Dynamic Behavior during Noninvasive Ventilation
Chaotic Support?

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Acute noninvasive ventilation is generally applied via face mask, with modified pressure support used as the initial mode to assist ventilation. Although an adequate seal can usually be obtained, leaks frequently develop between the mask and the patient's face. This leakage presents a theoretical problem, since the inspiratory phase of pressure support terminates when flow falls to a predetermined fraction of peak inspiratory flow. To explore the issue of mask leakage and machine performance, we used a mathematical model to investigate the dynamic behavior of pressure-supported noninvasive ventilation, and confirmed the predicted behavior through use of a test lung. Our mathematical and laboratory analyses indicate that even when subject effort is unvarying, pressure-support ventilation applied in the presence of an inspiratory leak proximal to the airway opening can be accompanied by marked variations in duration of the inspiratory phase and in autoPEEP. The unstable behavior was observed in the simplest plausible mathematical models, and occurred at impedance values and ventilator settings that are clinically realistic.

Noninvasive ventilation (NIV) is used in an increasing variety of clinical settings, including chronic respiratory failure, acute exacerbations of chronic obstructive pulmonary disease (COPD), and as a bridge to avoid reintubation in patients in whom extubation fails (1). In the setting of acute disease, NIV has been reported to be particularly effective, when tolerated, in treating exacerbations of COPD (2). Unfortunately, a significant fraction of patients fail to tolerate NIV for reasons that are often unclear, but which may relate to inspiratory interactions between patient demands and ventilator response (3, 4).

Acute NIV is generally applied via face mask, with modified pressure support ventilation (PSV) used as the initial ventilatory mode. Although an adequate seal can usually be obtained, leaks often develop between the mask and the patients' face. This leakage presents a theoretical problem, since the inspiratory phase of pressure support terminates when flow falls to a predetermined fraction of peak inspiratory flow. Adverse interactions between patient and ventilator are especially likely when mask leaks occur in the setting of airflow obstruction, because the inspiratory flow profile decelerates less rapidly in the setting of airflow obstruction, and because autoPEEP opposes PSV. To explore the issue of mask leakage and machine performance, we used a mathematical model to investigate the dynamic behavior of pressure supported NIV (PSNIV), and confirmed the predicted behavior through use of a test lung.

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METHODS

Mathematical Model

We analyzed two mathematical models of PSNIV. Both models incorporate PSV applied to a single compartment having a constant compliance, C, inspiratory resistance, R_I, expiratory resistance R_E, and a mask-to-face leak resistance, Rm (Figure 1). The models assume that airway pressure rises abruptly to a constant inspiratory pressure (PI_{set}) until the total flow applied by the ventilator falls to a predetermined percentage of peak flow; the applied pressure then cycles to the set value of PEEP (Figure 2). In the first model (fixed-frequency model), a fixed number of ventilatory cycles per minute (f) is assumed; therefore, total ventilatory cycle time (Ttot) is constant (Ttot = 60/f). Inspiratory time (T_I) is the duration of PI_{set}; expiratory time (T_E) is Ttot − T_I. In the second model (variable-frequency model), the instantaneous respiratory frequency and thus Ttot for a breath is assumed to vary as a linear function of the T_I of that breath (5):

$$f = 17.7 - 2.8 \cdot T_I \quad (1)$$

thus,

$$Ttot = \frac{60}{17.7 - 2.8 \cdot T_I} \quad (2)$$

Equation 1 was taken from the patient data of Laghi and colleagues (5). Modeling details are provided in the APPENDIX. For the work presented here, input variables were selected to simulate airflow obstruction.

Mechanical Model

A test lung model with the configuration shown in Figure 1 was used as a mechanical analogue. A purpose-built solenoid valve system was used to trigger a commercially available noninvasive ventilator (Knightstar 335; Nellcor Puritan Bennett, Lenexa, KS) at fixed frequencies over a range of ventilator settings and impedance parameters. Airway flow and test lung chamber pressures were continuously monitored. Further details of the test lung model may be found in the APPENDIX.

RESULTS

Mathematical Predictions

The fixed-frequency model predicts regions of unstable ventilator output and dynamic behavior within the clinical range of ventilator parameter settings. This is most clearly demonstrated when Rm is progressively reduced with all other impedance parameters and ventilator settings held constant (Figure 3A). In Figure 3, the values on the *y*-axis represent the predicted values of T_I over a range of Rm values; where multiple values are plotted, the system is predicted to cycle or oscillate between multiple values for T_I. Below a "critical value" for Rm, values of T_I lengthen sharply and the system becomes unstable, with T_I cycling through considerably wider ranges than those observed at higher resistances. Similar behavior is predicted for autoPEEP levels; below a critical value of Rm, the breath-to-breath variability of autoPEEP increases sharply (Figure 3B). The expanded ranges of T_I and autoPEEP levels persist as Rm is further lowered. Increasing the set frequency or resistance, or decreasing the flow cutoff, raises the critical value for Rm (data not shown). Increasing set PEEP at a fixed PI_{set} markedly worsens system stability, an effect that is partly

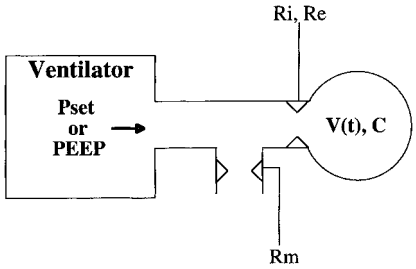

Figure 1. Schematic diagram of modeled ventilatory system. $P_{I_{set}}$ = set inspiratory pressure, C = compliance, R_I = inspiratory resistance, R_E = expiratory resistance, Rm = resistance of mask leak, V(t) = compartmental volume at time t.

attenuated if $P_{I_{set}}$ is also increased to maintain $P_{I_{set}}$-PEEP at a constant value. In the example shown in Figure 3, increasing PEEP from 3 cm H_2O to 6 cm H_2O while maintaining $P_{I_{set}}$ at 15 cm H_2O raises the critical Rm from $\sim$ 68 cm H_2O/L/s to $\sim$ 92 cm H_2O/L/s; increasing $P_{I_{set}}$ to 18 cm H_2O at a PEEP of 6 cm H_2O lowers the critical Rm to 82 cm H_2O/L/s (data not shown).

The variable-frequency model displays less variation in T_I than does the fixed-frequency model. However, this model predicts substantial breath-to-breath variation in Ttot and autoPEEP levels despite constant ventilator settings and impedance parameters; instability is observed over a wider range than in the fixed-frequency model (Figures 3C and 3D). Increasing C or lung resistances, decreasing the flow cutoff, or increasing set PEEP worsens this behavior (data not shown). Changing the gain or base frequency (2.8 cpm/s and 17.7 cpm, respectively, in the example shown in Figure 3) modulates the predicted quantitative behavior (critical values), but not the qualitative behavior (instability).

Mechanical Simulation

Nonuniform behavior was observed in physical simulations done with the test lung (Figure 4). The combinations of impedance parameters and ventilator settings tested in this simulation were predicted by the fixed-frequency model to result in unstable behavior as Rm or the inspiratory flow cutoff level were lowered. When a critical Rm was reached, values of T_I cycled through wider ranges than those observed with values of Rm above the predicted critical Rm (maximal range: 1.2 to 3.4 s, versus 0.7 to 1.2 s with no leak). AutoPEEP levels rose, and their range increased as Rm fell below the critical value (maximal range: 3.1 to 9.1 cm H_2O at Rm = 40 cm H_2O/L/s, versus 3.1 to 5.6 cm H_2O with no leak). Unstable system behavior was also observed with many other clinically realistic combinations of impedance parameters and ventilator settings. Values of T_I within the region of instability varied in a bounded but apparently aperiodic fashion. When the degree of complexity of T_I was analyzed with methods adapted from Glenny (6), it generally (but not always) displayed a fractal nature, with dimension greater than 1.5 (mean dimension: 1.61; range: 1.4 to 1.92).

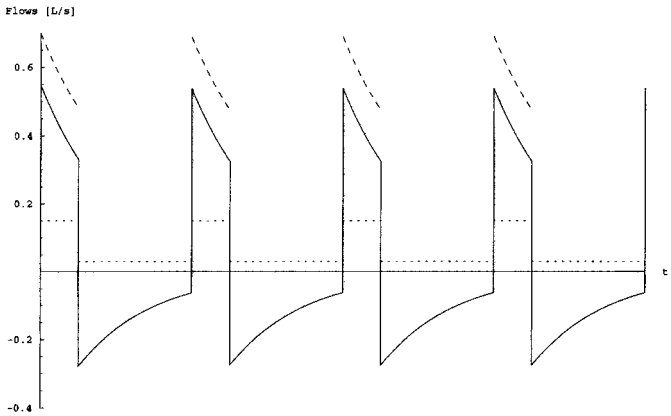

Figure 2. Schematic diagram of pertinent flows. At any point during inspiration, the total flow applied by the ventilator (*dashed line*) is the sum of the flow into the lung (*solid line*) and the flow through the mask leak (*dotted line*). When total inspiratory flow drops to a fixed percentage of peak total inspiratory flow (in this example, 69%), the ventilator cycles from $P_{I_{set}}$ to PEEP, and expiration commences. Here, $P_{I_{set}}$ = 15 cm H_2O, PEEP = 3 cm H_2O, flow cutoff = 69% of peak inspiratory flow; f = 15, C = 0.1 L/cm H_2O, Rm = 100 cm H_2O/L/s, R_I = 20 cm H_2O/L/s, and R_E = 20 cm H_2O/L/s.

DISCUSSION

Interpretation

Our analyses indicate that for patients with airflow obstruction, PSV applied at a fixed frequency in the presence of an inspiratory leak proximal to the airway opening can be accompanied by marked variations in both inspiratory-phase duration and autoPEEP, even when subject effort is unvarying. Conversely, if T_I is allowed to modulate respiratory frequency, the Ttot itself becomes unstable. The instability observed in the fixed-frequency model arises entirely from the interaction of this mode of ventilation with the impedance characteristics of the ventilated subject. The instability observed in the variable-frequency model results from modulation of respiratory frequency by variation in peak flow and T_I. The patient characteristics that appear most likely to increase instability at a given level of ventilatory support (set pressure and frequency) are an increased expiratory time constant (C · resistance) and a low Rm.

The unstable behavior that we observed in the mathematical models and the mechanical simulations may seem surprising, since all three systems that we examined are governed by a very simple set of differential equations. However, "chaotic" behavior of deterministic mathematical systems has clear precedent in the physics and mathematics literature (7–9). The simplest example of such behavior is given by the numerical sequence

$$X_{n+1} = \alpha X_n \cdot (1 - X_n), \qquad (3)$$

where X_n lies between 0 and 1, and α is an arbitrary constant (7). Here, a large value for X_n tends to decrease the subsequent value, X_{n+1}. For values of α less than 3, the sequence converges to a stable, single value for X. For $\alpha = 3$, the sequence oscillates between two values for X. As α is increased beyond 3, X cycles between first two, then four (at $\alpha = 3.444...$), and finally an infinite number of values between 0 and 1 (at $\alpha = 3.57$) (8). In this example, a very simple recursive algorithm, characterized by nonlinear, "tunable" negative feedback between successive values, displays very complicated behaviors.

Although more complex, our model bears qualitative similarity to the aforementioned sequence. Specifically, the fixed-frequency model predicts nonlinear, primarily negative feedback between successive values of T_I. For a given breath, a long T_I will shorten T_E due to the fixed Ttot. A shortened T_E will increase the autoPEEP of the current breath and decrease the peak inspiratory flow of the subsequent breath (by decreasing the pressure gradient for lung inflation at the initiation of inspiration). Since the T_I of a particular breath is a function of the autoPEEP of the preceding breath (APPENDIX), the T_I of breath number n is also a function of the T_I of breath number n − 1, in analogy to the previously cited example. Because PSV terminates inspiration at a fixed fraction of peak inspiratory flow, the balance of dynamic effects arising from the diminution of peak inspiratory flow and dynamic effects consequent to the presence of a mask leak will determine the subsequent

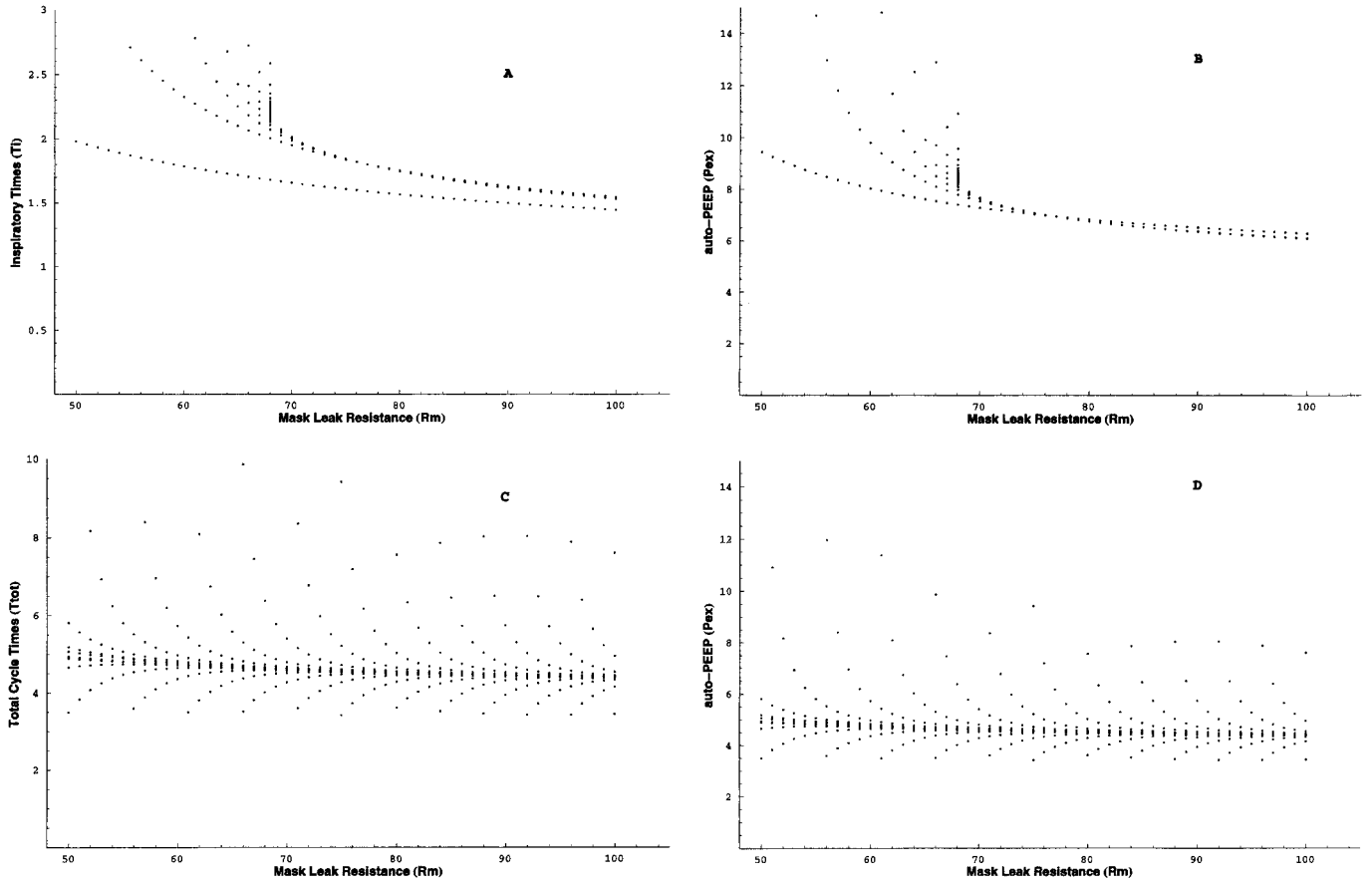

Figure 3. Predicted behaviors from the mathematical models. Panels are scatterplots of predicted outcome (inspiratory times or total respiratory cycle times in seconds or autoPEEP levels in cm H_2O) versus Rm (cm H_2O/L/s). In all panels, C = 0.1 L/cm H_2O, R_I = 20 cm H_2O/L/s, R_E = 20 cm H_2O/L/s, PEEP = 3 cm H_2O, $P_{I_{set}}$ = 15 cm H_2O, and inspiratory flow cutoff = 60% of maximal (peak) inspiratory flow. (*A*) Fixed-frequency model predictions for inspiratory times at f = 17.7 breaths/min. (*B*) Fixed-frequency model predictions for autoPEEP at f = 17.7 breaths/min. (*C*) Variable-frequency model predictions for values of Ttot. (*D*) Variable-frequency model predictions for total autoPEEP levels.

T_I. A prolonged T_I generally shortens the inspiratory phase of the next breath; shortened values of T_I, on average, have the opposite effect (data not shown). Because a given breath can only influence subsequent breaths through the presence of autoPEEP, an expiratory time constant that is "long" relative to Ttot (as seen in obstructive disease) is crucial to the development of instability. Allowing T_I to modulate respiratory frequency moderates the potential variation in T_I and autoPEEP at the expense of significant variability in respiratory frequency.

We did not study these behaviors in patients. Although dynamic instability may contribute to patient–ventilator dyssynchrony in PSNIV, unequivocally ascribing such irregular behavior in the clinical setting to underlying dynamic processes may be difficult. When confronted with unstable ventilator output, the patient may respond by actively "overriding" the ventilator. Furthermore, at present it would be difficult to ascertain whether clinically observed instability arises from unstable patient behavior (due to ventilatory drive or agitation), from dynamic effects, or from both. Our analyses indicate that effort-independent unstable behavior may exist in PSNIV; further characterization of the predicted dynamics is required before their role or importance in the clinical setting can be clearly delineated.

Limitations of the Model

The mathematical models that we used are the simplest plausible models of pressure-supported noninvasive ventilation. The rate of rise of inspiratory airway pressure was assumed to be abrupt, untapered, and always uniform (an "ideal" square wave). Furthermore, the models are linear, unicompartmental, and do not account for patient effort. The variable-frequency model incorporates only a very simple feedback loop, albeit one that is derived from clinical data (5), and does not address conscious modulation of the ventilatory pattern. Ad-

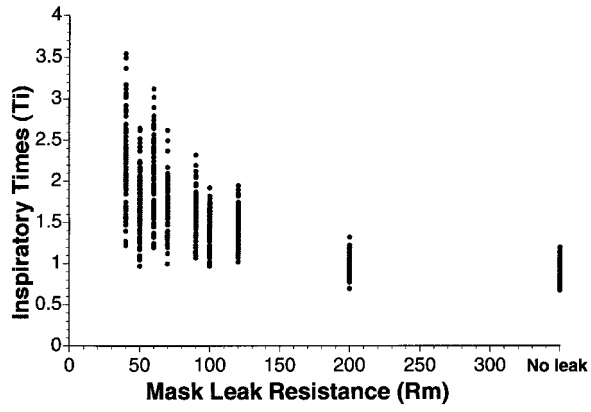

Figure 4. Observed experimental behavior of the fixed–frequency model, shown as a scatterplot of observed inspiratory times versus Rm (cm H_2O/L/s); each simulation was analyzed over at least 70 cycles. Impedance parameters and ventilator settings are identical to those in Figure 2, except that f = 15 breaths/min and flow cutoff is < 69%.

ditionally, the mask leak is assumed to be constant throughout inspiration; in patients, the leak probably varies during the respiratory cycle. No attempt is made to incorporate proprietary algorithms for leak compensation.

As is common practice in the physical sciences, we investigated simple models to ascertain qualitative behaviors and to highlight potential areas of further investigation. Assessing the quantitative modulation of these qualitative behaviors by incorporating higher-order nonlinearity (e.g., nonlinear resistances or compliances, multiple compartments, more complex patient feedback) requires significant assumptions about these complicating factors in the clinical setting, and these assumptions may not be universally valid. Moreover, the observation of unstable behavior in the mechanical model suggests that the underlying dynamics of PSNIV may override at least some leak-compensation algorithms of commercial ventilators.

The impedance values, leak resistances, and ventilator settings that we used in the examples presented in this report are clearly arbitrary but reasonable analogues for the clinical setting. The influence of T_I on frequency in the variable-frequency model was derived from published clinical data (5). The inspiratory flow cutoff in the examples is similar to that used by a number of commercially available noninvasive ventilation devices. In these devices, inspiratory flow generally terminates at a higher fraction of peak inspiratory flow than is commonly used in conventional intensive care unit ventilators, which apply PSV to the nearly leak-free circuits attainable with cuffed endotracheal tubes. Decreasing the level of inspiratory cutoff generally raises the threshold value of Rm below which the system becomes unstable, thereby broadening the range over which unstable behavior may occur. Furthermore an Rm of 50 cm H_2O/L/s corresponds roughly to flow through a fixed orifice of $\sim$ 4 mm I.D., and is probably not unrealistically low.

Conclusion

The results of the present study suggest that PSV applied in the context of an inspiratory leak proximal to the airway opening may result in substantial breath-to-breath variation in the duration of the inspiratory phase and autoPEEP levels if the respiratory frequency is fixed, or in variability in Ttot, T_I, and autoPEEP if the frequency is allowed to vary. The predicted instabilities are entirely independent of patient effort or volition. The unstable behavior is mediated by autoPEEP, suggesting that it is most likely to occur when the respiratory system time constant is long relative to the ventilatory frequency, as in COPD. Unstable ventilatory support and dynamics could affect patient comfort directly, require active (patient initiated) termination of inspiration, or impose breath-to-breath variability in the effort required for inspiratory triggering. In our study, unstable behavior was observed with impedance value/ventilator setting combinations that are clinically realistic. Given the increasing importance and use of noninvasive ventilation, elucidation of factors influencing patient–ventilator synchrony and tolerance in this setting is indicated not only to understand this problem, but to devise better treatment strategies and supportive equipment. Our results suggest that further investigation of both dynamic instability during noninvasive ventilation and of its clinical significance is warranted.

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APPENDIX

Mathematical Models

We modeled the dynamics of PSNIV by using the respiratory equations of motion for a passive system. For breath number n in a series, changes in lung volume are described by:

$$\text{Inspiration: } P_{I_{set}} = R_I \cdot \frac{dV}{dt} + \frac{V(t)}{C} + Pex(n-1) \qquad (1)$$

$$\text{Expiration: } PEEP = R_E \cdot \frac{dV}{dt} + \frac{V(t)}{C} + Pex(n) \qquad (2)$$

where $P_{I_{set}}$ = set inspiratory pressure, R_I = inspiratory resistance, R_E = expiratory resistance, C = compliance, V(t) = lung volume above C · Pex at time t, dV/dt = rate of change of lung volume, Pex(n − 1) = autoPEEP of preceding breath, and Pex(n) = autoPEEP of current breath. Resistances and compliances were considered to be constant, and it was assumed that pressure at the airway opening rose immediately to $P_{I_{set}}$ at the onset of inspiration. The equations were treated as a time series in which the end-expiratory pressure for each cycle was used to determine the initial inspiratory volume for the subsequent cycle. Ttot (inspiratory phase plus expiratory phase) in the fixed-frequency model was constant at Ttot = 60/f. Ttot for a given breath in the variable-frequency model was assumed to vary in the manner derived from the work of Laghi and colleagues:

$$f = 17.7 - 2.8 \cdot T_I \qquad (3)$$

thus,

$$Ttot = \frac{60}{17.7 - 2.8 \cdot T_I} \qquad (4)$$

Total flow from the ventilator at any time during inspiration (Qvent) was equal to the sum of flow into the lung and flow out of the mask leak (to atmosphere):

$$Qvent = \frac{dV}{dt} + \frac{P_{I_{set}}}{Rm} \qquad (5)$$

as before, Rm was assumed to be constant, and flow across this resistance was therefore linearly related to $P_{I_{set}}$.

The inspiratory phase was terminated when the total inspiratory flow fell to a predetermined fraction of the peak inspiratory flow (flow cutoff fraction, k):

$$k \cdot Qvent,peak = \left(\frac{P_{I_{set}}}{Rm}\right) + \frac{dV}{dt} \qquad (6)$$

where Qvent,peak = peak inspiratory flow from the ventilator for the breath under consideration. Because the pressure waveform was assumed to be square, and mask leak resistance was assumed to be constant, Qvent,peak occurred at the initiation of inspiration. T_E was calculated as Ttot − T_I. The foregoing equations were solved exactly for each segment of the respiratory cycle (inspiration or expiration), to avoid integration errors. The relationship between the end-expiratory pressure of breath number n − 1 and the duration of the subsequent breath (breath number n) can be shown to be:

$$T_I(n) = C \cdot R_I \cdot \ln\left(\frac{Rm \cdot \{P_{I_{set}} - Pex(n-1)\}}{k \cdot Rm \cdot \{P_{I_{set}} - Pex(n-1)\} + R_I \cdot P_{I_{set}} \cdot (k-1)}\right) \quad (7)$$

Interactive simulations for the model can be found at: http://mss.math.vanderbilt.edu/~pscrooke/MSS/maskscatter(Rm).html

Mechanical Model

The test lung model made use of a passive dual-chamber simulator (Michigan Instruments TTL, Grand Rapids, MI) and of fixed orifice resistors (Hans Rudolph, Kansas City, MO). One chamber ("experimental chamber") was connected to a commercially available noninvasive ventilator (Knightstar 335; Nellcor Puritan Bennett, Lenexa, KS) with the configuration shown in Figure 1. Pressure in the experimental chamber and inspiratory flow were measured (Validyne MP-45 pressure transducer; Validyne, Inc., Northridge, CA; Fleisch-type pneumotachometer; Hans Rudolph), continuously recorded, digitized (LabView; National Instruments, Austin, TX), and transferred to a spreadsheet. Pressure and flow tracings were also monitored directly (MT 95000 chart recorder; Astromed, West Warwick, RI). One limb of a purpose-built solenoid valve system was connected to a vacuum; the other limb was connected to the ventilator tubing distal to the pneumotachometer (between the pneumotachometer and the leak resistance). The frequency of solenoid opening, the duration of solenoid opening during each triggering cycle, and the magnitude of the applied vacuum were precisely adjustable. Inspiratory triggering of the driving ventilator was achieved by application of a brief pulse (approximately 0.1 s) of negative pressure to the airway distal to the pneumotachometer. The solenoid system was adjusted to obtain uniform triggering without distortion of the inspiratory pressure and flow waveforms for each array of settings (f, flow cutoff, $P_I$set, C, R_I, R_E, and Rm); in the test lung experiments, Ttot was kept constant, as in the fixed Ttot model. For each combination of tested parameters, the system was allowed to equilibrate for approximately 1 min before data collection, allowing initial transients to die out. T_I and autoPEEP were measured with an automated protocol applied to the digitized pneumotachograph and pressure transducer data.