Ventilatory assistance and respiratory muscle activity. 2: Simulation with an adaptive active ("aa" or "a-squared") model lung

J. S. MECKLENBURGH AND W. W. MAPLESON

Summary
The aim of this study was to develop a lung model which adapted its active simulation of spontaneous breathing to the ventilatory assistance it received—an "aa" or "a-squared" lung model. The active element required was the waveform of negative pressure ($p_{\text{mus}}$), which is equivalent to respiratory muscle activity. This had been determined previously in 12 healthy volunteers and comprised a contraction phase, relaxation phase and expiratory pause. Ventilatory assistance had shortened the contraction and relaxation phases without changing their shape, and lengthened the pause phase to compensate. In this study, the contraction and relaxation phases could be adequately represented by two quadratic equations, in addition to a third to provide a smooth transition. Therefore, the adaptive element required was the prediction of the duration of the contraction phase. The best predictive variables were flow at the end of contraction or peak mouth pressure. Determination of either of these allowed adjustment of the "standard" waveform to the level of assistance produced by an "average" ventilator, in a manner that matched the mean response of 12 healthy conscious subjects. (Br. J. Anaesth. 1998; 80: 434–439)

Keywords: model, lung; ventilation, spontaneous; ventilation, artificial; muscle respiratory; equipment, ventilators

Spontaneous breathing has been simulated by various techniques in order to test ventilators.1–4 Most of these techniques do not allow realistic interaction between the assistance generated by the ventilator and the activity of the respiratory muscles of the patient. In a previous article5 a model was described that interacted realistically: it reproduced the waves of flow and pressure at the mouth generated by a subject breathing through a ventilator set to each of a range of modes of operation. The model required a knowledge of the subject’s compliance, resistance and respiratory muscle activity, as represented by the equivalent waveform of (negative) generated pressure, $p_{\text{mus}}$. This is defined5 as that pressure which, if the subject’s respiratory muscles were paralysed, and the waveform of $p_{\text{mus}}$ were applied to the outside of the subject’s thorax, the waveforms of flow and pressure at the mouth of the subject would be the same as before paralysis.

To provide a model lung with the equivalent of spontaneous respiratory muscle activity, a mathematical representation of the typical waveform of $p_{\text{mus}}$ is required. In addition, a mechanism is needed to change that representation in the way that the waveform of $p_{\text{mus}}$ changes in response to the assistance or load imposed by any ventilator or breathing system under investigation.

A companion article6 described the interaction between spontaneous respiratory muscle activity and ventilatory assistance or a resistance load in healthy volunteers. The main findings of that article were: (1) $p_{\text{mus}}$ increased progressively during the contraction phase of the muscles and (2) on average, the trajectory of this increase remained constant, but the duration of the phase increased with resistance loading and decreased with ventilatory assistance. Consequently there were corresponding changes in the amplitude of $p_{\text{mus}}$ with the various conditions. There were similar changes in the duration of the relaxation phase; it increased with resistance loading and decreased with ventilatory assistance. Despite the shortening of the contraction and relaxation phases with ventilatory assistance, the frequency, and hence respiratory period, was the same for all types of assistance when averaged over all three ventilators. Thus the reduction in contraction and relaxation phase times was coupled with an extension of the expiratory pause. With a resistive load, the contraction phase time increased by 10% and the respiratory period increased by 8%.

This article describes the formation of a mathematical representation of spontaneous respiratory muscle activity and also provides a relationship between imposed assistance or load and duration of the phases of the $p_{\text{mus}}$ waveform. This information provides the basis for an “adaptive active” (“aa” or “a-squared”) model lung which can respond automatically to loads and assistance in the same way as healthy volunteers.

Thus this article uses data from healthy volunteers to establish the technique. Subsequent extension of the work to provide similar data from patients in need of ventilatory support should permit the application of the technique to those data and so lead to clinically relevant findings.

J. S. MECKLENBURGH, PHD, W. W. MAPLESON, DSC, FINSTP, FRCA (HON), Department of Anaesthetics and Intensive Care Medicine, University of Wales College of Medicine, Health Park, Cardiff CF4 4XX. Accepted for publication: November 25, 1997. Correspondence to J. S. M.
Subjects and methods

DATA COLLECTION AND PROCESSING

Waveforms of $p_{\text{mus}}$ were obtained from 12 healthy volunteers breathing under five different conditions: unloaded; resistance loaded, 0.5 kPa s litre$^{-1}$ (at 1 litre s$^{-1}$); pressure assistance of 0.5 kPa; pressure assistance of 1.0 kPa; and synchronized intermittent mandatory ventilation (SIMV) at a frequency of 6 bpm (breaths coincident with mandatory inflations were processed separately from the spontaneous-only breaths).

The ventilators used were the Hamilton Veolar, Engström Elvira and Puritan Bennett 7200.

Details of the experimental procedure, data collection and processing are given in the accompanying article.

PROCESSING OF EXPERIMENTAL DATA

The data forming the basis of the simulation were in the form of a mean $p_{\text{mus}}$ waveform for the unloaded condition, together with numerical data describing the effect on this waveform of resistance loading and ventilator assistance.

The averaging procedures used in the companion article to produce mean contraction phase and mean relaxation phase waveforms produced a slightly distorted shape at the end of the contraction phase and start of the relaxation phase. In order to obtain a smooth transition from the contraction to the relaxation phase a peak phase was defined, comprising the last 0.24 s of the contraction phase and first 0.24 s of the relaxation phase. The waveforms of these three (overlapping) phases were averaged over all breaths in each condition for each subject and then averaged over the 12 subjects. The resulting means for the three phases in the unloaded, unassisted condition are shown in figure 1 (top) together with 95% confidence limits. The transitions between the three phases, indicated by vertical lines, were chosen as the times, within ±0.24 s of the peak, where the relevant waveforms were most nearly coincident. The discontinuities at the joins arise because of the different durations of the contraction and relaxation phases in different subjects.

MATHEMATICAL FITTING PROCEDURES

To reduce this waveform to a set of equations, a separate polynomial equation was first fitted to the mean data for each phase by a least-squares fitting procedure (General LS Polynomial Fit, Lab View ver. 3.1, National Instruments). Adjustments were then made to the fitted curves to achieve smooth transitions between adjacent phases.

ADAPTATION OF FITTED WAVEFORM

It was noted in the accompanying article that almost the only effect of ventilatory assistance and resistance loading on the all-subject mean waveform was a change in duration of the contraction and relaxation phases. Therefore, to make an “a-squared” (adaptive active) model lung which could mimic the response of the average volunteer to the various forms of assistance and loading, it is necessary to predict the appropriate contraction time, $T_c$ (from the start of contraction to the peak of contraction) from variables which can be measured.

The companion article distinguishes two possible types of control of the contraction time during ventilatory support: breath-to-breath, in which the contraction time in any breath depends on what happened in previous breaths, and within-breath, in which the contraction time is determined by what is happening in the current breath. Explanatory variables, derived from the continuous measurement of flow ($\dot{v}$), volume ($v$) and pressure at the mouth ($p_{\text{mo}}$),
Results

MATHEMATICAL FITTING OF THE MEAN, UNLOADED $p_{mus}$ WAVEFORM

Second-order polynomials (parabolas) were considered to give an adequate fit to each of the three phases: those for the contraction phase and the peak lay close to the middle of the experimental confidence limits (fig. 1, bottom); the parabola for the relaxation phase swung from one confidence limit to the other and back again and marginally breached the upper limit near where the limits are narrowest.

Table 2: Regression results for the prediction of contraction time, $T_c$, from characteristics of the complete inspiratory phase; $b_1$, $b_2$ = slope coefficients for the first and second explanatory variables; SE = standard error of the coefficient; RSD = residual standard deviation of the regression; $P$ = probability that the improvement of fit produced by the only, or by the second, explanatory variable is caused by chance. $T_c$ is in seconds, pressures are in kPa, flows in litre s$^{-1}$, and volume in litres.

<table>
<thead>
<tr>
<th>Explanatory variables</th>
<th>Regression coefficients</th>
<th>RSD</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$p_{mus}$ peak</td>
<td>$b_0$ (SE): 1.833 (0.050)</td>
<td>0.134</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>$v_{peak}$</td>
<td>$b_1$ (SE): -0.666 (0.075)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$T_c$</td>
<td>$b_2$ (SE): -1.796 (0.181)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$P_{max}$</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$V_{peak}$</td>
<td></td>
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</tr>
<tr>
<td>$V_{max}$</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$T_{peak}$</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$P_{max}$ + $V_T$</td>
<td>$b_3$ (SE): 1.793 (0.063)</td>
<td>0.176</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>$V_{peak}$ + $V_T$</td>
<td>$b_1$ (SE): -0.965 (0.153)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$V_{max}$ + $V_T$</td>
<td>$b_2$ (SE): 0.908 (0.148)</td>
<td>0.096</td>
<td>0.009</td>
</tr>
<tr>
<td>$P_{max}$ + $V_T$</td>
<td></td>
<td></td>
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</table>

Table 3: Regression results for the prediction of contraction time, $T_c$, from characteristics at the end of the contraction phase of $p_{mus}$.

<table>
<thead>
<tr>
<th>Explanatory variables</th>
<th>Regression coefficients</th>
<th>RSD</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$v_{endl}$</td>
<td>$b_0$ (SE): 2.446 (0.099)</td>
<td>0.122</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>$T_{endl}$</td>
<td>$b_1$ (SE): -1.976 (0.181)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$P_{endl}$</td>
<td>$b_2$ (SE): 0.908 (0.148)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$P_{camatan} + V_T$</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

Reasons for accepting this as adequate are given in the discussion.) However, the abutment between the parabolas showed unrepresentative discontinuities in the fitted waveform (fig. 2, left).

These discontinuities were eliminated as follows. A new parabola, constrained to pass through the origin, was fitted to the contraction phase (the unconstrained parabola produced a small, non-significant intercept, 0.0024 kPa). In the resulting parabola, the curvature (the square coefficient $c$ in $p = a + bt + ct^2$) was then adjusted (from 0.1886 to 0.1848) to make the contraction parabola tangent to the fitted peak parabola, with the intercept $a$ and initial slope $b$ unaltered. In the fitted relaxation parabola, the shape was maintained but the position of the parabola was shifted, first in the pressure direction (by $-0.020$ kPa) to move the apex from its free, slightly positive position to zero, and then in the time direction (by $-0.036$ s) to make it tangent to the peak parabola. Figure 2 (right) shows the points of tangency in detail. The relaxation parabola was terminated at the apex (at zero pressure) and the remainder of the mean respiratory period was represented by a flat line at zero $p_{mus}$.

The complete, adjusted waveform, with transitions from each parabola to the next at the points of tangency, forms a smooth curve (fig. 3), falling well within the experimental confidence limits, apart from the minor discrepancies already noted in the relaxation phase.

The coefficients for the adjusted waveform are:

For $t = 0$ to 1.71 s (main part of the contraction phase),

$$p_{mus} = 0.0 - 0.8445 t + 0.1848 t^2$$

(1)

For $t = 1.71 - 1.97$ s (peak phase),

$$p_{mus} = 4.4408 - 6.0281 t + 1.6975 t^2$$

(2)

For $t = 1.97 - 4.59$ s (relaxation phase–main part),

$$p_{mus} = -2.5980 + 1.131 t - 0.1232 t^2$$

(3)

And for $t = 4.59 - 4.74$ s (terminal part of the waveform),

$$p_{mus} = 0$$

(4)
where \( t \) = time (in s) from the start of the \( p_{\text{max}} \) waveform and \( p_{\text{max}} \) is in kPa.

**RELATIONSHIP BETWEEN CONTRACTION TIME, \( T_c \), AND CHARACTERISTICS OF RESISTANCE LOADING OR VENTILATOR ASSISTANCE**

For the breath-by-breath mechanism of control, contraction time \( (T_c) \) showed a significant dependence on all five of the possible predictors, but barely so for tidal volume, \( V_T \) (table 1). For the within-breath mechanism of control, \( T_c \) showed a dependence on flow at \( T_c \) (\( \dot{V}_{TC} \)) and mouth pressure at \( T_c \) (\( P_{\text{mo pk}} \)) (table 2) but not for volume at \( T_c \). When \( V_T \) was added as a second predictor to each of the other variables in table 1, or when volume at \( T_c \) (\( V_{TC} \)) was added to each variable in table 2, there was a significant improvement in fit (reduced residual SD) but in both cases the coefficient of the added variable was positive. This indicates that \( T_c \) increases with \( V_T \) or \( V_{TC} \) whereas the classical theory of termination of inspiratory effort is that increase in tidal volume leads to a decrease in \( T_c \). Therefore, it must be concluded that the positive coefficient is a manifestation of the dependence, not of \( T_c \) on volume, but of volume on \( T_c \) -- the longer the subject continues to increase \( p_{\text{max}} \) the greater the tidal volume inspired. Accordingly, volume cannot be used in the control of \( T_c \). Therefore, given the present data, the prediction of \( T_c \) must be based on a single variable.

The best predictive equations are:

\[
T_c = 2.446 - 1.796 \dot{V}_{TC} \quad (5) \\
T_c = 1.883 - 0.666 P_{\text{mo pk}} 
\]

with residual SD values of 0.122 s and 0.134 s, respectively; therefore flow at the end of the contraction phase, \( \dot{V}_{TC} \) is a marginally better predictor than peak mouth pressure, \( P_{\text{mo pk}} \).

These equations are plotted in figure 4, together with the data points to which they were fitted, using different symbols for each condition. Surprisingly these equations apply equally to the volume-controlled modes (where tidal volume and inspiratory time are set on the ventilator) as to the pressure-assistance modes. This can be claimed because the mandatory breaths in SIMV lie within the spread of the other points in figure 4.

**Discussion**

**FIT OF PARABOLAS TO EXPERIMENTAL DATA**

The three parabolas provided a smooth curve which closely followed the mean observed waveform of \( p_{\text{max}} \) for the unloaded condition, except for a somewhat different shape during relaxation (fig. 3); this led to a marginal breach of the upper confidence limits where the limits are narrow. Adding a third term, \( dt^3 \), to the equation for the relaxation phase improved the fit over the central part of relaxation, but weakened it at the end. There are grounds for ignoring this breach of confidence limits: narrowing of the limits in the middle of the relaxation phase is artificial; it arises from deliberately synchronizing the different components of waveforms at this point. Other fitting methods were considered but any that improved the fit appreciably did so at the expense of increasing the complexity of the equation for the complete waveform. This increase in complexity would be a major drawback for implementing an active model lung.

Thus equations (1)–(4) provide an adequate mathematical representation of the waveform of \( p_{\text{max}} \) for healthy volunteers, during quiet breathing under normal, unloaded, unassisted conditions. They could therefore be used to quantify an active lung model such as that of Mecklenburgh, Al-Obaidi and Mapleson.

Similar equations are given for the same purpose in BS 5724:3:124 “Method of declaring the performance parameters of lung ventilators”. The individual
coefficients differ considerably from those given here, but the resulting waveform is very similar.\textsuperscript{7} The equations in BS 5724:3:12 were obtained in this department in a similar manner to that described here, but were based on only three subjects. Therefore, the present equations, based on 12 subjects, should provide a better representation for the healthy volunteer.

using the prediction equation in an “a-squared” model

For an active lung model to be truly versatile it must be capable of adjustment to provide varying magnitudes of respiratory muscle effort and various frequencies of breathing. BS 5724:3:12 specifies that this adjustment should be done “manually” by scaling the waveform appropriately in amplitude and duration and by extending the duration of zero $p_{\text{mus}}$ at the end of the relaxation phase for respiratory frequencies less than 6 bpm. However, our study provides quantitative information on the way that the average healthy subject responds to resistance loading and ventilatory assistance. Therefore, a model in which the $p_{\text{mus}}$ waveform was basically defined by equations (1)–(4), but in which $T_c$ was governed by equation (5) or (6), would constitute an “a-squared” model which would respond to pressure assistance and SIMV (and resistance loading–see below) in the same way as the mean of the 12 subjects used here. However, adapting equations (1)–(4) to changes in $T_c$ involves several steps.

adaptation of mean fitted waveform to loading and assistance

The total respiratory period in normal, unloaded breathing was 4.7 s. Ventilatory assistance decreased the period by up to 9\% (ns); resistance loading increased it by 8\%, to 5.1 s.\textsuperscript{6} For ventilator testing it would be convenient and reasonable to set the period to 5 s for all levels of assistance and resistance within the range of $T_c$ encountered (approximately 1–2 s). This would give an integer value for frequency of 12 bpm.

When the contraction and relaxation phases shorten, the beginning of the former and the end of the latter remain the same; it is the portions around the peak that are omitted.\textsuperscript{6} Therefore, to adapt the basic waveform to various types and magnitudes of resistance loading and ventilatory assistance, it is necessary to decrease the contraction phase time, decrease the relaxation phase time, and then increase the expiratory pause to make up the constant 5-s respiratory period. The procedure used to achieve this with the appropriate smooth transitions from contraction to peak and from peak to relaxation was as follows.

The peak parabola was time-shifted so that its peak occurred at the required $T_{\text{a}}$ and pressure-shifted so that it was tangent to the contraction phase parabola. Then the relaxation phase parabola was time-shifted to make it tangent to the shifted peak parabola. The remainder of the respiratory period was then padded with zeros.

A method for producing tangent parabolae\textsuperscript{7} has been used to generate the range of $p_{\text{mus}}$ waveforms shown in figure 5 which represent adaptation to several levels of assistance and, at $T_c=2$ s, a small degree of resistive loading.

This adaptation of the $p_{\text{mus}}$ waveform could be performed on-line during the laboratory testing of ventilators. Measurement of $\dot{v}_{\text{a}}$ or $P_{\text{v,ass}}$ poses few problems and, when a value had been obtained for a few breaths, the contraction phase time could be adjusted, with iteration of measurement and adjustment until the relationship between $T_c$ and $\dot{v}_{\text{a}}$ or $P_{\text{v,ass}}$ accorded sufficiently closely with equation (5) or (6).

With equation (6) there seems no danger of the iteration “running away” because reducing $T_c$ in response to $P_{\text{v,ass}}$ would mean that, in pressure assistance, there would be less time for the ventilator to generate the set pressure which would result in the same or lower $P_{\text{v,ass}}$ leading to less reduction in $T_c$ than initially calculated–negative feedback. In triggered CMV with time-cycled flow generation in the inspiratory phase, the mandatory breath would continue irrespective of the shortening of $T_c$. As a result, with a decreased $T_c$, $P_{\text{v,ass}}$ would increase at the end of the inflation because the decreased $p_{\text{mus}}$ would increase the “alveolar” pressure. This would lead to a further reduction in $T_c$, but a much smaller one than the initial reduction based on the first inflation, because of the much smaller increase in $P_{\text{v,ass}}$. Therefore, although there is positive feedback, it would rapidly diminish. In any case a limit is reached if contraction phase time reduces to zero when $P_{\text{v,ass}}$ would be determined only by the passive properties of the model. It is unclear how to make the “a-squared” model lung adapt independently to the mandatory and spontaneous breaths in SIMV; some algorithm would be needed to permit identification of the type of breath (mandatory or spontaneous) to allow separate processing.

Although equation (5) was devised for use for within-breath control of $T_c$, figure 5 shows that the point of transition from contraction to peak parabola varies with $T_c$. This would make implementation of within-breath control mathematically complex. However, with iteration it would be possible to “home in” on the appropriate $T_c$.

Thus we have developed a mathematical representation of the activity of the respiratory muscles of healthy volunteers. We have also shown how this representation can be modified in response to resistance loading and ventilator assistance in a manner that mimics the mean response of our healthy volunteers. We plan to extend this work to patients requiring ventilatory assistance so that an active lung model can be made to respond in a manner typical of patients, or at least of patients in specific circumstances, for example in anaesthesia, intensive care or recovering from cardiovascular surgery.

References

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