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Quantifying the shape of maximal expiratory flow-volume curves in healthy humans and asthmatic patients

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Abstract

Differences in the absolute flow and volume of maximal expiratory flow-volume (MEFV) curves have been studied extensively in health and disease. However, the shapes of MEFV curves have received less attention. We questioned if the MEFV curve shape was associated with (i) expiratory flow limitation (EFL) in health and (ii) changes in bronchial caliber in asthmatics. Using the slope-ratio (SR) index, we quantified MEFV curve shape in 84 healthy subjects and 8 matched asthmatics. Healthy subjects performed a maximal exercise test to assess EFL. Those with EFL during had a greater SR (1.15 ± 0.20 vs. 0.85 ± 0.20 , $p < 0.05$) yet, there was no association between maximal oxygen consumption and SR ($r = 0.14$, $p > 0.05$). Asthmatics average SR was greater than the healthy subjects (1.35 ± 0.03 vs. 0.90 ± 0.11 , $p < 0.05$), but there were no differences when bronchial caliber was manipulated. In conclusion, a greater SR is related to EFL and this metric could aid in discriminating between groups known to differ in the absolute size of MEFV curves.

Keywords

Expiratory flow limitation; Pulmonary system limitation; Ventilator constraints

1. Introduction

The maximal expiratory flow-volume (MEFV) curve depicts the inter-relationship between flow and volume during a maximal expiration. In young healthy subjects, the MEFV curve is highly reproducible within an individual, but shows between-subject variability (Green et al., 1974). Specifically, height and aged matched individuals can have MEFV curves that vary

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significantly with respect to volume, flow and the spatial shape when graphed in terms of flow-volume (ATS, 1995; Tien et al., 1979). The maximum volume of the MEFV curve is determined by the size of the thoracic cavity and, to a lesser degree, the ability of the inspiratory muscles to generate sufficient negative pressure (Mead and Whittenberger, 1953). Expiratory flow is greatest at maximum lung volume and is positively related to the magnitude of alveolar pressure created during a forceful contraction, thus the relationship is effort dependent (Hyatt and Flath, 1966; Hyatt et al., 1958). However, expiratory flow at mid and lower ($\sim <75\%$ max) lung volumes is effort independent and is unaffected by increasing alveolar pressure (Mead et al., 1967). The between-subject variation in expiratory flow over the effort independent region is explained by differences in airway resistance, which is determined by airway's length, radius and branching, and the static recoil pressure (Green et al., 1974). Overall, the shape of a MEFV curve is determined by all of the abovementioned factors and is the product of the mechanical interaction between airway conductance and lung elastance (Mead, 1978). As such, the shape of an MEFV curve can be a valuable metric when assessing overall lung function.

A method to quantify the shape of a MEFV curve is the slope-ratio (SR) index, which provides a unit-less ratio between the instantaneous and chord slope of any point along a MEFV curve (Mead, 1978). A ratio of 1.0 indicates a linear decrease in flow relative to volume, while values smaller or larger indicate a greater and smaller change in flow per unit volume, respectively. An important feature and benefit of the SR analysis is the ability to determine spatial changes in curvature throughout the entire range of lung volumes. The SR analysis has been used to detect difference in MEFV shape due to emphysema and asthma (Mead, 1978), mild chronic obstructive lung disease (Dominelli et al., 2015a) and particulate matter exposure from animal farming (Omeland et al., 2000). As the SR analysis is dimensionless, it is possible to compare MEFV curves between groups that are known to differ in absolute magnitude of flow and volume.

In most individuals, the pulmonary system has a large reserve to increase flow and volume in order to generate an appropriate alveolar ventilation to meet the metabolic demands of exercise (Dempsey, 1986). However, during intense exercise in some individuals, the large metabolic demand for pulmonary gas exchange necessitates a ventilation that meets or is near the maximal capacity of the ventilatory system (Dempsey, 1986). The maximal ventilatory capacity is determined by mechanical properties of the lungs and airways and is unaffected by habitual exercise training (Saltin et al., 1968). Thus, with the exception of detrimental effects of pulmonary disease or normal aging (McClaran et al., 1995), maximal ventilatory capacity is relatively static within an individual. One common mechanical ventilatory constraint is expiratory flow limitation (EFL), which occurs when the tidal flow-volume loop intersects the MEFV curve. In healthy subjects, EFL is only present during high intensity exercise (Guenette et al., 2007; Johnson et al., 1991b). In younger healthy subjects, EFL is related to: aerobic fitness (McClaran et al., 1998), sex (Guenette et al., 2007) and the absolute magnitude of the MEFV (Dominelli et al., 2011). However, the relationship between MEFV curvature and EFL magnitude or occurrence is unknown. Specifically, if a subject has a MEFV curve displaying a concavity (relative to the volume axis) they may be less susceptible to EFL due to the greater amounts of expiratory flow. The SR index provides

a simple numerical assessment of the degree of concavity present and may provide a method of determining who is most susceptible to develop EFL.

Bronchial asthma is a disease that is characterized by inflammation of the airway tree. However, the degree, severity and specific location of airway inflammation is variable within and between subjects (de Lange et al., 2006). Nonetheless, a consistent consequence of asthma is some degree of heterogeneous distribution of ventilation throughout the lungs due to bronchial smooth muscle contraction, mucosal edema and small airway closure (Samee et al., 2003; Wagner et al., 1996). Given the non-uniformity of airflow in the lungs, we expect that the MEFV curve of an asthmatic subject would have a curvature associated with heterogeneous lung emptying. If the heterogeneity were altered in an asthmatic, through the use of a bronchodilator, we would expect to see a detectable change in the SR.

The primary purpose of this study was to determine if MEFV curvature was related to the occurrence of EFL during exercise in healthy young subjects and if altering the inspired gas resistance altered the SR. Additionally, we questioned if the SR varied with bronchial smooth muscle tone in asthmatic subjects. We hypothesized that healthy subjects who develop EFL will have a greater SR, indicating a relative convexity in the MEFV curve, compared with those who do not develop EFL. Likewise, by inspiring a low density gas and decreasing airway resistance will be associated with a lower SR. Finally, pharmacologically inducing bronchodilation in asthmatic subjects will be associated with a lower SR compared to control and eucapnic hyperventilation induced broncho-constricted conditions.

2. Methods

2.1. Subjects and experimental overview

The current study is a retrospective analysis of previously collected data. All procedures in the original investigations received institutional ethical approval. To determine the relationship between the SR and EFL, eighty-four young healthy subjects were analyzed from published data (Dominelli et al., 2013, 2011, 2015b, 2014b). All subjects were non-smokers and had normal spirometry (Tan et al., 2011). Resting spirometric data was assessed by a qualified respirologist who was blinded to whether or not subjects developed EFL during exercise.

Exercise consisted of a graded exercise test to exhaustion, with discrete step-wise increments in workload using either a cycle ergometer ($n = 56$) or treadmill ($n = 28$). The MEFV curves were collected according to a similar standardized procedure (ATS, 1995). We accounted for exercise-induced bronchodilation and thoracic gas compression by having subject perform FVC maneuvers before and after exercise with maximal and graded efforts and used the largest flow at any given volume as the outer boundary of the MEFV curve (Guenette et al., 2010). Expiratory flow limitation was assessed via superimposing tidal flow-volume loops on the MEFV curve (Johnson et al., 1999). Tidal flow-volume loops were determined by creating a composite average of several (15–20) breaths immediately prior to an inspiratory capacity (IC) maneuver. Near the end of each exercise stage (~20 s remaining), subjects were instructed to perform the IC maneuver. In most subjects (74%) we measured esophageal pressure and could verify the maximal negative pressure during IC maneuver

was consistent between attempts. Offline, volume during the IC maneuver was corrected for drift and end-expiratory lung volume was calculated by subtracting IC from FVC. Finally, tidal flow-volume loops were placed in the MEFV curve according to end-expiratory lung volume and considered EFL only if a minimum of 5% overlap was observed (Derchak et al., 2000). In addition, the effect of heliox (21% O₂: 79% He) inspiration on the SR was assessed in a subgroup of women ($n = 21$). A heliox inspire was used to determine the effect of altering gas properties, namely airflow resistance on the SR. To generate a MEFV curve on heliox, subjects inspired the gas mixture for approximately 5 min and then performed graded forced vital capacity maneuvers (Guenette et al., 2010). Pneumotachographs were calibrated with the respective inspire for each maneuver.

To determine the effects of bronchial smooth muscle tone on SR, eight asthmatic subjects were analyzed from previous work (Rossman et al., 2014). Each subject performed spirometry under three different conditions on three different days: baseline, after administration of a standard dose (400 mcg) of albuterol and after completing six minutes of eucapnic (5% CO₂, 21% O₂, balance N₂) voluntary hyperpnea at a ventilation rate calculated as FEV1.0 $\times$ 30 (Anderson and Brannan, 2003). Age, height and sex matched healthy controls were matched to the asthmatic subjects in order to compare resting pulmonary function and SR.

2.2. Slope-ratio method for MEFV curve quantification

The SR method was used to quantify the shape of the MEFV curves. We have recently detailed the SR method and its utility in detecting differences in MEFV curvature (Dominelli et al., 2015a). Briefly, at all points of interest along a MEFV curve, a line of tangency and a chord line (intersecting the point of interest and residual volume which was assumed to be zero) was determined (Fig. 1). The change in flow and change in volume used in the tangent line was 200 ml above and below the point of interest. Other deltas in flow/volume were used (50–400 ml) and no difference in SR was observed. Therefore, 200 ml was chosen to minimize the possibility of erroneous values due to small oscillatory noise. Moreover, 200 ml also approximates 4–5% of our entire cohort's VC (~4.5l) and it is the similar change employed by others (Tien et al., 1979), allowing for direct comparison between reported results. The SR is unit-less and we report it as arbitrary unit at percentages of maximal volume. At every volume increment between 80 and 20% (*i.e.*, the effort independent range) of the MEFV curve, we calculated the average SR and the SR at 30 specific points in 2% increments of FVC (*e.g.*, 80, 78, 76% FVC). Volumes above 80% and below 20% were not calculated due to the effect of effort dependence and passive opposition of the chest wall over-riding the flow limiting mechanism (Mead, 1978), respectively. An average SR of 1.0 indicates a linear decrease in flow with decreasing volume, whereas <1 designates a concave shape or “bump” and >1 defines a convex shape or “scoop” (Fig. 1). A SR between 0.5–2.5 is indicative of homogenous lung emptying, whereas >2.5 indicates heterogeneous lung emptying and is consistent with obstructive lung disease (Mead, 1978). However, the spatial change in the SR throughout lung volumes is often not consistent. For example, a MEFV curve could have a SR > 1.0 (scoop) at high lung volumes but be equal to one (a linear decline) later in expiration (Dominelli et al., 2015a). Accordingly, the spatial change in SR throughout different lung volumes was assessed in each subject. If there was a significant

correlation between SR and % FVC we also report the direction. Specifically, if the SR falls with decreasing lung volumes, it was termed a positive SR-% FVC relationship. A spatial pattern of change in the SR-% FVC relationship can also be indicative of heterogeneous emptying, even if the specific SR values are in the homogenous range (0.5–2.5). A single investigator preformed the SR analysis in all subjects.

2.3. Statistical analysis

Descriptive variables between groups were computed and means were compared using independent *t*-tests. Independent *t*-tests with Bonferroni adjustments for multiple comparisons were used to determine differences in the average MEFV curve shape and compare the groups at different % FVC. Fisher's exact test was used to compare the frequency of positive SR-volume relationships between groups. To determine if a significantly greater portion of the EFL individual had a SR above unity (1.0) we performed a proportion test. The relationship between SR and $\dot{V}_{O_{2max}}$ was determined using Pearson product moment correlations. Different conditions in asthmatic subjects were compared using a repeated measures analysis of variance. When significant F ratios were detected a Tukey post hoc test was performed. Data from the heliox condition was compared using paired *t*-test. Significance was set at $p < 0.05$.

3. Results

3.1. Young healthy subjects

Table 1 provides descriptive data including spirometry, average SR, and exercise variables. Subjects with EFL during exercise had significantly smaller FVC, FEV₁, and FEV₁/FVC ratio relative to non-EFL subjects ($p < 0.05$). Maximal exercise variables were similar between groups (Table 1) and there was no significant relationship between the SR and $\dot{V}_{O_{2max}}$ when all subjects were pooled (Fig. 2; $r = 0.14$, $p > 0.05$) or split into groups based on the presence (EFL, $r = 0.21$, $p > 0.05$) or absence (NEFL, $r = 0.03$, $p > 0.05$) of EFL. The MEFV curve of the NEFL group was greater in terms of absolute volume and flow compared to the EFL group (Fig. 3A). Subjects who developed EFL during exercise had a greater SR at lung volumes between 80 and 48% FVC (Fig. 3B) ($p < 0.05$). However, all healthy subjects (regardless of flow limitation) had specific SR values that minimally changed throughout expiration (as volume decreased), with the EFL group staying above unity (SR > 1) and the NEFL group predominantly below (SR < 1). With a threshold set at a SR of 1.0, we found that the EFL group had a significantly greater proportion of the group above unity compared to the NEFL subjects (76 vs. 19%, $p < 0.001$ for EFL and NEFL respectively). There was no statistical difference in the frequency of positive SR-volume slopes between the groups (10 out of 20 and 4 out of 19 for the EFL and NEFL respectively), with the remaining subjects showing no significant trend in SR during expiration. While the EFL group had a significantly larger SR, there was overlap between the groups (Fig. 4). There were no differences when the EFL and NEFL subjects were pooled and re-grouped based on sex (1.03 ± 0.2 vs. 0.99 ± 0.3 , $p > 0.05$ for men and women respectively). Inspiring heliox in the subset of healthy women resulted in greater forced expiratory flows with no change in lung volume (Fig. 5A). However, there was no change in

the average SR (1.05 ± 0.3 vs. 1.02 ± 0.3 for air and heliox respectively; $p > 0.05$) or in SR at specific lung volumes (Fig. 5B).

3.2. Asthmatics

Compared to the healthy controls, asthmatic subjects had similar FVC, but significantly reduced FEV₁ and FEV₁/FVC (Table 2) ($p > 0.05$). Compared to the control condition, the FEV₁ after albuterol was $12.2 \pm 7.5\%$ greater, whereas the hyperpnea challenge resulted in a $26.6 \pm 15.3\%$ reduction. Although there was overlap with healthy controls, the asthmatic group's average SR was greater and all subjects displayed a positive SR dependence with lung volume. Composite MEFV curves and SR over different % FVCs for the asthmatic group is shown in Fig. 6. The albuterol and voluntary hyperpnea challenge increased and decreased the magnitude of MEFV curve respectively, but no systematic change in the average or volume specific SR was observed with either intervention (average SR: 1.35 ± 0.09 vs. 1.38 ± 0.17 vs. 1.30 ± 0.15 ; for the baseline, albuterol and hyperpnea respectively).

4. Discussion

4.1. Main findings

Our study demonstrates that the shape of the MEFV curve is associated with the occurrence of EFL during exercise in young healthy subjects. Specifically, those who developed EFL have a MEFV curve that showed greater convexity compared to those who did not develop flow limitation. We also found that the average SR was unaffected by modifying the physical characteristics of the inspired gas (*via* heliox breathing) and that there was no relationship between the average SR and $\dot{V}_{O_{2max}}$. Finally, asthmatic subjects had a greater average SR relative to matched controls, and MEFV curvature did not change when the airways were dilated with albuterol or narrowed following a hyperpnea challenge. Our results indicate that a higher average SR is associated with EFL during exercise in healthy young individuals. As the SR is dimensionless and insensitive to absolute magnitude, it could be used to compare group's predisposition to EFL when other variables associated with the MEFV curve, such as absolute volume and flow, are confounded by age, height and sex.

4.2. Maximal expiratory flow-volume curvature and expiratory flow limitation during exercise

Using the SR method, we demonstrated that the MEFV curvature differs between those who did and did not develop EFL during exercise despite considerable variation in values. However, all subjects, regardless of the presence of EFL, had an average SR value that is consistent with homogenous lung emptying (Mead, 1978). Using the SR method, a lung that empties in a perfectly homogenous fashion will have an average SR equal to 1.0, representing a linear decrease in flow as a function of expired volume. On average, the NEFL subjects had an average SR that was 0.15 units below unity ($=1.0$), while the EFL subjects were 0.15 units above unity, indicating a very minor concavity and convexity, respectively. We emphasize that the subjects in both groups were healthy; therefore, these differences between subjects likely represent normal biological variation, similar to how

lung volumes vary between individuals with similar demographics characteristics (ATS, 1995) and does not represent any underlying pathology. We found no systematic change in the volume specific SR throughout expiration, which has been observed by others in young healthy subjects (O'Donnell et al., 1986), but is in contrast to subjects with obstructive disease and those who are older but healthy (Dominelli et al., 2015a). Rather, our subjects showed minor spatial variation in the SR from 80 to 20% lung volume. A likely explanation for the variation is minor difference in location and movement of the equal pressure point during the forced expiration (Mead, 1978).

We found no relationship between the average SR and $\dot{V}_{O_{2max}}$ (Fig. 2). For example, at a $\dot{V}_{O_{2max}}$ of 50 ml kg⁻¹ min⁻¹ we had SR values ranging from 0.5 to 1.75, which represents the range of our measure. The lack of effect of habitual exercise training on pulmonary function has been observed by others in both cross-sectional (Dempsey et al., 1984; Johnson et al., 1992) and longitudinal data (Dominelli et al., 2014a; McClaran et al., 1995; Saltin et al., 1968).

Previous work has shown that a myriad of variables are associated with EFL. For example, dynamic variables such as maximal oxygen uptake (McClaran et al., 1998) and operational lung volumes (Guenette et al., 2007), as well as static anatomical factors such as lung and airway size (Dominelli et al., 2011; Smith et al., 2014) have been shown to predict EFL. The current study suggests that the curvature of the MEFV curve also plays a role in predicting those who may develop EFL during exercise. Using a SR threshold of >1.0 to predict flow limitation, we would have successfully identified 76% of the EFL group and been erroneous with 19% of the NEFL subjects. While it is clear that the SR is not entirely predictive of flow-limitation, it can still be useful. Specifically, our finding that SR and EFL are related is of significance because SR is independent of magnitude, allowing for comparisons between groups known to differ in other predictor variables such as lung/airway size and aerobic fitness between men and women (Guenette et al., 2007; Mead, 1980; Sheel et al., 2009; Dominelli et al., 2015c) or older individuals (Johnson et al., 1991a; McClaran et al., 1995). For example, an average male would have greater lung volumes and expiratory flows compared to a height and age matched female. However, the male could have a greater SR compared to the female and this might predispose him to EFL despite the greater absolute flows and volume. Overall, our data further supports the concept that EFL during exercise is rarely an “all or nothing” phenomenon (Babb, 2013); rather, it is a dynamic process with multiple determinants and the SR is one of multiple contributors. It is unlikely that any one variable is a principle determinant of EFL during exercise in healthy young subjects. Rather, a combination of factors would predispose one to developing EFL. Finally, the effect of EFL on exercise should also be viewed as a continuum, rather than a finite conclusion. For example, the effect of EFL would differ substantially between subjects who develop minimal flow limitation (~10–20%) only at max workloads compared to a subject who develops considerable EFL (>50%) at several exercise intensities.

Inspiring heliox gas had no effect on the shape of the MEFV curves (Fig. 5). When nitrogen is replaced with helium as a backing gas, flow is less likely to become turbulent. Although the viscosity of helium is greater than nitrogen, the gas is much less dense and the overall

result is an increased propensity towards laminar flow. The increased laminar flow results in lower resistance, which in turn allows for greater maximal flow. As shown in Fig. 5A, the maximal expiratory flow is significantly greater when subjects inspired helium, but the volume is unchanged. Despite the greater expiratory flow, the average and volume specific SR was identical throughout the entire expiration (Fig. 5B). The lack of effect with helium, suggests that the mechanism(s) responsible for difference in SR amongst healthy subjects is not influenced by resistance. Similarly, when resistance was lowered in the asthmatics subjects, via albuterol, there was a similar increase in expiratory flow without a systematic change in SR (Fig. 6).

4.3. Asthma

As expected, compared to matched controls the asthmatic subjects in our study had a significantly reduced FEV_1 , FEV_1/FVC ratio and a greater SR (Table 2). While the average SR was significantly greater in asthmatic subjects, it was still within the range that is thought to represent homogenous lung emptying (<2.5) (Mead, 1978). However, all of the asthmatics subjects displayed a positive SR-lung volume relationship, whereas there was no spatial relationship in the healthy subjects. The positive SR-lung volume relationship is indicative of serial lung unit emptying, which has been described extensively elsewhere (Mead, 1978; O'Donnell et al., 1986).

Despite the differences in expiratory flows, there was no difference in the shape of the MEFV curve between the various conditions in asthmatics (Fig. 6). Even when examined in greater detail using SR over the range of lung volumes, all three conditions overlap from ~70% vital capacity onwards. Our initial hypothesis was that albuterol would reduce overall bronchoconstriction and make the MEFV curve more linear relative to the control condition. While the albuterol did cause an increased in the absolute magnitude of flow and volume, the curvature and mild scoop remained unchanged. Similarly, when we induced bronchoconstriction with the eucapnic hyperventilation, expiratory flow was reduced over all lung volumes, but the SR was similar (Fig. 6). Our finding is in keeping with previous reports that also found that absolute magnitude of MEFV was easily manipulated, but the curvature was relatively unchanged (Mead, 1978). By contrast, others have used similar methods and found that asthmatics differ in SR with varying bronchial smooth muscle tone when compared to normal subject given the same bronchoactive agents (O'Donnell et al., 1986). Why do the changes in bronchial tone not lead to consistent changes in the MEFV curvature? One possibility is the differences in the extent and location of airway narrowing among asthmatics. The bronchoconstriction would affect the SR depending on whether the reactivity is throughout the whole conducting unit or specific components (O'Donnell et al., 1986). Evidence for this comes from recent studies using hyperpolarized helium to image airways of asthmatics after bronchoactive stimuli (Samee et al., 2003), where the location of ventilation defects (specific area with reduced airflow) in the airways appears to be stable within an individual, but highly variable between individuals (de Lange et al., 2009). There also appears to be moderate correlations between many pulmonary function measures (FEV_1 , FEV_1/FVC and FEF_{25-75}) and the number of ventilation defects, but there are many exceptions whereby asthmatics had abnormal spirometry, but no ventilation defects (de Lange et al., 2006). Overall, while the magnitudes of expiratory flows are easily manipulated

in asthmatics, the overall shape of the MEFV curve remains similar. The persistence of MEFV curve shape despite changes in magnitude is akin to the effect of helium on healthy subjects, indicating that resistance may play a minimal role in determining the SR.

4.4. Limitations

There are potential limitations of our study. First, our healthy subjects completed exercise either on a treadmill ($n = 28$) or a cycle ergometer ($n = 56$). There is evidence to suggest that the ventilatory response to exercise differs depending on modality (Tanner et al., 2014). However, we did not find a bias EFL between modality between group (treadmill subjects: $n = 12$ in EFL, $n = 16$ in NEFL). Second, the current study was a retrospective analysis of previously published work spanning several years. As such, minor variability between experimental set-up, such as flow meter device or external resistance, could have influenced our findings. However, the data in each specific comparison (EFL vs. NEFL; three asthmatic conditions) was collected and analyzed by a single investigator, and the experimental set-up was not appreciably different. Specifically, a pneumotachograph was used to assess flow in every condition and the mouthpiece and expired tubing was similar. Finally, both the EFL and NEFL groups were predominantly women. While there are many notable sex differences in the respiratory system, we did not find any differences in the SR between the sexes.

5. Conclusion

In summary, we found that those who developed EFL during exercise had a greater average SR compared to those who did not develop EFL. However, in healthy subjects there was no effect of aerobic fitness, gas density, or sex on the shape of MEFV curves. In the healthy subjects, the average value, along with the spatial change in SR over different lung volumes, indicates that lung emptying occurs in a homogenous manner. Conversely, those with asthma had an average SR that was significantly higher than healthy subjects. Yet, we were unable to detect any changes in the average or volume specific SR between conditions of high and low bronchial smooth muscle tone in asthmatics, indicating airways resistance may not be an important determinant of the SR. Overall, the SR is another metric associated with EFL in healthy young subjects. The SR index has the advantage of being independent of several other variables that are influenced by height, age and/or sex.

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Representative values for maximal flow-volume curve shapes using the different analysis

Method	Shape of the MEFV with corresponding value		
	Linear	Convex* or “scoop”	Concave* or “bump”
Slope-Ratio (SR)	SR=1	SR > 1	SR < 1
Schematic			

*, shape is with respect to the x-axis.

Fig. 1. Examples of the procedure of determining the SR of a MEFV curve. The examples represent a MEFV curve from the same young healthy subject. $\dot{V}$ flow; V_{exp} , volume remaining to be expired; Tan, tangent; $\dot{V}$ change in flow; V , change in volume.

Fig. 2.

Relationship between the slope-ratio quantification of MEFV curves and maximal oxygen uptake in all healthy subjects. No relationship was observed in the younger group as a whole or split between the flow limited and non-flow limited subjects. Au, arbitrary units; EFL, expiratory flow limited; NEFL, non-expiratory flow limited; $\dot{V}O_{2max}$ maximal oxygen uptake. $P < 0.05$.

Fig. 3.

Composite average maximal expiratory flow-volume curves (Panel A) and average slope-ratio unit at varying lung volumes (Panel B). Groups have been aligned to total lung capacity in Panel A to ease curvature comparison. *, significantly different between EFL and NEFL group. Au, arbitrary units; EFL, expiratory flow limitation, FVC, forced vital capacity; NEFL, non-expiratory flow limited. Values are mean $\pm$ SE. $P < 0.05$.

Fig. 4.

Individual average slope-ratio values for each subject along with box-and-whisker plots for the each group. The dots in each box plot represent the 5th and 95th percentile and the thin line within the box is the median. Vertical dashed line is to visually show a slope-ratio of 1.0. Au, arbitrary units; EFL, expiratory flow limited; NEFL, non-expiratory flow limited.

Fig. 5.

Composite average maximal expiratory flow-volume curves (Panel A) and average slope-ratio unit at varying lung volumes (Panel B) for 21 female subjects breathing room air or heliox gas. Au, arbitrary units; FVC, forced vital capacity; He, heliox. Values are mean $\pm$ SE.

Fig. 6.

Composite average maximal expiratory flow-volume curves (Panel A) and average slope-ratio unit at varying lung volumes (Panel B) for asthmatic subjects during three experimental conditions. Au, arbitrary units, FVC, forced vital capacity. Values are mean $\pm$ SE.

Table 1

Descriptive variables for healthy subjects at rest and maximal exercise.

	EFL <i>N</i> = 42	NEFL <i>N</i> = 42
Age (years)	27 ± 5	26 ± 5
% Female	76	76
Height (cm)	171 ± 9	173 ± 8
Mass (kg)	65 ± 9	65 ± 10
BMI (kg m ⁻²)	22.3 ± 2	21.8 ± 3
FVC (l)	4.4 ± 0.9	4.7 ± 1.0
% Pred	103 ± 8 *	108 ± 11
FEV ₁ (l)	3.5 ± 0.7 *	4.0 ± 0.8
% Pred	97 ± 9 *	106 ± 11
FEV ₁ /FVC(%)	81 ± 6 *	85 ± 5
% Pred	97 ± 7 *	101 ± 6
PEF (l s ⁻¹)	8.2 ± 2.0	8.7 ± 1.9
% Pred	103 ± 15	106 ± 22
Average SR (au)	1.15 ± 0.20 *	0.85 ± .20
Range	0.75–1.76	0.44–1.32
Maximal exercise		
$\dot{V}_{O_2}$ (ml kg ⁻¹ min ⁻¹)	51.9 ± 8.2	53.7 ± 9.5
$\dot{V}_{O_2}$ (l/min)	3.3 ± 0.7	3.4 ± 0.8
$\dot{V}_{CO_2}$	3.6 ± 0.8	3.7 ± 0.7
$\dot{V}_E$ (l/min)	116 ± 28	118 ± 27
$\dot{V}_E/\dot{V}_{O_2}$	36 ± 5	35 ± 4
$\dot{V}_E/\dot{V}_{CO_2}$	32 ± 4	33 ± 4
RER	1.10 ± 0.04	1.09 ± 0.05
<i>V</i> _T (l)	2.2 ± 0.6	2.2 ± 0.6
<i>f</i> _b (bpm)	55 ± 8	56 ± 9

Values are mean ± SD. Abbreviations: Au, arbitrary units; EFL, expiratory flow limitation; NEFL, no expiratory flow limitation; BMI, body mass index; FVC, forced vital capacity; Pred, predicted; FEV₁, forced expiratory volume in 1 s; PEF, peak expiratory flow; SR, slope-ratio; $\dot{V}_{O_2}$

maximal oxygen uptake; $\dot{V}_{CO_2}$, maximal carbon dioxide production; $\dot{V}_E$, minute ventilation; *V*_T, tidal volume, *f*_b, breathing frequency.

* Significantly different from NEFL group. *P* < 0.05.

Table 2

Descriptive variables for asthmatics during control condition and matched healthy subjects.

	Asthma ^a N = 8	Healthy N = 8
Age (years)	33 ± 6	31 ± 3
% Female	29	29
Height (cm)	172 ± 7	176 ± 2
Mass (kg)	76 ± 18	70 ± 4
BMI (kg m ⁻²)	25.7 ± 4.0	22.5 ± 1.0
FVC (l)	5.0 ± 1.0	5.1 ± 0.4
% Pred	106 ± 18	106 ± 3
FEV ₁ (l)	3.3 ± 0.6 [*]	4.3 ± 0.3
% Pred	88 ± 15 [*]	106 ± 5
FEV ₁ /FVC(%)	69 ± 15 [*]	83 ± 2
% Pred	83 ± 5 [*]	101 ± 2
PEF (l s ⁻¹)	7.6 ± 2	9.9 ± 0.9
% Pred	90 ± 18	93 ± 15
SR (au)	1.35 ± 0.03 [*]	0.90 ± 0.11
Range	1.25–1.45	0.65–1.47
$\dot{V}_{O_{2max}}$ (ml kg ⁻¹ min ⁻¹)	45 ± 7	55 ± 5

Values are mean ± SD. Abbreviations: Au, arbitrary units; BMI, body mass index; FVC, forced vital capacity; Pred, predicted; FEV₁, forced expiratory volume in 1 s; PEF, peak expiratory flow; SR, slope-ratio $\dot{V}_{O_{2max}}$, maximal oxygen uptake.

^a Asthmatic variables are taken from the control condition

^{*} Significantly different from young healthy group. $P < 0.05$.