between the LFEV₁ and the Controls (**Table 3**).

Following the administration of albuterol, there was no change in the PV relationship among the HFEV₁ asthmatics, while there was a significant shift in the PV curve to the left among the LFEV₁

asthmatics indicating a loss of elastic recoil pressure without a significant shift in lung volume (e-**Figure 2**).

3.3 Pressure-maximum expiratory flow relationships

The relationship between maximum expiratory airflow and static transpulmonary pressure, which reflects the resistance to flow in the upstream segment of the airways is shown in **Figure 2**. In the model, the three-way interaction between groups, pressure and TLC volumes was not significant ($p=0.27$ from Type 3 test, linear mixed model); however, the interaction between groups and TLC volumes were nearly significant ($p=0.06$). Iso-volume flow rates were significantly different between HFEV₁ and LFEV₁ groups for lung pressures at all the defined cutoffs of patients' TLC (**Figure 2**). Significant differences were not found between the HFEV₁ group and the Control group. In contrast, iso-volume flow rates were significantly lower in the LFEV₁ group for lung pressures at all the cutoffs of patients' TLC compared to the Control group, which reflects increased resistance to flow at all lung volumes studied. The pressure-flow curve in the HFEV₁ group was shifted upward and was similar to that of the Control group. On the other hand, the slope of the pressure-flow curve was also displaced downward in the LFEV₁ group, indicating that the flow rates were diminished due to increased Rus.

3.4 Flow-volume relationships

The HFEV₁ group generated significantly larger flows than children with LFEV₁ values at 30%, 45%, 60%, 75%, and 90% of the patients' TLC (**Figure 3**). No significant differences were found between the HFEV₁ and Control groups. The LFEV₁ group had significantly lower iso-volume flow rates at any defined cutoffs of the patients' TLC, compared to the Control group. Visual inspection of the flow-volume curve of the LFEV₁ group showed marked concavity of the curve with little change in flow despite increasing volumes up to 60% of TLC (**Figure 3**). Plots of flow-volume curves from representative children in the HFEV₁ and LFEV₁ groups are available in the online supplement (**e-Figure 3**).

4. DISCUSSION

Childhood asthma is a heterogeneous disease with several distinct clinical phenotypes, among which is a group of children with FEV₁ values of $\geq 100\%$ of predicted when clinically stable (1-3). The finding of this phenotype of persistent asthma with high FEV₁ values even in some children with severe asthma (4-6) is of significant clinical relevance as these children are at greater risk of being under-treated when compared to severe asthmatics with reduced FEV₁ values (7). As a few studies have attempted to understand the respiratory mechanisms underlying asthmatic children with normal lung function versus those with impaired lung function at baseline, we characterized the lung mechanical properties of these two asthma phenotypes.

Our study found HFEV₁ asthmatic children to display distinct lung mechanical properties compared to LFEV₁ asthmatics. First, HFEV₁ asthmatics had large airways (FEV₁ z-scores > 1) with normal SGaw and normal Raw. Second, they had large lung volumes and decreased lung elasticity (PV curve shifted upward and to the left [**Figure 1**]). Third, the HFEV₁ group had an increased K, a variable that accounts for both the position and the shape of the PV curve, which also indicated increasing loss of lung parenchymal elasticity, increased lung compliance and enlarged alveolar size (19). From the work of Greaves and Colebatch, who performed post-mortem static PV curves in normal and emphysematous lungs, they found that the constant K was closely related to morphometric measurements of mean alveolar size (20). Whether this is the case in children with HFEV₁ asthma is not known. Lastly, analysis of the pressure-flow curves (**Figure 2**) revealed the HFEV₁ group to have Rus values similar to those of the Controls. In contrast, the LFEV₁ asthmatics had a low K value, indicating that their lungs were less compliant (stiffer) than expected. In addition, LFEV₁ group's pressure-flow curve was shifted downward and to the right indicating higher airway resistance at all lung volumes. This observation indicates that airways disease, as opposed to diminished lung elastic recoil pressure, was responsible for airflow limitation of this group of asthmatics. Inspection of the flow-volume curve (**Figure 3**) of the LFEV₁ group revealed it to be shifted downward and concave, indicating diminished airflow at all lung volumes. In stark contrast, the large airways and low airways resistance noted in HFEV₁ group allowed for greater airflows at all lung volumes.

Although the LFEV₁ asthmatics' lung function improved with albuterol, it failed to normalize. This could be due to dysanapsis and/or airway remodeling. Although controversial, airway remodeling may result in airflow limitation due to its effects on airway caliber (20-23). Dysanapsis is a term used to describe the disproportionate growth of the airways to that of the lung parenchyma that is exaggerated in patients with asthma. The FEF₂₅₋₇₅ and FEF₂₅₋₇₅/FVC ratio are measures of dysanapsis (24), and both were diminished in the LFEV₁ group, suggesting that dysanapsis played a role in their airflow limitation. As airway biopsies were not performed, what role airway remodeling played could not be determined. The HFEV₁ had no evidence for having dysanapsis as their FEF₂₅₋₇₅ and FEF₂₅₋₇₅/FVC ratios were similar to those of the Controls.

Our findings raise several intriguing questions that need further investigation. First, why did the HFEV₁ asthmatics have larger than expected lung volumes? It is possible that the HFEV₁ asthmatics had an arrest in the normal increase in lung elasticity that occurs in the transition from childhood to adulthood (13). Decreased elastic recoil pressure would allow for enhanced lung growth. Support for this hypothesis comes from a study by Greaves and Colebatch (25), who found that adult asthmatics with childhood-onset asthma had larger lung volumes and increased lung distensibility compared to normal controls and adult asthmatics with onset of asthma in adulthood.

Second, what is the natural history of the HFEV₁ asthma phenotype? Although little if anything is known about asthmatic children with loss of elastic lung recoil pressure, it has long been known that loss of elastic recoil pressure can occur in some adult asthmatics (26,27). Adults with loss of elastic recoil pressure comprise a well-described phenotype of severe, high-risk asthma, based primarily on studies performed by Gelb et al. (28-31). In this subgroup of asthmatics with severe airflow limitation, at least 50% of their airflow limitation could be attributed to the loss of lung elasticity (28). In addition, this phenotype of severe asthmatics was at greater risk of having had near-fatal asthma attack than asthmatics with severe airflow limitation with normal lung elasticity (29).

It is possible that some HFEV₁ asthmatic children are at risk of a rapidly progressive decline in their lung function due to ongoing airway inflammation and remodeling, such that by the time they reach adulthood, they will have developed airflow limitation similar to the group described by Gelb et al. (28-31). Such was noted in an asthmatic we evaluated. When initially seen at 14 years of life and following a near-fatal asthma event, he was noted to have an FEV₁ of 103% of predicted with

associated enlarged lungs and loss of elastic recoil pressure. When re-evaluated at 34 years of life, he had similarly enlarged lungs with diminished lung elastic recoil pressure, yet his baseline FEV₁ had fallen to 29% of predicted.

Third, and most importantly, our observations may explain why an asthmatic with a baseline FEV₁ of $\geq 100\%$ and with no evidence for airflow limitation can develop a life-threatening asthma exacerbation. We propose that some HFEV₁ asthmatics can very rapidly develop profound increases in their airways resistance due to the combination of reduced lung elasticity and “uncoupling” of airway-lung parenchymal interdependence as described in **Figure 4**. These high-risk HFEV₁ asthmatics, when well, have a mechanical advantage over children with chronic airflow limitation as their work of breathing is lower, due to the lower inspiratory pressures required to overcome elastic resistance during inhalation. This situation could quickly reverse during an acute asthma exacerbation, as these individuals would not benefit from the outward radial traction on the airways due to “uncoupling” of tethering elements connecting the airway to the lung parenchyma. This “interdependence” of the airway and lung parenchymal has significant physiologic significance as it serves to resist the intrinsic inward recoil of the airways due to the surface tension of the alveoli, airway compression during forced exhalation, and the ability of airway smooth muscle to narrow the airway.

Mechanical uncoupling of the airways from the lung parenchyma has been demonstrated in patients with nocturnal asthma, a distinct phenotype of severe asthma, which is at increased risk of having near-fatal asthma attacks (32, 33). These asthmatics develop profound drops in their lung function while sleeping that is associated with an influx of inflammatory cells with uncoupling of the airway-lung parenchyma identified as the mechanism responsible, and while the cause of uncoupling was unknown, the authors concluded that it was not due to asthma per se or postural changes, but may have been neurally-mediated (34).

There are some limitations to this study. The first issue has to do with whether the FEV₁ should be used as a measure of airflow limitation in children with asthma, as it is clear that many severe childhood asthmatics will have normal lung function when clinically stable. Second, our study was small due to the invasive nature of the procedures used. Third, we did not collect data regarding exacerbation rates among the asthmatics studied, and not all subjects underwent methacholine

challenges. Of those that underwent bronchial challenges, three HEV₁ asthmatics had profound drop in their lung function (>40% drop in FEV₁) during their challenges, suggesting that they had the high-risk phenotype of unlimited airway narrowing during bronchospasm.

In summary, our study showed that the lung mechanical properties of children with severe asthma who have normal lung function are distinct from children with severe asthma with impaired lung function. Loss of lung elasticity, uncoupling, and risk for exaggerated airway closure provide a potential explanation for the paradox of severe asthmatic children, whom when clinically stable can have an FEV₁ >100% of predicted, but during an acute bronchospastic episode can experience a life-threatening asthma event. Our study should serve as a starting point to better understand this group of children with severe asthma characterized by normal lung function. To accomplish this, larger numbers of children with severe asthma characterized by normal lung function will need to undergo physiologic studies at centers with expertise in performing pressure-volume studies.

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Table 1: Baseline characteristics of the study population

	HFEV₁ (n=13)	LFEV₁ (n=14)	Control (n=10)	<i>p</i>-value*
Age (years)	13.0 ± 3.0	12.2 ± 2.3	14.8 ± 2.4	.06
Height (cm)	153.5 ± 15.7	154.8 ± 13.4	168.0 ± 15.2	.05
BMI (kg/m²)	24.7 ± 6.5	21.9 ± 6.3	22.3 ± 6.0	.47
Male Gender, n (%)	4 (45)	4 (55)	5 (50)	.97
Race, n (%)				
Caucasian	7 (54)	7 (54)	9 (90)	
African American	4 (30)	4 (30)	0	.16
Hispanic	2 (15)	2 (15)	0	
Other	0	0	1 (10)	
Asthma duration (years)	9.2 ± 1.3	9.7 ± 1.3	N/A	.7 †
Staff assessment of Asthma				
Severity‡, n (%)				
• Mild-Moderate	4 (31)	3 (23)	N/A	.4 †
• Severe Persistent	9 (69)	10 (78)		
ICS dose (BUD equivalent), mcg/day	956.4 ± 223.8	1600.0 ± 163.3	N/A	.02 †

HFEV₁, asthmatics with high FEV₁ (forced expiratory volume in 1 second); LFEV₁, asthmatics with low FEV₁; BMI, body mass index; BUD, budesonide; ICS, Inhaled corticosteroid dose; N/A, not applicable;

Data expressed as number (%) for categorical variables, and mean ± standard deviation for continuous variables. Statistical significant *p*-value (*p* < .05) are shown in bold.

**P*-value corresponds to overall ANOVA for continuous variables, or Fisher's exact test for categorical variables across the 3 groups.

†*P*-value corresponds to comparison between 2 asthmatic groups using Student's *t* test and Fisher's exact test for categorical variables.

‡Based on NHLBI guidelines (reference 8)

Table 2: Baseline pre-bronchodilator pulmonary function tests

	HFEV₁ (n=13)	LFEV₁ (n=14)	Control (n=10)	p-value*
FVC				
% predicted	121.8 ± 9.2	90.5 ± 9.0	100.6 ± 13.3	< .0001 † ‡
Z score	1.94 ± 0.23	-0.36 ± 0.24	0.10 ± 0.27	< .0001 † ‡
FEV₁				
% predicted	111.8 ± 8.2	68.1 ± 9.8	100.5 ± 4.7	< .0001 ‡ §
Z Score	1.12 ± 0.91	-2.37 ± 0.65	0.03 ± 1.38	< .0001 † ‡ §
FEV₁ GLI % predicted	113.1 ± 10.8	71.0 ± 8.4	100.2 ± 16.2	< .0001 † ‡ §
FEV₁ GLI %^{tile}	79.8 ± 16.7	2.3 ± 3.7	52.9 ± 37.0	< .0001 † ‡ §
FEV₁/FVC				
%	81.5 ± 6.7	66.9 ± 8.3	85.5 ± 2.4	< .0001 ‡ §
Z Score	-1.17 ± 0.88	-2.82 ± 0.81	-0.15 ± 1.04	< .0001 † ‡ §
FEF₂₅₋₇₅				
% predicted	91.4 ± 26.1	41.7 ± 14.4	99.3 ± 24.6	< .0001 ‡ §
Z Score	-0.45 ± 1.01	-2.45 ± 1.27	-0.20 ± 1.19	< .0001 ‡ §
FEF₂₅₋₇₅/FVC (%)	76.4 ± 19.0	48.7 ± 26.0	93.6 ± 22.9	.0002 ‡ §
TLC % predicted	134.8 ± 10.1	109.6 ± 12.6	113.5 ± 9.6	< .0001 † ‡
FRC % predicted	134.4 ± 13.6	117.7 ± 17.2	110.1 ± 21.4	.007 †
FRC/TLC (%)	46.3 ± 4.48	50.8 ± 6.05	44.5 ± 6.4	.027 §
RV % predicted	216.6 ± 44	251.2 ± 64	136.8 ± 27	.014 § .0001 † §
RV/TLC (%)	25.9 ± 4.56	32.0 ± 4.23	18.8 ± 3.0	< .0001 † ‡ §

RV/TLC % predicted	182.4 ± 32.9	226.3 ± 46.1	108.7 ± 18.0	< .0001 †‡§
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HFEV₁, asthmatics with high FEV₁ (forced expiratory volume in 1 second); LFEV₁, asthmatics with low FEV₁; FVC, forced vital capacity; FEF₂₅₋₇₅, forced expiratory flow between 25% and 75% of vital capacity; GLI, Global Lung Function Initiative; TLC, Total lung capacity; FRC, Functional residual capacity; RV: Residual volume.

Data expressed as and mean ± standard deviation. Statistical significant p-value is $p < .05$. * P-value corresponds to overall ANOVA for continuous variables; pairwise comparisons were adjusted for using Tukey's HSD method at $P < .05$ where:

† = significant difference between HFEV₁ and Control groups

‡ = significant difference between HFEV₁ and LFEV₁ groups

§ = significant difference between LFEV₁ and Control groups

Table 3: Lung mechanical measurements

	HFEV₁ (n=13)	LFEV₁ (n=14)	Control (n=10)	p-value*
Pst (L) max (cmH₂O)	15.1 ± 3.7	22.2 ± 6.4	26.3 ± 11.2	.003 †‡
K (L/cm H₂O) % predicted	139.5 ± 48.9	57.5 ± 38.3	83.0 ± 45.8	<.001 †‡
Coefficient of Retraction (cm H₂O/L)	0.31 ± 0.10	0.54 ± 0.24	0.49 ± 0.23	.012 ‡
Compliance (L/cm H₂O)	0.21 ± 0.14	0.09 ± 0.05	0.09 ± 0.04	.002 †‡
Specific Compliance/TLC (L/cm H₂O) / L	0.04 ± 0.02	0.02 ± 0.01	0.016 ± 0.01	.0006 †‡
Rus (cm H₂O/[L/sec])	2.7 ± 1.6	8.9 ± 9.5	2.6 ± 1.4	.02 ‡§
Raw (cm H₂O/[L/s]) % predicted	101.9 ± 42.6	199.9 ± 106.9	123.4 ± 50.3	.005 ‡

SGaw (L/s/cm H₂O/L)				
% predicted	87.3 ± 30.2	53.4 ± 18.5	88.4 ± 41.1	.01‡§

HFEV₁, asthmatics with high FEV₁ (forced expiratory volume in 1 second); LFEV₁, asthmatics with low FEV;

Raw, airway resistance; SGaw, specific airway conductance; Rus, upstream resistance; K, shape constant; Pst, Pressure-static; TLC, Total lung capacity

Data expressed as mean ± standard deviation. Statistical significant p-value is $p < .05$. * *P*-value corresponds to overall ANOVA for continuous variables across the 3 groups; pairwise comparisons were adjusted for using Tukey's HSD method at $P < .05$ where:

† = significant difference between HFEV₁ and Control groups

‡ = significant difference between HFEV₁ and LFEV₁ groups

§ = significant difference between LFEV₁ and Control groups

FIGURE LEGENDS

Figure 1: Static expiratory lung pressure-volume curves of the lungs.

This pressure-volume plot shows an upward and left shift of the High FEV₁ asthma group (red large dashed lines) compared to the Normal FEV₁ (black solid lines) and Low FEV₁ asthma (blue small dashed lines) groups. Maximal recoil pressure was lower in the High vs. Low and Non-asthmatic groups. A linear mixed model was used to determine static transpulmonary pressures obtained at 60 (diamonds), 75 (triangles), 90 (circles), and 100% (squares) of the subject's TLC between the 3 groups according to TLC% of predicted values. The high FEV₁ group's TLC % predicted was different from the Non-asthmatic group at 100% of TLC ($p<0.0001$). Similarly, the Low FEV₁ and Non-asthmatic groups had significantly different TLC % predicted at 100% of TLC ($p=0.0004$). The high FEV₁ group's TLC % predicted was different from the Low FEV₁ group at 90% and 100% TLC ($p=0.045$ and 0.01 , respectively).

Figure 2: Relationship between maximal expiratory flow and static transpulmonary pressure of the lungs.

Transpulmonary pressure is plotted against geometric estimates ($\pm$ geometric standard error) of expiratory flow rate (liters per second) on the ordinate at 60 (diamonds), 75 (triangles), 90 (circles), and 100% (squares) of the subject's TLC (% predicted) between High FEV₁ asthma group (red large dashed lines) compared to the Normal FEV₁ (black solid lines) and Low FEV₁ asthma (blue small dashed lines) groups. A linear mixed model showed differences in iso-volume flow rates between High and Low FEV₁ groups for lung pressures at 60% ($p < 0.0001$), 75% ($p < 0.0001$), 90% ($p < 0.0001$) and 100% ($p = 0.01$) of patients' TLC. Significant differences were not found between the High FEV₁ group and the Non-asthmatic group. Iso-volume flow rates were significantly lower in the Low FEV₁ group for lung pressures at 60% ($p < 0.0001$), 75% ($p < 0.0001$), 90% ($p < 0.0001$), and 100% ($p = 0.007$) of patients' TLC than in the Non-asthmatic group.

Figure 3: Relationship between maximal expiratory flow and lung volume.

Lung volume (TLC % predicted) is plotted against geometric estimates ($\pm$ geometric standard error) of expiratory flow rate (liters per second) between High FEV₁ asthma group (red large dashed lines) compared to the Normal FEV₁ (black solid lines) and Low FEV₁ asthma (blue small dashed lines) groups at 30 (crosses), 45 (stars), 60 (diamonds), 75 (triangles), 90 (circles), and 100% (squares) of the subjects' TLC. A linear mixed model showed that the High FEV₁ group generated larger flows than the Low FEV₁ group at 30% ($p=0.004$), 45% ($p<0.0001$), 60% ($p<0.0001$), 75% ($p<0.0001$), and 90% ($p=0.007$) of the patients' TLC. The Low FEV₁ group had lower iso-volume flow rates at 30% ($p=.02$), 45% ($p<0.0001$), 60% ($p<0.0001$), 75% ($p<0.0001$), 90% ($p=0.0003$), and 100% ($p=0.02$) of the patients' TLC compared to the Non-asthmatic group. No significant differences were found between the High FEV₁ and Non-asthmatic groups.

Figure 4. Diagram of the 2 phenotypes of asthma studied compared to non-asthmatic controls depicted as cross-sections of the airways at baseline and during a bronchospastic event.

4 A. At baseline, the High FEV₁ group has larger airways than that of the Non-asthmatics and Low FEV₁ asthmatics. This is the result of the High FEV₁ groups' airways being proportionate to their lung size. Although they display diminished recoil, this is overcome by a greater decrease in resistance due to their enlarged airways; as a result, they can generate greater than expected airflows. This significant decrease in resistance is the result of Poiseuille's Law that states that resistance is equal to 1 over the radius to the fourth power. In contrast, the Low FEV₁ group has a significantly smaller airway diameter due to their intrinsic airways disease. As a result, their increased resistance results in a significant decrease in airflow.

4 B. When High FEV₁ asthmatics experience a severe bronchospastic event, they are at great risk of experiencing airways collapse and profound limitations to airflow rendering them susceptible to near-fatal asthma (NFA). With a large decrease in airway diameter, the resultant increase in resistance becomes exponentially greater, and airflow drops precipitously. The proposed mechanism for the airway collapse is that during a bronchospastic event, the loss of lung elasticity and associated uncoupling of the airway from the lung parenchyma allows unlimited airway smooth muscle constriction and allows for the intrinsic inward recoil of the airways due to increased surface tension. In contrast, although those with Low FEV₁'s will also develop increased resistance during a bronchospastic event, their airways remain patent due to the function of the tethering elements to allow normal airway-lung parenchyma interdependence. In addition, airway remodeling may also render their airways less distensible, and thus less likely to collapse. This scenario explains the previously reported data that children with high FEV₁ values associated with lung hyperinflation and loss of elastic recoil pressure are far more likely to have suffered a near-fatal event than severe asthmatics with airflow limitation, normal lung volumes, and normal lung elasticity.

E-FIGURE LEGENDS

e-Figure 1: Static transpulmonary pressure of the 3 groups normalized to the subjects' TLC (0 to 100%). This figure enables the evaluation of elastic recoil pressure at comparable fractional lung volumes and at any given lung volume, the HFEV₁ group had lower lung pressures compared to both the LFEV₁ and Controls

e-Figure 2: Pressure-Volume relationship before and after β -agonist administration.

Following the administration of albuterol, there was no change in the pressure-volume relationship among the HFEV₁ asthmatics, while there was a significant shift in the pressure-volume curve to the left among the LFEV₁ asthmatics indicating a loss of elastic recoil pressure without a significant shift in lung volume.

e-Figure 3A: Representative Flow-Volume Curves from HFEV₁ Subjects

Flow-volume curves generated by body box plethysmography before and after β -agonist administration. Subject #1: 16-year old female with pre- and post-albuterol FEV₁ values of 113% and 103% respectively. Subject #2: 14-year old female with pre- and post-albuterol FEV₁ values of 119% and 126% respectively. Subject #3: 16-year old female with pre- and post-albuterol FEV₁ values of 116% and 130% respectively. Subject #4: 14-year old female with pre- and post-albuterol FEV₁ values of 113% and 119% respectively.

e-Figure 3B: Representative Flow-Volume Curves from LFEV₁ Subjects.

Flow-volume curves generated by body box plethysmography before and after β -agonist administration. Subject #1. 14-year old male with pre- and post-albuterol FEV₁ values of 73% and 81% respectively. Subject #2. 13-year old male with pre- and post-albuterol FEV₁ values of 72% and 93% respectively. Subject #3. 15-year old male with pre- and post-albuterol FEV₁ values of 59% and 77% respectively. Subject #4. 9-year old female with pre- and post-albuterol FEV₁ values of 56% and 62% respectively.

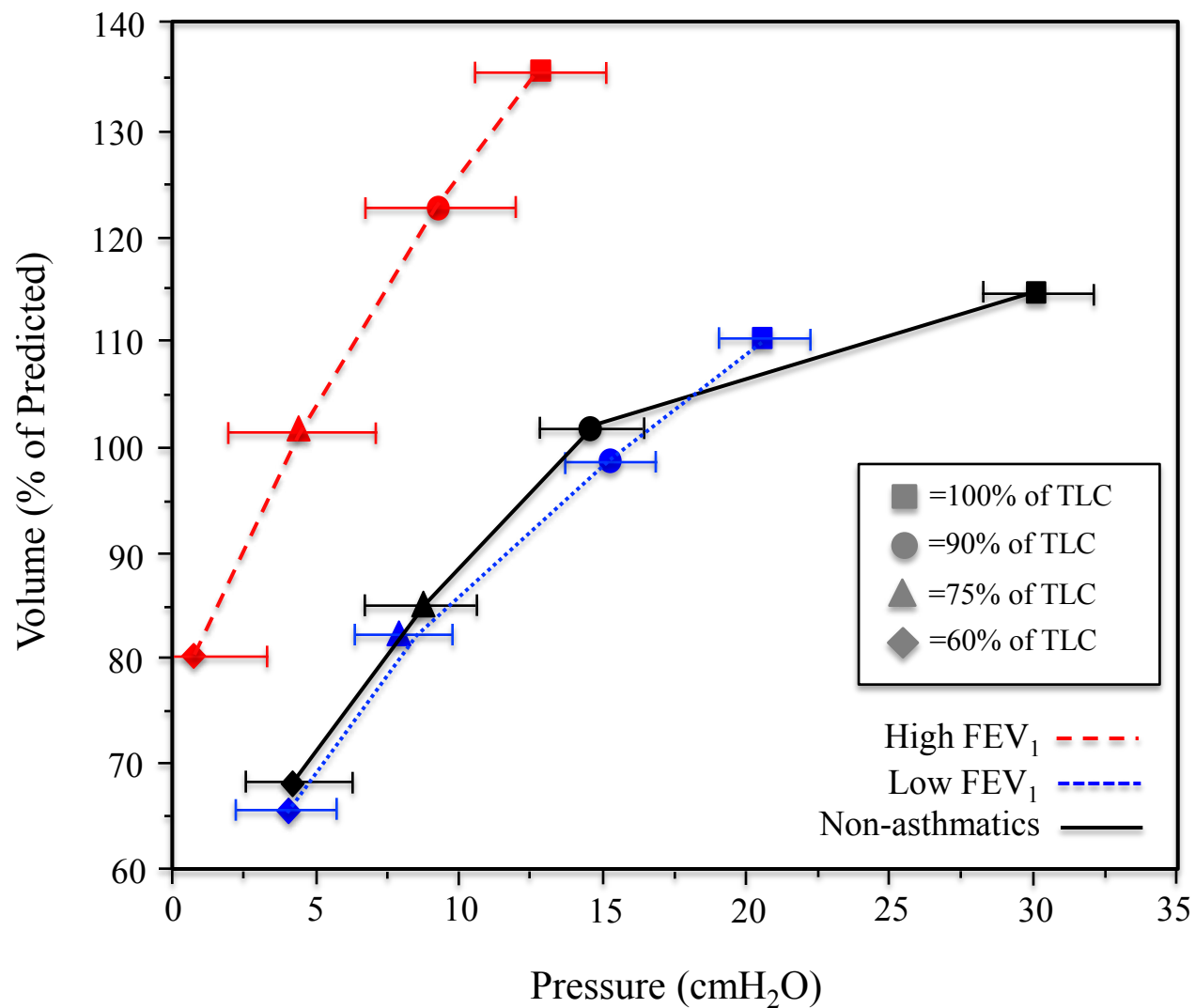


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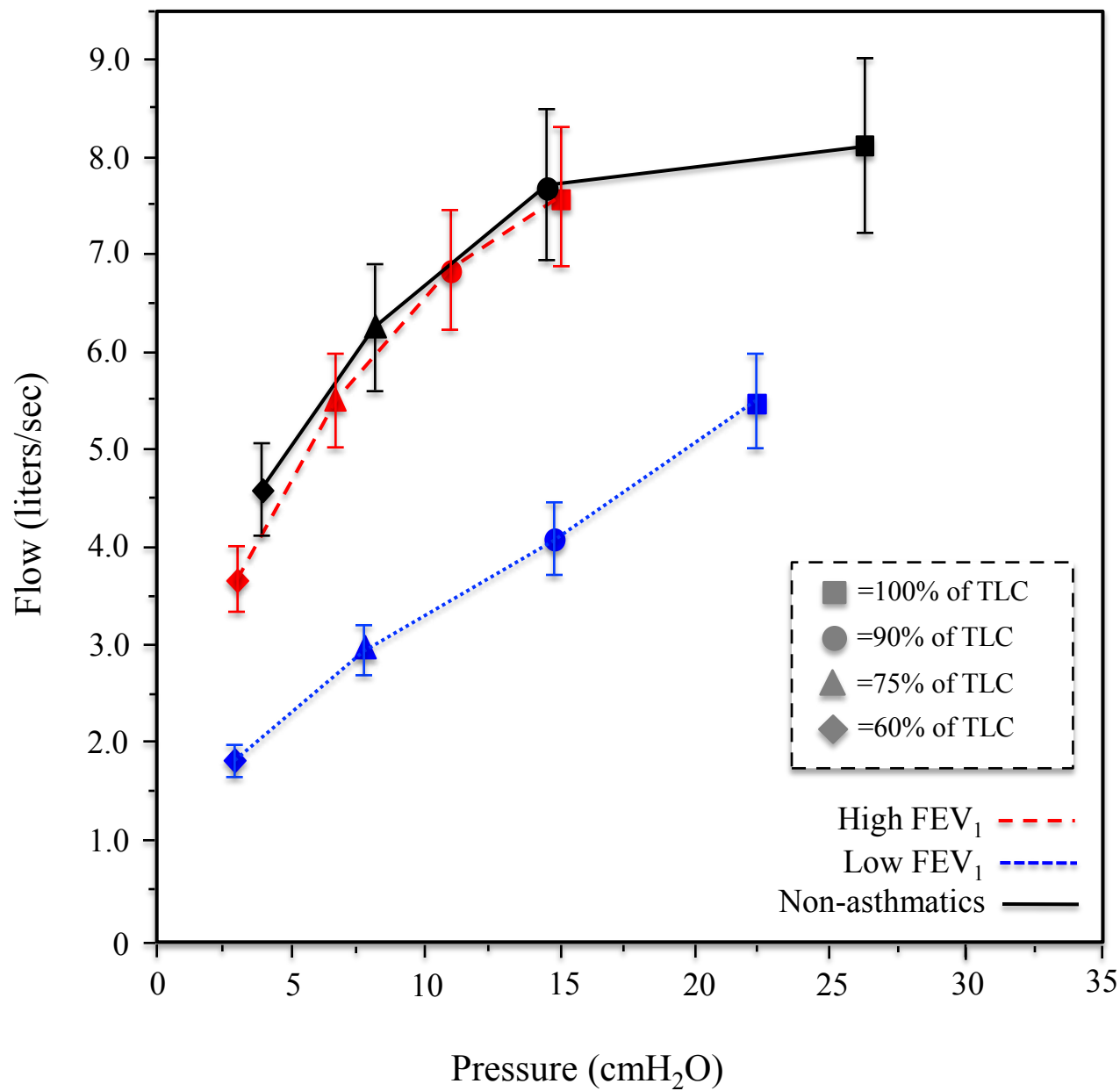


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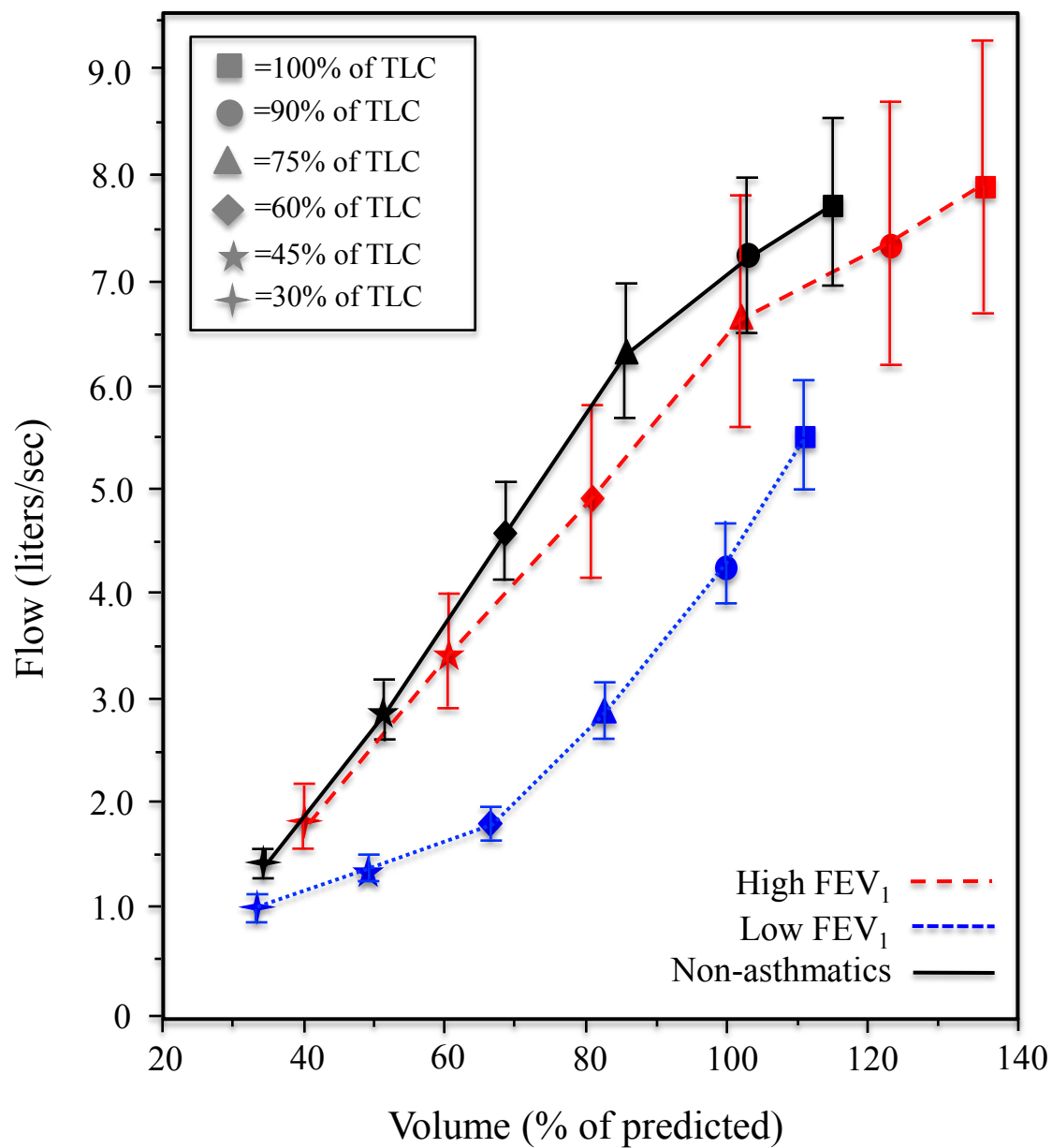


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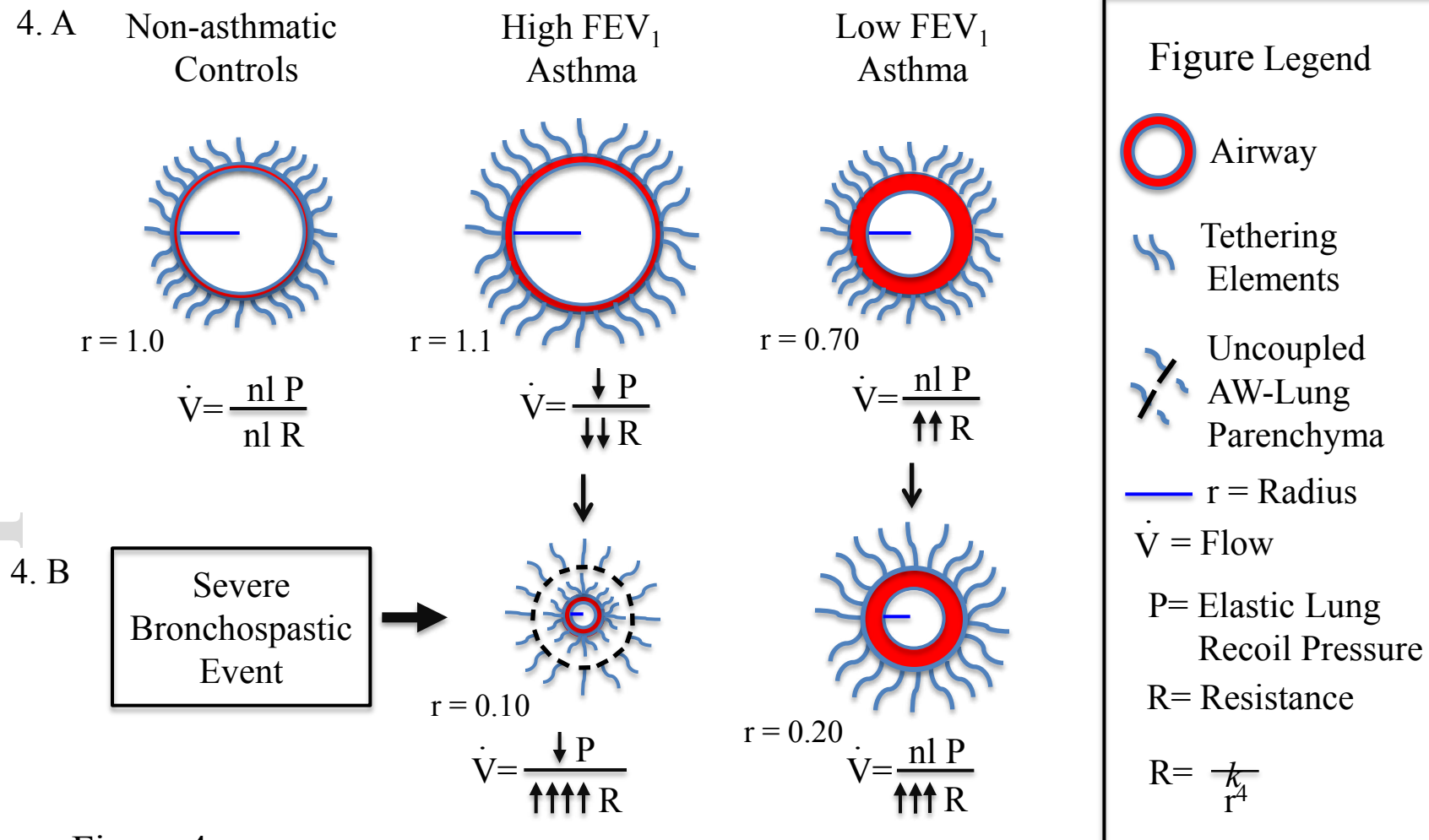
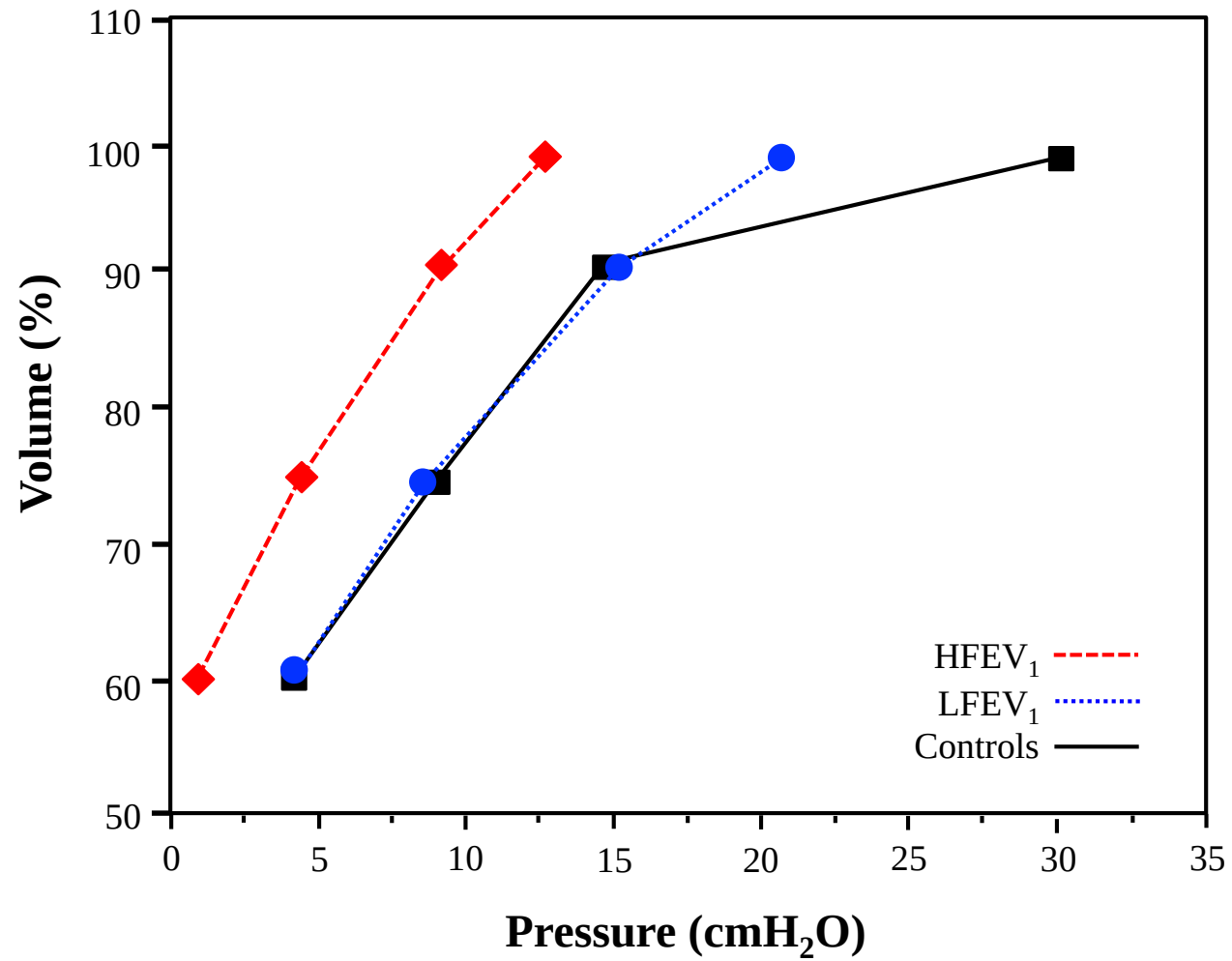
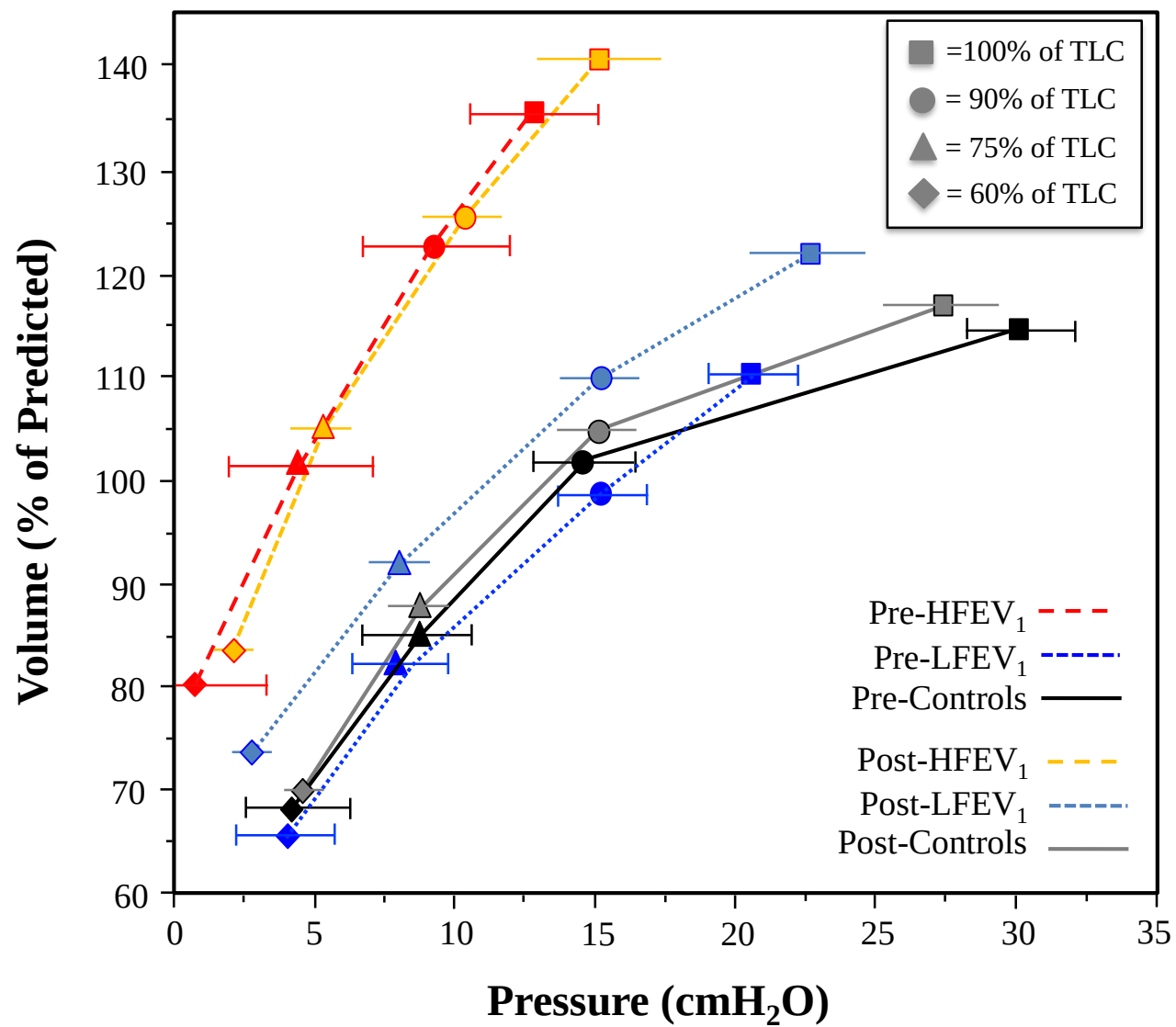
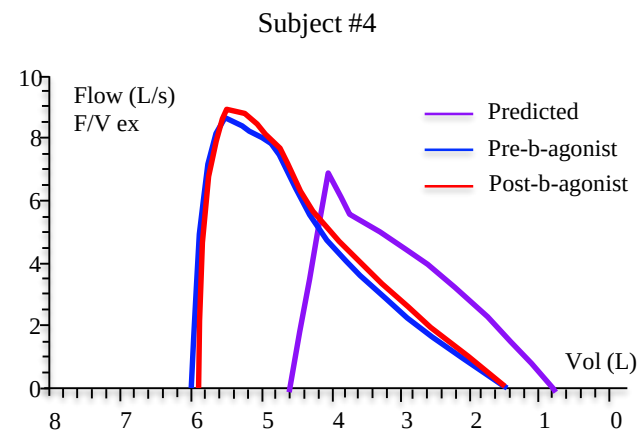
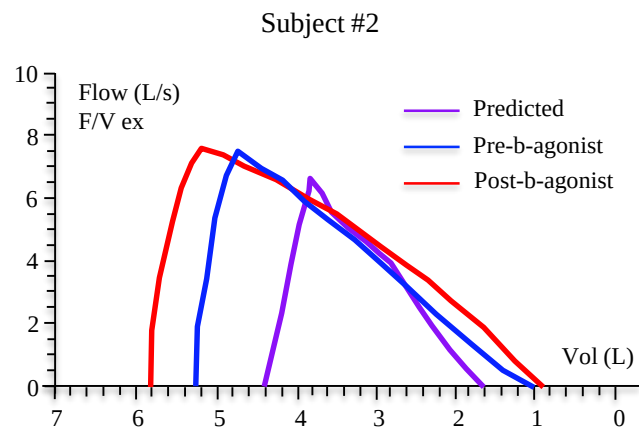
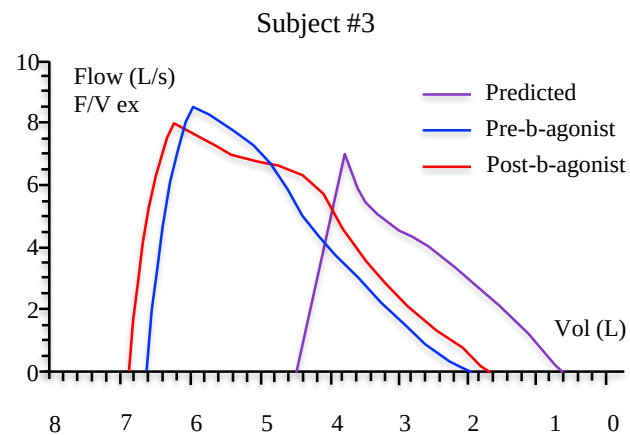
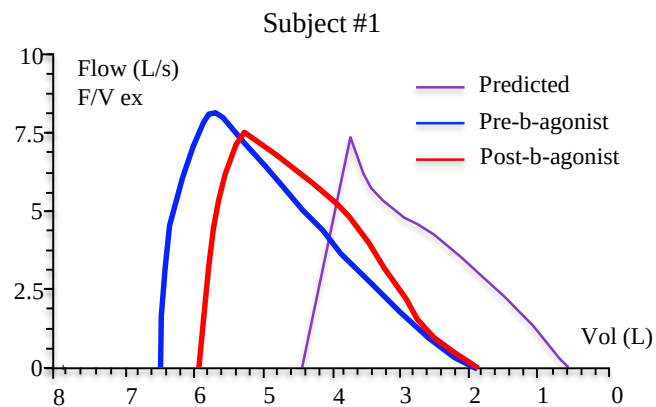


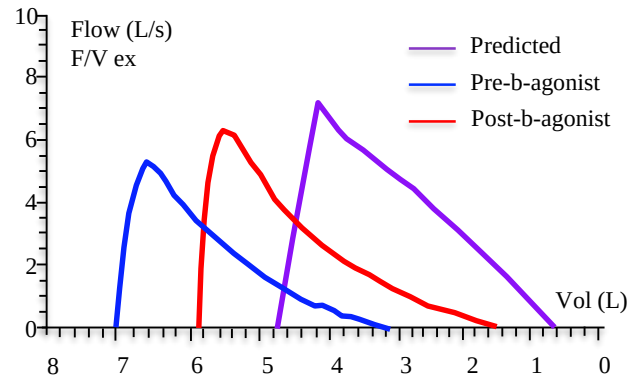
Figure 4



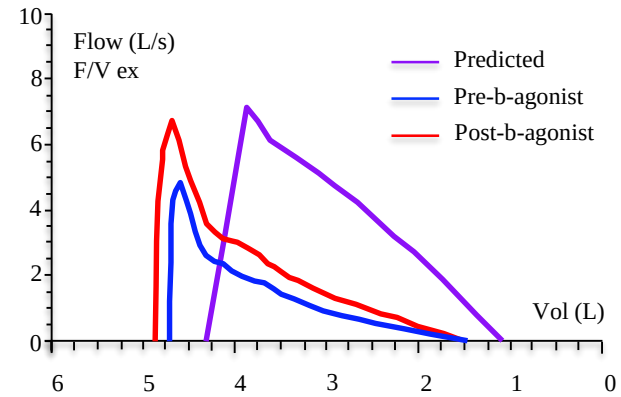




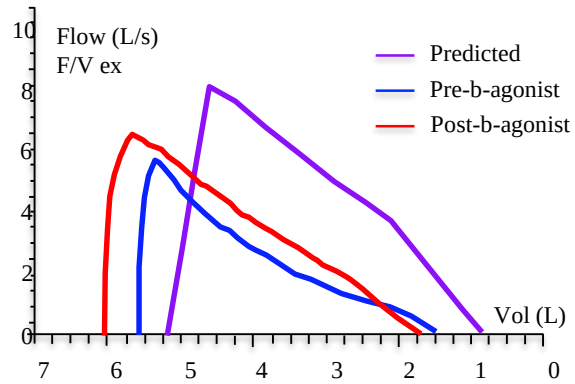
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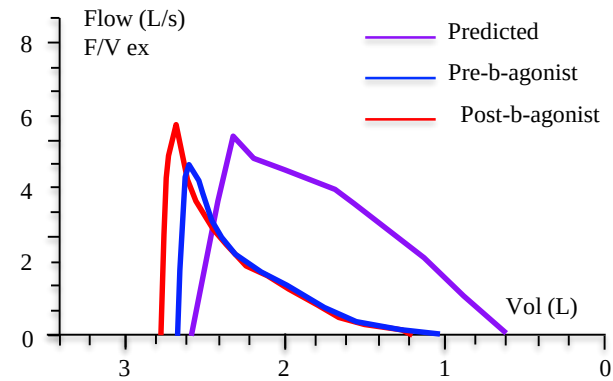
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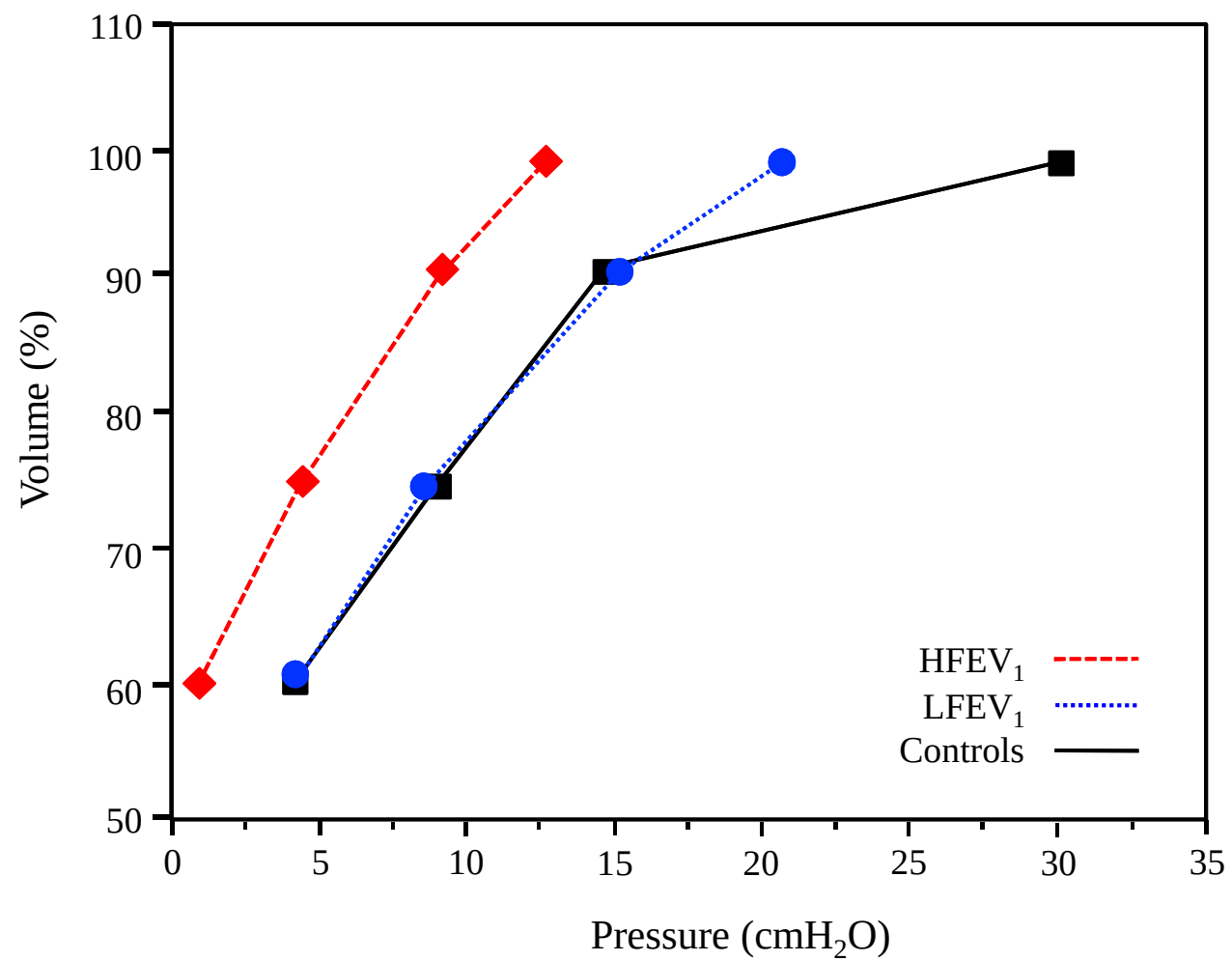


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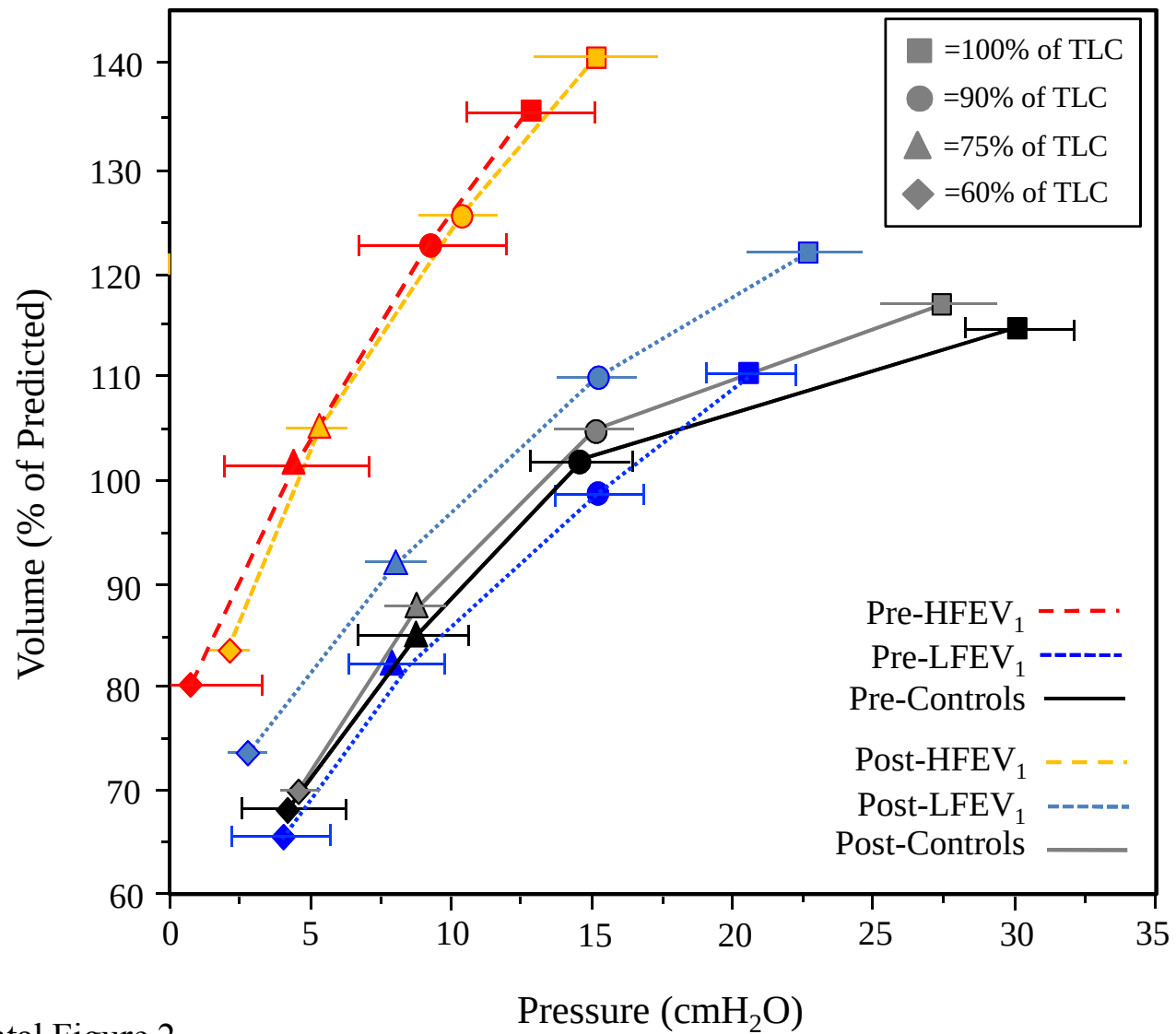


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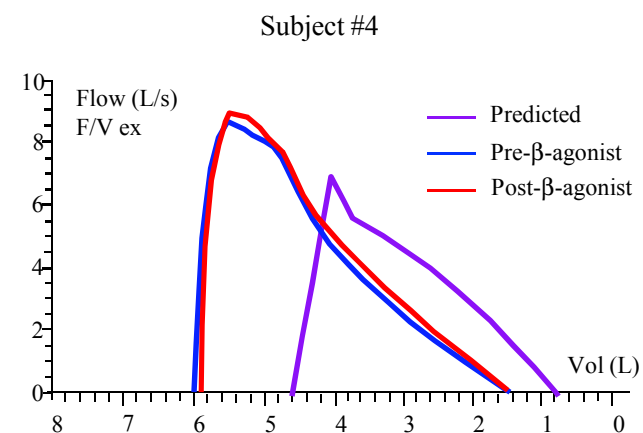
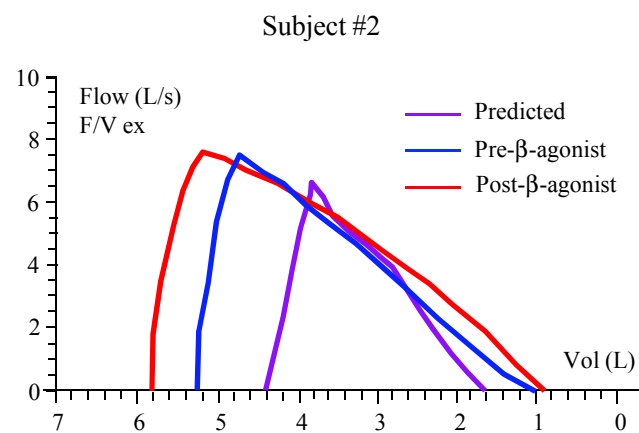
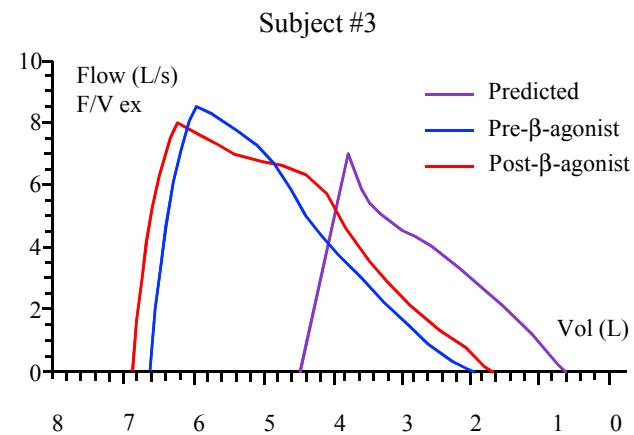
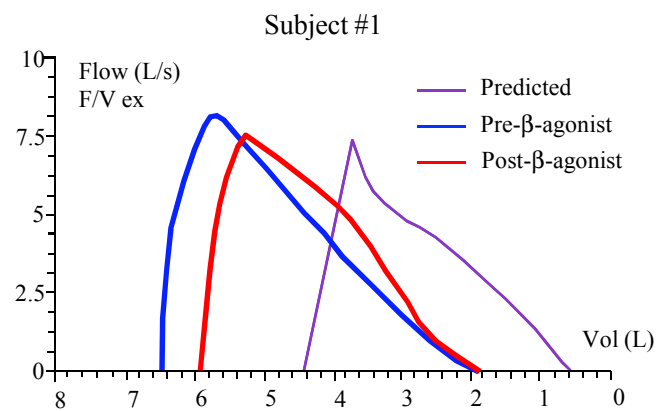




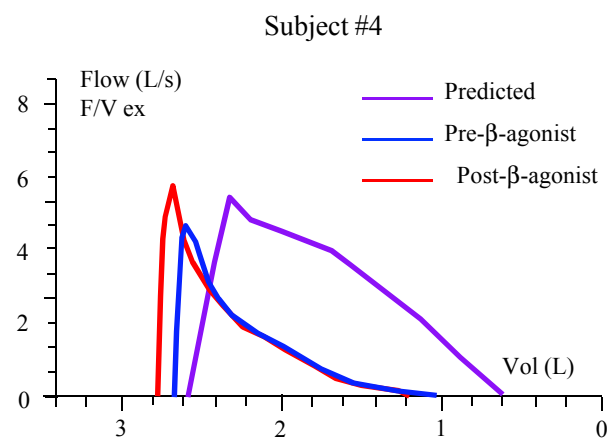
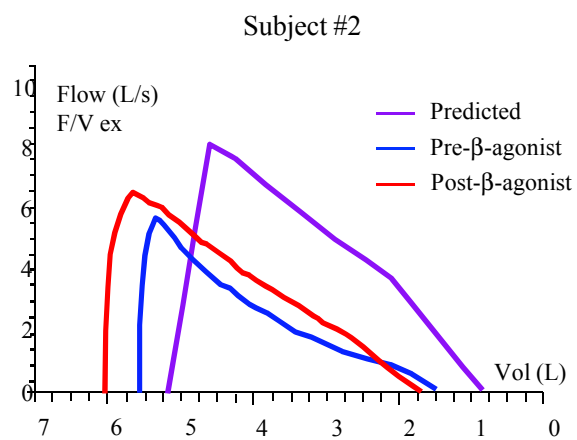
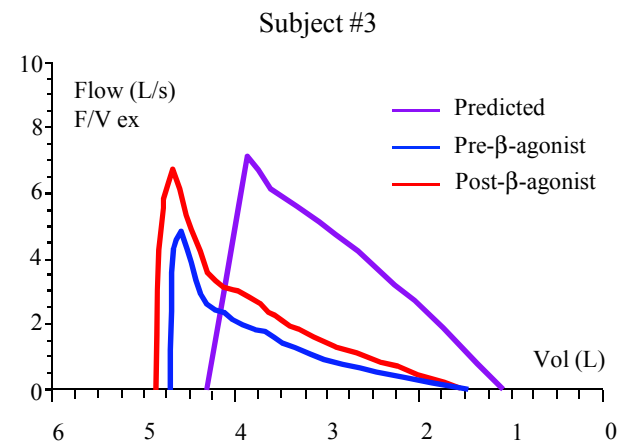
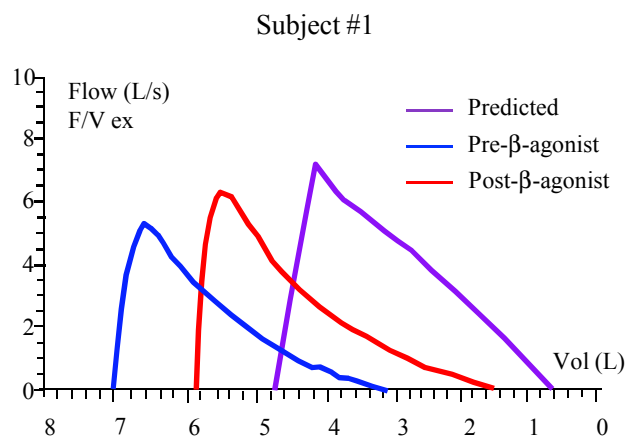
Supplemental Figure 1



Supplemental Figure 2



Supplemental Figure 3A



Supplemental Figure 3B

e-Table 1. Post-bronchodilator spirometry

	HFEV₁ (n=13)	LFEV₁ (n=14)	Control (n=10)	p-value*
FVC % predicted	121.4 ± 12.7	95.7 ± 10.8	101.9 ± 13.6	< .0001 ^{†‡}
FEV₁ % predicted	116.5 ± 11.4	81.1 ± 10.4	105.1 ± 13.77	< .0001 ^{‡§}
Delta-Change in FEV₁ after albuterol (%)	4.5 ± 10.5	20.1 ± 15	4.9 ± 4.7	.002 ^{‡§}
FEV₁/FVC (%)	85.8 ± 6.9	76.1 ± 8.13	90.3 ± 3.9	< .0001 ^{‡§}
FEF₂₅₋₇₅ % predicted	104.3 ± 28.6	60.8 ± 18.5	118.9 ± 26.6	< .0001 ^{‡§}
FEF₂₅₋₇₅/FVC (%)	92.3 ± 21.9	60.4 ± 25.2	111.9 ± 26.09	<.0001 ^{‡§}

HFEV₁, asthmatics with high FEV₁ (forced expiratory volume in 1 second); LFEV₁, asthmatics with low FEV₁; FVC, forced vital capacity; FEF₂₅₋₇₅, forced expiratory flow between 25% and 75% of vital capacity;

Data expressed as mean ± standard deviation for continuous variables. Statistical significant p-value is $p < .05$.

* P-value corresponds to overall ANOVA for continuous variables; pairwise comparisons were adjusted for using Tukey's HSD method at $P < .05$ where:

† = significant difference between HFEV₁ and Control groups

‡ = significant difference between HFEV₁ and LFEV₁ groups

§ = significant difference between LFEV₁ and Control groups