Smooth muscle dynamics and maximal expiratory flow in asthma

Rodney K. Lambert1 and Theodore A. Wilson2

1Institute of Fundamental Sciences, Massey University, Palmerston North, New Zealand; and 2Department of Aerospace Engineering and Mechanics, University of Minnesota, Minneapolis, Minnesota

Submitted 21 April 2005; accepted in final form 17 June 2005

Lambert, Rodney K., and Theodore A. Wilson. Smooth muscle dynamics and maximal expiratory flow in asthma. J Appl Physiol 99: 1885–1890, 2005. First published June 30, 2005; doi:10.1152/japplphysiol.00450.2005.—A computational model for maximal expiratory flow in constricted lungs is presented. The model was constructed by combining a previous computational model for maximal expiratory flow in normal lungs and a previous mathematical model for smooth muscle dynamics. Maximal expiratory flow-volume curves were computed for different levels of smooth muscle activation. The computed maximal expiratory flow-volume curves agree with data in the literature on flow in constricted nonasthmatic subjects. In the model, muscle force during expiration depends on the balance between the decrease in force that accompanies muscle shortening and the recovery of force that occurs during the time course of expiration, and the computed increase in residual volume (RV) depends on the magnitude of force recovery. The model was also used to calculate RV for a vital capacity maneuver with a slow rate of expiration, and RV was found to be further increased for this maneuver. We propose that the measurement of RV for a vital capacity maneuver with a slow rate of expiration would provide a more sensitive test of smooth muscle activation than the measurement of maximal expiratory flow.

mathematical model; mechanics; constricted lungs; flow-volume curve

Some years ago, Lambert et al. presented a computational model for maximal expiratory flow from the lung (11). In this model, the areas of the trachea and 16 generations of a symmetric bronchial tree were specified as functions of transmural pressure. For a given lung volume, flow was prescribed, and the convective and dissipative pressure losses were integrated along the airways, from the entrance to the 16th generation to the end of the trachea, to obtain the pressure distribution agreed well with the somewhat limited data on the relative contributions of convective and dissipative losses to the total pressure drop during maximal flow and data on the location of the flow-limiting site as a function of lung volume. More recently, Anafi and Wilson (1) have presented a mathematical model for the dynamic length-tension behavior of airway smooth muscle. This model consists of a set of differential equations relating muscle force, length, and the time derivatives of force and length. Solutions to these equations for a given oscillatory length history match the observed force-length behavior of smooth muscle for different amplitudes of length excursions and a wide range of oscillatory frequencies (3, 20). Anafi and Wilson also incorporated this model into the model of Gunst et al. (5) for the mechanics of an intact airway containing smooth muscle and subjected to a transmural pressure that includes the forces exerted by the attachments to the surrounding parenchyma, the interdependence force. They calculated the time course of muscle shortening and airway narrowing that would occur after a deep breath, and this agreed well with the observed time course of the increase in airway resistance after a deep breath (18).

Here, we describe a computational model for maximal flow in constricted lungs. The model was generated by introducing the Anafi model for constricted airways into the Lambert model for expiratory flow. Flow-volume curves were calculated for different levels of muscle activation. The computed flow-volume curve for maximal muscle activation agrees well with data for flow in maximally constricted normal subjects, and the model provides insight into the mechanics of flow in constricted lungs.

MODEL

All of the elements of the model have been described in detail in earlier papers, and these descriptions will be reviewed briefly here.

Airway geometry and mechanics. As in the original Lambert model (11), the conducting airways are represented by the trachea (r = 0) plus 16 generations of a symmetric dichotomously branching network (r = 1–16) extending peripherally from the trachea. Thus each generation consists of 2r identical airways in parallel.

The model for the mechanics of the airways is a combination of the models proposed by Lambert et al. (11) and Anafi and Wilson (1). A schematic diagram of an airway cross section is shown in Fig. 1. The radius and area of the lumen of the airway are denoted r and A, respectively. The airway wall consists of a layer of incompressible tissue surrounded by a thin band of smooth muscle with radius rm. The airway is embedded in the surrounding parenchyma.

Pressure in the lumen of the airway is denoted P. This pressure is balanced by forces exerted by the tissue components of the airway and the surrounding parenchyma. The first of these is the elastic recoil pressure generated by distortion of the connective tissue in the airway wall (Pel). The second is the interdependence stress in the parenchyma that is the result of distortion of the surrounding parenchyma (Pint). The third is the compressive pressure that results from active force in the layer

The costs of publication of this article were defrayed in part by the payment of page charges. The article must therefore be hereby marked “advertisement” in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.
of smooth muscle (Pm). Thus the equilibrium equation for the airway wall is the following.

\[ P = P_{el} + P_{int} + P_{m} \] (1)

The terms on the right side of Eq. 1 are functions of A, and these functions are described in the following paragraphs.

The relation between Pel and A is the same as that used by Lambert et al. (11).

\[ \text{For } P_{el} \leq 0, \frac{A}{A_{max}} = \alpha_0(1 - \text{Pel} / P_{el})^{-n_1} \]
\[ \text{For } P_{el} \geq 0, \frac{A}{A_{max}} = 1 - (1 - \alpha_0)(1 - \text{Pel} / P_{el})^{-n_2} \] (2)

The parameters in Eq. 2, maximal area (A_{max}), normalized area when Pel = 0 (\alpha_0), P_1, P_2, n_1, and n_2, have different values for each generation in the bronchial tree, and the values that are used here are the same as those listed in Ref. 8.

For the intraparenchymal airways (z = 3–16), the relation between Pint and A is the one proposed by Lai-Fook (7) and subsequently used in models of airway mechanics (1, 2, 5).

\[ \text{Pint} = -P_L(1.4x + 2.1x^2) \] (3)

In this equation, P_L denotes lung recoil pressure, and x describes the mismatch between the outer radius of the airway and the radius of the hole in the undeformed parenchyma. It is assumed that, for the conditions, A = A_{max}, r_m, equal to its corresponding maximal value, denoted r_o, and lung volume equal to total lung capacity (TLC), airway radius matches the radius of the hole in the undeformed parenchyma. At other lung volumes, the radius of the hole in the undeformed parenchyma is assumed to equal \( r_oV^b \), where v denotes the ratio of lung volume to volume at TLC. The variable x in Eq. 3 is defined as the difference between the radius of the airway and the radius of the undeformed hole, nondimensionalized by the radius of the undeformed hole, and x is therefore given by the following equation.

\[ x = 1 - \frac{r_m}{r_oV^b} \] (4)

To complete this description of the relation between Pint and A, the relation between r_m and A is required. The area of the tissue inside the muscle is assumed to be 16% of the area inside the muscle at r_m = r_o. This value for the fractional area occupied by tissue is consistent with the data of James et al. (6). The tissue is assumed to be incompressible, and, therefore, A and r_m are related by the following equation.

\[ A = \pi(r_o^2 - 0.16 r_m^2) \] (5)

Finally, the relation between Pm and A is the same as that proposed by Gunst et al. (5). The active force in the muscle layer per unit distance in the axial direction along the airway (transverse to the plane of Fig. 1) is denoted F. That is, F equals the active stress in the muscle times the thickness of the layer. The compressive pressure exerted by the muscle layer is given by the ratio of F to r_m.

\[ P_m = F/r_m \] (6)

The value of F depends on the level of muscle activation, muscle length, and length history. The muscle layer is assumed to have adapted to generate maximal force (F_0) when r_m = r_o. Data for the relation between isometric force (Fiso) and muscle length (4) are approximated by the following equation.

\[ F_0 = F_0[1.25(r_m/r_o) - 0.25] \] (7)

During dynamic muscle shortening, F is smaller than Fiso by the factor f. That is,

\[ F = fF_0 \] (8)

Combining Eqs. 6–8 yields the following expression for Pm.

\[ P_m = (F_0/r_o)F[1.25(r_m/r_o) - 0.25](r_m/r_o) \] (9)

The factor F_0/r_o in this equation describes the amount of smooth muscle in the airway and the degree of activation of the muscle. Based on the data of Gunst and Stropp (4), for maximal muscle activation, this factor is assigned the value of 40 cmH_2O. Finally, the factor f in Eq. 9 depends on muscle history. For muscle shortening, the factor f is determined as the solution to the following empirical differential equation, where k and a are constants and the superscripted dot denotes the time derivative.

\[ f = \frac{1}{k} \exp[k(r_m/r_o - 0.66)] \] (10)

The values of k and a that were obtained by fitting solutions of this equation to the data of Shen et al. (20) are k = 28 and a = 0.12 s^{-1}. Thus the first term on the right side of Eq. 10 describes a very sharp decrease in f with decreasing r_m, and the second term describes a relaxation of f toward the value 1 with a time constant of \( \sim 8 \) s.

The relation between A and P for airways with active smooth muscle is, therefore, given by the solution to Eq. 1 for different values of P, using Eqs. 2, 3, and 9; together with the auxiliary Eqs. 4, 5, and 10 to evaluate the terms on the right side of Eq. 1. The relation between A and P depends on the history of the maneuver.

An example of a particular A-P relation is shown in Fig. 2. This example shows the airway-area curve for the airways in generation 6 at a value of P_L = 20 cmH_2O. In Fig. 2, the value of A as a function of Pel is shown by the dashed line. This is the airway-area curve that was used in the original computational model (8). The curve shown by the dotted dashed line is the curve A vs. Pel + Pint. This is the airway-area curve with interdependence forces included. Interdependence has little effect near the isometric value. We, therefore, assume that, at the end of inspiration, f = 1, and airway area is given by the solution to Eq. 1 with f = 1. For generation 6 with P_L = 20 cmH_2O and f = 1, \( A_{max} = 0.32 \) and \( r_m/r_o = 0.66 \). Thus, for maximal smooth muscle force, airway area is significantly reduced. As flow begins, P drops below 20 cmH_2O, the airways narrow, and muscle shortens rapidly. For rapid muscle shortening, the first term on the right side of Eq. 10 dominates, and the solution to Eq. 10 is f = \( \exp[k(r_m/r_o - 0.66)] \). The...
The value of $V$ was successively increased, and the calculation was repeated until a value of $V$ was reached for which flow speed equaled wave speed at some point in the bronchial tree, or $P$ at the end of the trachea reached $-100$ cmH$_2$O. The flow for which one of these two conditions was met was taken as maximal flow at the given lung volume. Flow increments were reduced as maximal flow was approached.

For a small time step, the changes in lung volume and $P_t$ were calculated from the value of maximal flow at $P_t = 20$ cmH$_2$O, and the change in $f$ was computed from the second term on the right side of Eq. 10. New A-P curves were calculated, and a value of maximal flow for this volume was obtained. These calculations were repeated for successive time steps until a volume was reached for which maximal flow was essentially zero. In this process, the time step was adjusted to be appropriate to the rate of muscle shortening. The initial time step was $5$ ms, followed by $20$ ms, and $100$ ms late in expiration.

**RESULTS**

The MEFV curves calculated for different values of $F_0/r_0$ are shown in Fig. 3. For values of $F_0/r_0 < 20$ cmH$_2$O, smooth muscle activation has little effect on flow. For $F_0/r_0 > 20$ cmH$_2$O, maximal flow decreases, and residual volume (RV) increases with increasing $F_0/r_0$. For maximal smooth muscle activation, maximal flow is less than one-half that in the control state at all lung volumes, and RV is increased by 16% of VC.

Isovolume pressure-flow curves for $F_0/r_0 = 40$ cmH$_2$O, and lung volumes of 75, 50, and 25% VC are shown in Fig. 4. The shapes of these curves are similar to the shapes of the isovolume pressure-flow curves for the control state. The limitation on flow due to turbulent dissipative losses and the wave speed limit on flow depend essentially on the same parameters (9). Therefore, these two mechanisms for flow limitation are inex-
These authors measured the dose-response relationship of flow in constricted normal lungs is that of Moore et al. (15). The major results of the modeling are the computed MEFV curves to inhaled methacholine in 73 normal subjects of both genders and a wide range of ages. Although not all of the subjects reached a plateau in response to increasing doses of methacholine, many did, and one might expect that muscle activation was near maximal at the maximal response. Moore et al. reported the fractional decrease in flow at 30 and 50% VC. The average maximal response of the subjects was a 53% reduction in flow at 50% VC and a 66% reduction at 30% VC. Points with these percentage decreases in flow are shown in Fig. 3. These points lie close to the model prediction for maximal muscle activation. Also, Moore et al. report that the average maximal decrease in forced expiratory volume in 1 s (FEV1) in their subjects was 24%, and, for maximal muscle activation in the model, the decrease in FEV1 is essentially the same, 26%. Thus the quantitative agreement between the predicted flows and the data is good. We would like to emphasize the fact that the values of the parameters in the current model were all set by previous matching to independent anatomic and physiological data, and no parameter values were adjusted to match the data for flow in constricted lungs.

A computational model constitutes a quantitative expression of our understanding, and that is its primary use. To the extent that predictions of a model can be compared with data, it provides a quantitative test of our understanding. Also, with a model, quantities that are inaccessible to measurement can be evaluated, and the results of impossible experiments can be calculated, and these exercises can extend our understanding. In the following paragraphs, the information that the model provides about the mechanisms of flow limitation in constricted lungs is discussed.

One notable feature of the curves shown in Fig. 3 is the insensitivity of the MEFV curve to lower levels of smooth muscle activation. For F0/ρ0 = 20 cmH2O, the MEFV curve and FEV1 are nearly the same as those for the control state. For this value of F0/ρ0, A/Amax for the peripheral airways is 0.7. As a result, the pressure losses in the periphery, which are proportional to A−2, are twice those in the control state. However, the peripheral losses in the control state are small, and, with an increase by a factor of 2, they remain small. More importantly, at lower levels of activation, the A-P curve for the constricted airway merges with the A-P curve for the unconstricted airway at positive pressures, rather than at negative pressures, as shown in Fig. 2. As a result, for negative values of P, the areas of the constricted airways are nearly the same as the areas of unconstricted airways. Thus the A-P curve in the region where flow limitation occurs is nearly the same as in the control case. Because FEV1 is insensitive to lower levels of muscle activation, one might expect the dose-response curve of FEV1 to methacholine (15) to be narrower than the dose-response curve of smooth muscle force in vitro (13), and this is the case.

At higher values of F0/ρ0, this drop in muscle force with decreasing muscle length also diminishes the effect of muscle activation on the MEFV curve. To illustrate this point, an MEFV curve for F0/ρ0 = 40 cmH2O, and no effect of length on force (k = 0 in Eq. 11) was calculated, and this curve is shown in Fig. 5. In this case, muscle force remains equal to the isometric force for maximal muscle activation as the muscle shortens. Flow is drastically reduced at higher lung volumes and drops sharply with decreasing volume. The airways close at a lung volume for which Pτ = 10.4 cmH2O. This is consistent with the observation that, under static conditions,
maximally activated smooth muscle closes the airways for values of \( P_L \) is less than \( 10 \text{ cmH}_2\text{O} \) (5).

The sharp drop in muscle force with decreasing lung volume explains the difference between maximal flows initiated at lung volumes lower than TLC and maximal flows for the full forced VC maneuver (17). For the full maneuver, \( f \) and muscle force decrease significantly during the volume decrease from TLC to the volume at which the partial maneuver begins. If it is assumed that \( f = 1 \) at the initial volume for the partial maneuver, \( f \) and muscle force are higher than for the full maneuver at that volume and remain higher for all succeeding lung volumes. As a result, flows are lower for the partial than for the full maneuver.

The second term on the right side of Eq. 10, the equation that governs smooth muscle dynamics, also plays a significant role in determining the MEFV curves shown in Fig. 3. This term describes the recovery of force over time that occurs when muscle force is depressed below the isometric force. To illustrate the effect of this term, an MEFV curve for \( F_0/r_0 = 40 \text{ cmH}_2\text{O} \) and no force recovery \((a = 0 \text{ in Eq. 10})\) was calculated, and this curve is shown in Fig. 5. It can be seen from Fig. 5 that this term affects the MEFV curve at later times in the expiration, and it is the term that determines the magnitude of the increase in RV in the constricted lung.

It can be seen from Fig. 3 that, at \( F_0/r_0 = 40 \text{ cmH}_2\text{O} \), flow is decreasing rapidly with increasing \( F_0/r_0 \). Therefore, muscle hypertrophy would be expected to have a big effect on flow. To model muscle hypertrophy, the MEFV curve for a 25% increase in \( F_0/r_0 \) from 40 to 50 cmH2O was calculated, and the result is shown in Fig. 6. The increase in \( F_0/r_0 \) caused a nearly parallel shift of the MEFV curve, and FEV1 decreased to 46% of the control value. The effect of inflammation was modeled by increasing the amount of tissue in the wall. Maximal flow was calculated for \( F_0/r_0 = 40 \text{ cmH}_2\text{O} \) and a 25% increase in the tissue volume, from 16% of the area inside the muscle ring to 20%. The result is shown in Fig. 6. The change in wall area also caused a nearly parallel shift in the MEFV curve, but the magnitude of the shift was less than one-half that for the model of muscle hypertrophy. In asthma, muscle hypertrophy and inflammation would be expected to be nonuniform, whereas, in the modeling, the changes in airway properties were applied uniformly. Therefore, these results only indicate the potential magnitude of the effects of muscle hypertrophy and inflammation.

Because RV depends on force recovery and force recovery depends on time, we reasoned that the increase in RV would be greater if expiration were prolonged. We, therefore, calculated the value of RV for a slow expiration. Flow was set at a value of 200 ml/s, and this flow was continued as lung volume decreases to TLC (Fig. 7). The percent change from control in expired volume in 1 s (FEV1) for the forced VC maneuver vs. level of activation (\( F_0/r_0 \)), and change in RV from control as a fraction of VC for a VC maneuver with slow expiration.

Fig. 5. Effects of muscle dynamics on flow. The MEFV curves for the control (dotted line) and maximal smooth muscle activation states (solid line) are compared with those calculated for no dynamic effect of shortening (constant \( k = 0 \) \text{ in Eq. 11} \), dotted dashed line) and no force recovery \((a = 0 \text{ in Eq. 11})\) dashed line). Also shown is the flow-volume curve for expiration limited to 200 ml/s (solid line at low flow). The value of residual volume (RV) for this slow expiration is considerably higher than that for the forced VC maneuver.

Fig. 6. Effects of inflammation and muscle hypertrophy on flow. MEFV curves are shown for the following cases: the base model with maximal muscle activation (solid line); inflammation, modeled by increasing the volume of wall tissue by 25% (dotted line); muscle hypertrophy, modeled by increasing muscle force by 25% (dashed line); and combined inflammation and muscle hypertrophy (dotted dashed line).

Fig. 7. Percent change from control in expired volume in 1 s (FEV1) for the forced VC maneuver vs. level of activation (\( F_0/r_0 \)), and change in RV from control as a fraction of VC for a VC maneuver with slow expiration.

J Appl Physiol • VOL 99 • NOVEMBER 2005 • www.jap.org
decreased until flow limitation reduced flow below 200 ml/s. The resulting curve for $F_0/r_0 = 40$ cmH$_2$O is shown in Fig. 5. The value of RV is higher than the value of RV for the forced VC maneuver. A plot of the increase in RV for this maneuver, expressed as percentage of VC, vs. $F_0/r_0$ is shown in Fig. 7. For smaller values of $F_0/r_0$, the change in RV with $F_0/r_0$ for slow expiration is considerably greater than the change in FEV$_1$ for the forced VC maneuver. That is, RV for the slow-expiration maneuver is more sensitive to $F_0/r_0$ than FEV$_1$, and we suggest the measurement of RV for slow expiration as a more sensitive test of the responsiveness of smooth muscle to agonists.

REFERENCES