History dependence of vital capacity in constricted lungs

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Submitted 8 December 2009; accepted in final form 16 April 2010

Olson TP, Wilson TA, Johnson BD, Hyatt RE. History dependence of vital capacity in constricted lungs. J Appl Physiol 109: 121–125, 2010. Measurements of dynamic force-length behavior of maximally activated strips of smooth muscle during oscillatory length changes show that force decreases well below the isometric force during the shortening phase of the oscillation. The magnitude of the decrease depends on the rate of shortening; for slower shortening, the decrease is smaller and force is larger. Modeling of expiratory flow, based on these data, predicts that vital capacity in constricted lungs depends on the rate of expiration. In maximally constricted lungs, forced vital capacity (FVC) is predicted to be 16% smaller than control, and vital capacity for a very slow expiration (SVC), 31% less than control. These predictions were tested by measuring FVC and SVC in constricted normal subjects. In the first group of 9 subjects, four maneuvers were made following the delivery of two doses of methacholine in the order: SVC, FVC, SVC. In a second group of 11 subjects, two maneuvers were performed at each dose in the order: FVC, SVC. At the highest dose of methacholine, FVC for both trials in group 1 and for the one trial in group 2 were all ~13% less than control, a slightly smaller decrease than predicted. SVC for the 1st trial in group 1 was 27% less than control, also slightly smaller than predicted. The difference between FVC and SVC for this trial, 13%, was close to the predicted difference of 15%. However, SVC for the 2nd trial in group 1 (preceded by 3 vital capacity maneuvers) and for group 2 (preceded by 1) were no different from FVC. We conclude that vital capacity in constricted lungs depends on the dynamic force-length properties of smooth muscle and that the history dependence of the dynamic properties of smooth muscle is more complicated than has been inferred from oscillatory force-length behavior.

asthma; smooth muscle; force-length properties

GUNST AND COLLEAGUES (5, 14) have reported extensive data on force-length curves of maximally activated strips of trachealis muscle during oscillatory length changes. The descending limbs of these curves begin at a force near the isometric force, and force decreases below the isometric force as the muscle shortens. The magnitude of the decrease is smaller for slower rates of shortening. Anafi and Wilson (1) formulated an empirical mathematical representation of these data and incorporated this model into a model for the dynamic behavior of intact constricted airways. Some data on the dynamic behavior of constricted lungs that can be compared with the predictions of this model have been reported. Pellegrino et al. (13) reported the time course of the rise in pulmonary resistance in humans during quiet breathing following a deep breath, and Shinozuka et al. (15) reported the time course of increasing lung resistance in dogs, measured by low-amplitude oscillations, during breath hold after a deep breath. In both cases, the time for recovery of lung resistance was ~20 s, in agreement with the prediction of the model. Jackson et al. (8) also measured the time course of resistance increase following a deep breath in humans. They report an exponential relaxation toward the limiting resistance with a time constant of 35 s, somewhat larger than the prediction, but the constriction in their subjects was rather mild. Lambert and Wilson (10) incorporated the model for the dynamic behavior of constricted airways into a computational model for expiratory flow. For maximally constricted lungs, the model predicts a forced expiratory volume in 1 s (FEV1) that is 26% smaller than the control value for nonconstricted lungs. This agrees well with the drop in FEV1 at maximum constriction observed in a study of 74 constricted normals by Moore et al. (12). The model also predicts that forced vital capacity (FVC) is reduced by 16% in maximally constricted lungs.

Lambert and Wilson noted that FVC was determined by the dynamic force-length curve that was followed as the muscle shortened during expiration, and because this depends on the rate of shortening, vital capacity would depend on the rate of expiration. For an expiration with a duration of ~25 s, the model predicts that the vital capacity (VC) for this very slow expiration (SVC) would be 31% smaller than control FVC, a considerably bigger decrease in vital capacity than the decrease in FVC. The objective of the study reported here was to test the predictions of the model, in particular, the prediction that VC in constricted lungs depends on the rate of expiration.

METHODS

The subjects consisted of 20 young healthy individuals who were recruited from the surrounding community. Inclusion criteria consisted of the following: body mass index (BMI) < 30 kg/m2, nonsmokers, normal cardiac function, and no history of hypertension, lung disease, or coronary artery disease. All participants gave written informed consent after being provided a description of study requirements. The study protocol was approved by the Mayo Clinic Institutional Review Board; all procedures followed institutional and HIPAA guidelines.

Participants were recruited in two groups. Group 1 consisted of 9 subjects, and group 2 consisted of 11 subjects. All subjects underwent pulmonary function testing via body plethysmography to measure baseline pulmonary function and screen for existing obstructive and restrictive pulmonary function abnormalities. Demographic and pulmonary function characteristics are listed in Tables 1 and 2, respectively. There were no significant differences between the characteristics of the two groups.

Vital capacity was measured for two maneuvers. The first was the standard forced vital capacity maneuver (FVC) in which the subject inspired to total lung capacity (TLC) and then expired forcefully until flow fell to essentially zero. The second was a very slow vital capacity maneuver (SVC). In this maneuver, the subject inspired to TLC and expired through an orifice inserted in the expiratory port of the nonrebreathing valve. The orifice size was adjusted to the individual’s TLC so that expiratory times for all subjects for the maneuver were ~25 s. During this maneuver, the subject first relaxed against the
orifice resistance and then increased expiratory effort gradually as lung volume decreased until flow fell to essentially zero. The average duration of the SVC maneuvers for all subjects was 25.5 ± 0.6 s. This was ~4 times the duration of the FVC maneuvers, 6.5 ± 0.2 s.

**Protocol.** All subjects completed the following baseline maneuvers. In the first maneuver, a deep breath of room air inspired through a dosimeter was followed by a 5-s breath hold guided by an audible prompt, relaxed expiration, and resting breathing for 3 min. The subjects then performed vital capacity maneuvers in the sequences listed in Table 3. Subjects in group 1 performed the maneuvers with intervening rest periods in the following order: SVC, 30 s rest, FVC, 1 min rest, FVC, 30 s rest, SVC. The subjects in group 2 then took a single deep breath of saline (1 ml 0.9 % sodium chloride solution) through the dosimeter followed by a 5-s breath hold, resting breathing for 3 min, and the four vital capacity maneuvers with rest periods in the same order.

After the air and saline baseline measurements were completed, vital capacities were measured at each of two doses of methacholine. Subjects in group 1 performed the following maneuvers: a single deep breath of a 25 mg/ml solution of methacholine from the dosimeter with a 5-s breath hold, followed by 3 min of quiet breathing, and then four vital capacity maneuvers in the same order as the baseline maneuvers. The subject then took four deep breaths of methacholine from the dosimeter with a 5-s breath hold at the end of each breath, followed by 3 min of quiet breathing and the same four vital capacity maneuvers. The subjects were instructed to relax and breathe quietly during the 3-min rest following the dose of methacholine and no deep breaths were noted.

Subjects in group 2 performed essentially the same protocol as that for group 1, except for the order of the vital capacity maneuvers. For group 2, the order of the baseline maneuvers was SVC, SVC, SVC, FVC. With the methacholine challenge, these subjects performed two vital capacity maneuvers in the order FVC, SVC.

**Data analysis.** For both groups, the values of FEV1, FVC, and SVC for the first and second trials with room air were not significantly different. The same was true for saline, and the values for saline were not different from the values for room air. Therefore, control values of FEV1, FVC, and SVC for each subject were determined by selecting the largest two values of each variable among the four trials (2 for room air and 2 for saline), and averaging these two values. The values of FEV1, FVC and SVC for each dose of methacholine were normalized by their control values. The control values of SVC and the values of SVC for each dose were normalized by the control value of FVC. Difference from zero was assessed for FVC − SVC for both groups using the one-sample t-test. Two-sample t-tests were conducted to determine differences between group 1 and group 2. Pearson’s correlation was used to determine the relationship between FEV1 and FVC − SVC. Statistical significance was set at an α-level of 0.05. Data are presented as means ± standard error of the mean (SE) unless otherwise noted.

### RESULTS

For group 1, the first two maneuvers after a dose of methacholine (SVC, then FVC) will be denoted group 1, trial 1, and the third and fourth maneuver (FVC, SVC) will be denoted group 1, trial 2. In Fig. 1, average ± SE normalized values of FEV1, FVC, and SVC for group 1, trial 1 (Fig. 1A); group 1, trial 2 (Fig. 1B); and group 2 (Fig. 1C) are shown plotted vs. dose number.

To focus on the difference between FVC and SVC at dose 2, the difference between the values of FVC and SVC are shown plotted against FEV1 for each subject in Fig. 2. For group 1, trial 1 (Fig. 2A), the average difference is 13 ± 4%, and this is significantly different from zero (P < 0.05). Also, it can be seen that the difference is correlated with the decrease in FEV1, and this correlation is statistically significant (r = 0.74, P < 0.05). For group 1, trial 2 and group 2 (Fig. 2, B and C), the average differences are 3 ± 2% and 3 ± 3%, respectively, and not significantly different from zero. For two subjects in group 2, the FVC − SVC is much larger than the average. These subjects were also peculiar in that SVC in the control state was >15% smaller than control FVC, considerably different from the average difference in the control state. We cannot explain these peculiarities for these two subjects, but we do not think they affect the overall results or conclusions.

### DISCUSSION

Surely, the objective of measuring the mechanical properties of airway smooth muscle in vitro is to provide the basis for understanding the mechanics of constricted lungs. However, to translate the data obtained in vitro into an understanding of behavior in vivo, modeling is required, and the predictions of

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**Table 1. Participant characteristics**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>All Participants (n = 20)</th>
<th>Group 1 (n = 9)</th>
<th>Group 2 (n = 11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>27.0 ± 1.6 (19–47)</td>
<td>28.0 ± 3.0 (20–47)</td>
<td>26.1 ± 1.6 (19–37)</td>
</tr>
<tr>
<td>Sex, M/F</td>
<td>10/10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Height, m</td>
<td>1.74 ± 0.02 (1.6–2.0)</td>
<td>1.74 ± 0.05 (1.6–2.0)</td>
<td>1.73 ± 0.03 (1.6–1.9)</td>
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<tr>
<td>Weight, kg</td>
<td>27.2 ± 2.5 (51.5–93.2)</td>
<td>27.1 ± 4.4 (51.5–93.2)</td>
<td>73.2 ± 3.1 (55.9–84.5)</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>23.9 ± 0.4 (19.6–26.5)</td>
<td>23.5 ± 0.7 (19.6–26.2)</td>
<td>24.2 ± 0.5 (20.6–26.5)</td>
</tr>
</tbody>
</table>

Data are presented as means ± SE (range). BMI, body mass index; M, men; F, women.

**Table 2. Pulmonary function**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>All Participants (n = 20)</th>
<th>Group 1 (n = 9)</th>
<th>Group 2 (n = 11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TLC, liters</td>
<td>6.6 ± 0.3</td>
<td>6.5 ± 0.4</td>
<td>6.7 ± 0.4</td>
</tr>
<tr>
<td>TLC, %Pred</td>
<td>109.1 ± 2.7</td>
<td>108.4 ± 2.7</td>
<td>112.6 ± 4.1</td>
</tr>
<tr>
<td>FVC, liters</td>
<td>5.0 ± 0.2</td>
<td>4.9 ± 0.4</td>
<td>5.1 ± 0.3</td>
</tr>
<tr>
<td>FVC, %Pred</td>
<td>105.8 ± 3.2</td>
<td>102.7 ± 4.2</td>
<td>108.3 ± 4.7</td>
</tr>
<tr>
<td>FEV1, liters</td>
<td>4.0 ± 0.2</td>
<td>3.8 ± 0.3</td>
<td>4.1 ± 0.3</td>
</tr>
<tr>
<td>FEV1, %Pred</td>
<td>100.6 ± 2.7</td>
<td>97.0 ± 4.3</td>
<td>103.7 ± 3.3</td>
</tr>
<tr>
<td>FEV1/FVC</td>
<td>79.1 ± 1.0</td>
<td>77.4 ± 1.1</td>
<td>80.4 ± 1.6</td>
</tr>
</tbody>
</table>

Data are presented as means ± SE. TLC, total lung capacity; FVC, forced vital capacity; FEV1, forced expiratory volume in 1 s; %Pred, percentage of predicted.
the modeling must then be compared with data for constricted lungs.

For static conditions, this program has essentially been completed. In the first step, Gunst and Stropp (6) measured the area-pressure curve of maximally constricted excised airways and compared this curve to that predicted for a model of the airway. In the airway model, smooth muscle fibers are pictured as running circumferentially around the airway near the outer surface of the airway wall, and the tension in these fibers exerts a compressive pressure. The area-pressure curve, calculated using the isometric force-length curve for smooth muscle and the law of Laplace, agreed with the data. In both, a transmural pressure of >30 cmH₂O was required to balance the effective pressure exerted by the muscle and hold the

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**Fig. 2.** Individual values of normalized FVC−SVC plotted vs. individual values of normalized FEV₁ for dose 2 for the same cases as in Fig. 1. Average ± SE is shown by the larger filled square symbols. For group 1, trial 1, the difference between FVC and SVC is statistically significant, and the correlation between FVC−SVC and FEV₁ is also statistically significant. For the other cases, the difference is not significant.
airway open. The next step was to test the behavior of airways in the lung. Gunst et al. (7) measured the transmission of small-amplitude pressure oscillations from the airway opening to alveolar capsules at different transpulmonary pressures (Ptp). They found that the airways were closed for Ptp < 10 cmH2O, and open for higher values of Ptp. This result was compared with modeling of the intact airway. In the model of the airway in the lung, with no flow, transmural pressure is provided by parenchymal attachments on the outer surface of the airway. In a uniformly expanded lung, stress in the parenchyma equals Ptp. Near a constricted airway, this stress is augmented by interdependence forces, the additional stress required to deform the surrounding parenchyma. Using Lai-Fook’s formulation of interdependence forces (9), the model predicted that the value of Ptp required to open the airway is ~10 cmH2O, in good agreement with the data. At this value of Ptp, the uniform stress is 10 cmH2O, and the interdependence forces provide 20 cmH2O.

The program for translating dynamic smooth muscle properties, measured in vitro, into an understanding of the dynamics of constricted lungs has barely begun. The most extensive data on dynamic force-length behavior of smooth muscle are those reported by Gunst and colleagues (5, 14). These data describe force-length loops for oscillatory length changes. The descending limbs of these loops lie near the isometric line at the upper limit and fall below the isometric line as the muscle shortens. The decrease in force is greater for faster shortening.

Anafi and Wilson (1) found that the descending limbs of the force-length loops were fit well by solutions to the following differential equation.

\[
\frac{df}{dt} = k_1 f \frac{dl}{dt} + k_2 (1 - f)
\]

In Eq. 1, \(f\) is muscle force as a fraction of isometric force, \(l\) is muscle length as a fraction of optimal length, \(t\) denotes time, and \(k_1\) and \(k_2\) are constants with the values 28 and 0.16 s\(^{-1}\) respectively. For a rapid decrease in muscle length, the first term on the right of the equation is the dominant term, and the solution to the equation is a sharp exponential decrease in force with decreasing length. For a fixed value of \(l\), the first term on the right side of the equation is zero, and the solution to the equation is an exponential relaxation of force to the isometric force for the fixed value of \(l\). For an intermediate rate of shortening, muscle force is a result of the balance between the two terms over the course of the shortening.

The mathematical model expressed by Eq. 1 is a purely empirical model. Other mathematical models of smooth muscle dynamics that are based entirely (11) or partially (4) on concepts of molecular kinetics have been proposed. These models are more complex than that given by Eq. 1. Solutions of the equations for these models for oscillatory length changes also match the data for oscillatory length changes, but the length histories for which solutions have been described is limited.

The data of Gunst (5) and Shen et al. (14) describe dynamic force-length behavior for oscillatory length changes. The data cover a large range of frequencies and a range of amplitudes, but the class of maneuvers is restricted. The mathematical model of these data provide a differential equation that can be applied to different maneuvers, but this implies an assumption that the behavior inferred from data on oscillatory length changes applies to other length histories, and this assumption has not been fully tested.

Some tests of the applicability of Eq. 1 have been made. This equation has been used to predict the time course of the rise of lung resistance after a deep breath (1). At the end of the deep inspiration, the force in the smooth muscle is assumed to be equal to the isometric force for the equilibrium diameter of the airway in the lung. Muscle force and airway diameter are then calculated during expiration and during breath hold at the end of expiration. Airway diameter decreases during expiration and during the subsequent breath hold. The time predicted for reaching final isometric force, minimum airway diameter, and maximum lung resistance is ~20 s. It should be noted that during breath hold, airway diameter continues to decrease and smooth muscle continues to shorten as the force increases, and the time for reaching the final steady state is somewhat longer than that predicted for force recovery at fixed length. The prediction agrees well with the observed rise in resistance after a deep breath in constricted dog lungs reported by Shinozuka et al. (15) and with the observed rise in resistance in constricted normals during quiet breathing following a deep breath reported by Pellegrino et al. (13). The time for recovery after a deep breath for mildly constricted subjects reported by Jackson et al. (8) is somewhat longer.

More recently, Lambert and Wilson (10) used Eq. 1 in a computational model of maximal expiratory flow. In that modeling, muscle force at TLC was assumed to be the isometric force, and Eq. 1 was used to follow muscle force and airway diameter during the expiration. It was assumed that smooth muscle was uniformly activated throughout the bronchial tree, and predictions of the flow-volume model were obtained for different levels of muscle activation. For maximal activation, the model predicted a nearly parallel shift of the flow volume curve with a 26% reduction of FEV\(_1\) and a 16% reduction in FVC. Lambert and Wilson noted that residual volume, the volume at which the constricted airways closed, was determined by the balance between the two terms in Eq. 1 over the time course of expiration. For slower expiratory flows and longer expiratory times, the balance would be shifted toward higher muscle force, and the airways would close at a higher volume. They calculated that for an expiration with a duration of ~25 s (SVC), VC would be reduced by 31% from control FVC, 15% more than the reduction for FVC. This study was intended to test these predictions.

The results of the study are shown in Fig. 1. The values of FEV\(_1\) and FVC for group 1, trial 1 (Fig. 1A), group 1, trial 2 (Fig. 1B), and group 2 (Fig. 1C) for both doses are quite consistent. The values of SVC for the three are not. At dose 1, the decreases in FVC and SVC are about the same for all cases. However, at dose 2, SVC decreases more than FVC for group 1, trial 1, whereas, for group 1, trial 2 and group 2, the decrease in SVC parallels the decrease in FVC.

One unexpected result was the difference between FVC and SVC for the control state. This was small, ~4% FVC, but statistically significant. Part of this difference was likely due to increased gas absorption for the longer expiration time. Several effects would increase gas absorption for longer expiration times: for a respiratory quotient < 1, net absorption increases with time; for a slower expiration, muscle force and intrathoracic gas pressure would be higher and this would increase absorption; and finally, CO\(_2\) concentration and hence, absorption, would rise near end expiration. The largest of these effects is the increase in CO\(_2\) concentration. We estimate this would reduce expired volume by
approximately 50 ml. This is smaller than the difference between the control values of FVC and SVC, ~160 ml. Part of the difference may also be due to the difficulty of maintaining an expiratory effort for a longer duration of expiration; the within-subject variability of the four control tests was a bit larger for SVC, 4%, than for FVC, 2%. On the other hand, lung viscoelasticity would be expected to produce a larger recoil during the slow expiration and hence, a larger SVC.

The objective of this study was to test the predictions of the computational model for expiratory flow in maximally constricted lungs, and therefore, we focus on the results for the higher dose. At dose 2, FEV1 for group 1, trials 1 and 2 and group 2 were 28 ± 3%, 25 ± 4%, and 25 ± 5% less than control, respectively. These values agree well with the prediction of 26% reduction and also agree with the maximum reduction in FEV1 in 74 subjects, 24%, reported by Moore et al. (12).

The decreases in FVC for the three cases were 13 ± 2%, 12 ± 2%, and 14 ± 4%. These are slightly smaller than the model prediction of 16%. Moore et al. did not report values of FVC, and we know of no other data in the literature on FVC in maximally constricted normal subjects. For group 1, trial 1, SVC was 27 ± 5% less than control FVC, also slightly less than the prediction of the model, 31%. However, for group 1, trial 2, SVC was only 15 ± 3% less than control FVC, and this was only 3% greater than the decrease in FVC. We thought that SVC for trial 2 might have been larger than SVC for trial 1 because in trial 2, SVC was preceded by three deep breaths, and these may have blunted the constriction. We therefore studied a second group in which one deep breath preceded the SVC. SVC in this group, 18 ± 4% below control FVC, was essentially the same as that in group 1, trial 2.

The differences between FVC and SVC for individual subjects are plotted against individual values of FEV1 in Fig. 2. For group 1, trial 1 (Fig. 2A), both FVC and SVC are slightly larger than predicted, but the average difference between the two, 13%, is close to the predicted difference, 15%. Also, it can be seen that FVC – SVC is correlated with the degree of constriction, as measured by the decrease in FEV1. Both the average difference and the correlation with FEV1 are statistically significant. For the other two cases (Fig. 2, B and C), the average values of FVC – SVC are 3 ± 2% and 3 ± 3%, and not significantly different from zero.

In summary, the data match the flow-volume model predictions for FEV1 and FVC well. The data also match the prediction of SVC well for the case where SVC is the first maneuver after the delivery of the constricting agent but do not match the prediction if SVC is preceded by even one FVC. We reviewed the data, searching for differences in flows that would explain the difference between the value of SVC for group 1, trial 1, and the values for the other cases. Flows appeared to be the same for all cases. The duration of the SVC maneuver for dose 2 for group 1, trial 1 (22.8 ± 1.3 s) was slightly smaller than those for group 1, trial 2 (24.9 ± 1.1 s) and group 2 (23.7 ± 1.8 s), consistent with the smaller VC for that case. Perhaps the 30 s rest between vital capacity maneuvers was too short to allow the smooth muscle to recover. However, 30 s is sufficient for resistance to reach its limiting value after a deep breath (13, 15), and with 30 s rest, FVC was not affected by a previous deep breath. We conclude that the history dependence of smooth muscle force is more complicated than that inferred from data on oscillatory length changes. It appears that the force-length curve for slow and fast muscle shortening are different if each is the first maneuver following constriction. However, if the slow shortening is preceded by a faster shortening, the force-length curve is different from that for a de novo slow shortening.

The ultimate objective of studies of smooth muscle in vitro and studies of constricted normal lungs is to understand the mechanics of asthmatic lungs. Studies of constricted normal subjects, such as the study reported here, provide information about the effects of smooth muscle activation without the complications of muscle hypertrophy, inflammation, and inhomogeneity that usually accompany asthma. Our conclusion, that dynamic smooth muscle force-length properties affect vital capacity, implies that if smooth muscle dynamics were altered in asthma, this would affect vital capacity.

ACKNOWLEDGMENTS

We thank the participants who volunteered for this study. We also thank Minelle Hulsebus for providing critical technical support.

GRANTS

This study was supported by National Institutes of Health Grant HL-71478 and National Center for Research Resources Grant 1-KL2-RR-024151.

DISCLOSURES

No conflicts of interest (financial or otherwise) are declared by the authors.

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