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Uttman, Leif; Jonson, Björn

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Computer-aided ventilator resetting is feasible on the basis of a physiological profile

L UTTRAN and B JONSON
Department of Clinical Physiology, University Hospital, Lund, Sweden, Supported by the Swedish Medical Research Council(02872) and the Swedish Heart Lung Foundation

Background: Ventilator resetting is frequently needed to adjust tidal volume, pressure and gas exchange. The system comprising lungs and ventilator is so complex that a trial and error strategy is often applied. Comprehensive characterization of lung physiology is feasible by monitoring. The hypothesis that the effect of ventilator resetting could be predicted by computer simulation based on a physiological profile was tested in healthy pigs.

Methods: Flow, pressure and CO₂ signals were recorded in 7 ventilated pigs. Elastic recoil pressure was measured at post-inspiratory and post-expiratory pauses. Inspiratory and expiratory resistance as a function of volume and compliance were calculated. CO₂ elimination per breath was expressed as a function of tidal volume. Calculating pressure and flow moment by moment simulated the effect of ventilator action, when respiratory rate was varied between 10 and 30 min⁻¹ and minute volume was changed so as to maintain PaCO₂. Predicted values of peak airway pressure, plateau pressure, and CO₂ elimination were compared to values measured after resetting.

Results: With 95% confidence, predicted pressures and CO₂ elimination deviated from measured values with 1 cm H₂O and 6%, respectively.

Conclusion: It is feasible to predict effects of ventilator resetting on the basis of a physiological profile at least in health.

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upon a simple lung model. The main objective was to test the hypothesis that mechanical behavior and VCO₂ after resetting the ventilator could be predicted by simulation in healthy pigs. The study also complements the knowledge about lung physiology in anesthetized paralyzed pigs.

Methods

The local Ethics Board of Animal Research approved the experimental protocol. Seven pigs of the Swedish landrace, average weight 30.8 kg (27.1–33.5), were fasted overnight with free access to water. The animals were premedicated with azaperon (Stresnil®, Jansen, Beersel, Belgium), 7 mg/kg, anesthetized with ketamin (Ketalar®, Parke-Davis, Morris Plains, USA), 5 mg/kg, into an ear vein, intubated with a 7.0-mm ID tracheal tube, and connected to a ventilator (Servo Ventilator 900C, Siemens-Elema, Solna, Sweden). The ventilator produced a square inspiratory flow pattern at a baseline setting of respiratory rate (RR) 20 min⁻¹, inspiratory time (TI) 33%, postinspiratory pause time 10% and a positive end-expiratory pressure set on the ventilator (PEEP) of 6 cm H₂O. The fraction of inspired oxygen was 0.21. The baseline minute ventilation (MV) was adjusted to achieve a PaCO₂ of 4.5–5.0 kPa. A mainstream analyzer (CO₂ Analyzer 930, Siemens-Elema, Solna, Sweden) measured concentration of CO₂ in expired and inspired gas (C CO₂). Anesthesia was maintained by continuous infusion of ketamin, 17 mg/kg/h, midazolam (Dormicum®, Hoffmann-La Roche AG, Basel, Switzerland), 1.7 mg/kg/h and pancuronium bromide (Pavulon A, Organon A, Parke-Davis, Morris Plains, USA), 0.5 mg/kg/h. The ventilator/computer system used for data recording has previously been described (4). Signals from the ventilator (PEEP) of 6 cm H₂O. The fraction of inspired oxygen was 0.21. The baseline minute ventilation (MV) was adjusted to achieve a PaCO₂ of 4.5–5.0 kPa. A mainstream analyzer (CO₂ Analyzer 930, Siemens-Elema, Solna, Sweden) measured concentration of CO₂ in expired and inspired gas (C CO₂). Anesthesia was maintained by continuous infusion of ketamin, 17 mg/kg/h, midazolam (Dormicum®, Hoffmann-La Roche AG, Basel, Switzerland), 1.7 mg/kg/h and pancuronium bromide (Pavulon A, Organon Teknika, Boxtel, Holland), 0.5 mg/kg/h. The ventilator/computer system used for data recording has previously been described (4). Signals from the ventilator and CO₂ analyzer representing flow rate, pressure in the expiratory line of the ventilator (Pvent) and CCO₂ were sampled by a personal computer at the frequency of 50 Hz. Flow, pressure and CO₂ signals had a 50% response time of 12 ms and were synchronous within ±8 ms (5). There were no dropouts among the animals.

Protocol

After preparation of the pigs a recruitment maneuver was performed by inflating the lungs with a pressure of 35 cm H₂O for 10 s to standardize conditions among the animals by reducing airway closure and atelectasis induced during the induction of anesthesia (6). The system was tested for leakage. A study sequence comprised 10 normal breaths, one breath with a postinspiratory pause, another four normal breaths and one with a post-expiratory pause. The recording continued during ventilator resetting and two minutes thereafter.

The experimental protocol was designed to allow five settings to be studied during a short period at a physiological steady state. After a perturbation of CO₂ equilibrium extended periods are needed to restore a steady state (3). Perturbation of CO₂ equilibrium was avoided by increasing MV at higher RR in order to compensate for the higher physiological dead space fraction associated with reduced tidal volume (VT). In order to keep VCO₂ constant we performed in each pig a an initial study sequence to examine how CO₂ elimination per breath (VCO₂,T) varied in relation to VT, as further described below.

Then, alternative settings were studied. These were changes in RR from 20 to 10, 15, 25 and 30 coupled to estimated changes in MV in randomized order. Recorded data immediately before each resetting were used to establish the physiological profile serving as basis for simulation of the ensuing setting. Recorded data starting 30s after resetting, covering 10 breaths were used to measure peak airway pressure (Ppeak), postinspiratory quasi-static elastic recoil pressure (Pplateau) and VCO₂ which were compared to simulated data.

Data analysis

Data sampled during a study sequence were transferred to a spreadsheet (Microsoft® Excel 97, Microsoft Corp., Redmond, WA) for analysis. Flow measured in the inspiratory and expiratory circuits within the ventilator included flow that did not reach the animal. In order to obtain airway flow rate (V′aw), measured flow rate was corrected for the compliance in the tubings by subtraction from each flow sample the product between compliance and rate of pressure change (7). The expiratory flow signal was normalized so that, at steady state, expired VT equaled inspired VT (7). Volume relative to end-expiratory volume (V) was calculated by integration of V′aw.

A lung model was defined prior to data analysis. As a goal was to develop methods, which can be applied in the clinic, the model should only incorporate features, which can easily be studied with techniques available at the bedside. Accordingly, minimal interference with ordinary pattern of mechanical ventilation at the phase of parameter estimation to establish the physiological profile should yield sufficiently detailed information to allow proper simulation of alternative ventilator settings. As a result, a monocompartment model without viscoelastic properties or inertia was employed. Furthermore, constant values
for compliance of the respiratory system (C) and inspiratory conductance (G_I) were applied on the basis of prior data (6, 8). Expiratory conductance (G_E) was assumed to vary as a linear function of volume (9). The resistance of the Y-piece, CO₂ transducer connector, tracheal tube, ventilator tubing and the expiratory line of the ventilator were considered flow dependent according to Rohrer (10). The coefficients defining resistance of the connecting system were determined in vitro by measuring flow rate and pressure at variable flow rate delivered from the ventilator through the connecting system into open air. Tube compliance was measured as the quotient between volume of gas expired from the tubing after an inspiration, during which the tracheal tube was completely occluded, and the preceding P_plateau. VCO₂,T and VCO₂ and their variation with V_T was determined from the single breath test for CO₂ (SBT-CO₂).

The following equations 1–9 were used for the establishment of the physiological profile and in the simulation process.

\[ C = \frac{V_T}{(P_{\text{plateau}} - P_{el,E})} \]  

(1)

The pressure that drives flow through the tracheal tube (P_{tube}) was determined as a function of flow

\[ P_{\text{tube}} = R_{\text{tube}} \cdot \dot{V}'_\text{aw} = (k_0 + k_1 \cdot |\dot{V}'_\text{aw}|) \cdot \dot{V}'_\text{aw} \]  

(2)

k_0 and k_1 describe tube resistance (R_{tube}) and its variation with flow due to turbulence. Tracheal pressure (P_{tr}) was calculated from measured P_{vent} and calculated P_{tube}:

\[ P_{tr} = P_{\text{vent}} - P_{\text{tube}} \]  

(3)

The pressure overcoming resistance of the respiratory system (P_{res}) was calculated as the difference between P_{tr} and the elastic recoil pressure, i.e. V/C:

\[ P_{res} = P_{tr} - \frac{V}{C} \]  

(4)

G_I and G_E were calculated as \( \dot{V}'_{\text{aw}} / P_{\text{res}} \). For each respiratory phase a linear regression of conductance over the volume range from 15 to 85% of V_T was made, thus avoiding the influence from fast accelerations and decelerations at flow transitions. As G_I does not vary significantly during the V_T a constant value for G_I was calculated from the regression at mid-inspiration. G_E may according to previous studies be described as a linear function of volume (9). Accordingly:

\[ G_E = g_0 + g_1 \cdot V \]  

(5)

g_0 denotes conductance at zero volume and g_1 gives variation of G_E and its reciprocal expiratory resistance (R_E) with volume.

\[ VCO_2,T \]  reflects the difference between volume of CO₂ expired (VCO₂,E) and the volume of CO₂ re-inspired at the start of inspiration (VCO₂,I) (Fig. 1). VCO₂,T at current ventilation was calculated by integration of CCO₂ by volume over the respiratory cycle. To determine how VCO₂,T would vary in response to variations in V_T the SBT-CO₂ was further analyzed. The alveolar plateau of the CO₂ concentration during expiration (CCO₂,A) was approximated according to .6 applied over the last 40% of the volume expired (VE):

\[ CCO₂,A(VE) = f_0 + f_1 \cdot \ln(VE) \]  

(6)
The equation has been applied in previous studies (11, 12)

\[ V_{CO2,E}(V_{T,alt}) = V_{CO2,E}(V_T) + \int_{V_T}^{V_{T,alt}} C_{CO2,ET} \cdot A \cdot dV_E \] (7)

The second term in .7 is derived from .6 as illustrated in Fig.1.

\[ V_{CO2,I}(V_{T,alt}) = \frac{V_{CO2,I}(V_T) \cdot C_{CO2,ET}(V_{T,alt})}{C_{CO2,ET}(V_T)} \] (8)

\[ C_{CO2,ET} \] is the end-tidal \( C_{CO2} \).

The parameters (\( V_{CO2,E}, V_{CO2,I}, C_{CO2,ET}, f_0, f_1, C, G_0, g_0 \) and \( g_1 \)) together with corresponding equations mathematically characterize lung function. These parameters represent the physiological profile of the subject.

**Simulation of an alternative mode of ventilation**

In the present study simulations of volume controlled ventilation were performed. The simulation process mimics this mode by keeping the simulated inspiratory flow rate constant and, during expiration, by not allowing \( P_{vent} \) to fall below PEEP. During early expiration \( P_{vent} \) is higher than PEEP. This prevails as long as ventilator resistance at fully open expiratory valve multiplied by expiratory flow is higher than PEEP.

Mathematical simulation of ventilator function was stepwise performed by dividing the respiratory cycle into short time intervals. During each interval the pressures in the Y-piece, trachea and alveoli, as well as flow rate and lung volume were calculated. The basic time interval used in the simulation was 1% of the breathing cycle so as to divide the breath into 100 intervals. In order to avoid oscillations at sudden pressure and flow changes the time interval during phase transitions was reduced to 0.001% of the cycle. For the same reason, filtering of the values for \( R_{tube}, P_{vent} \) and expiratory \( V'_{aw} \) was performed. The fraction 0.7 of the filtered value from the previous time interval was added to the value calculated for the current interval. This sum was divided by 1.7 in order not to change the magnitude of the parameters. The first time interval during expiration needed a special ‘filter’. For that interval \( V'_{aw} \) was set to be 0.4 times a value of \( V'_{aw} \) calculated as described in .9. The coefficients 0.7 and 0.4 were empirically found to allow simulation of various patterns of ventilation without severe artifacts related to system oscillation.

During inspiration \( V'_{aw} \) was determined by \( MV, RR \) and \( T_t \). \( V \) was obtained as the integral of \( V'_{aw} \). Elastic recoil pressure (\( P_{el} \)) and \( P_{tube} \) were calculated using .1 and .3. During expiration \( V'_{aw} \) was calculated as

\[ V'_{aw} = \frac{(P_{el} - P_{vent,E})}{(R_E + R_{tube})} \] (9)

The value of \( V \) was transferred from the previous interval. Other variable’s values were calculated from the current interval. Six consecutive breaths were simulated. Simulated values of \( P_{peak}, P_{plateau} \) and \( VCO2 \) at the 6th simulated breath were compared to the average recorded values from 10 breaths starting 30 s after resetting. The spreadsheet used for simulations is available from the authors.

**Statistical methods**

The Student’s paired two-tailed \( t \)-test was used to analyze differences between simulated values and measured values of \( P_{peak}, P_{plateau} \) and \( VCO2 \). Wilcoxon matched pair signed rank sum test was used to determine whether the precision of \( P_{peak} \) and \( P_{plateau} \) simulations made at RR 10, 15, 25 and 30 was significantly different from those made at baseline RR 20. A \( P \)-value of < 0.05 was considered significant.

**Results**

Baseline characteristics of the animals including the physiological profile are shown in Table 1. To reach the target end-tidal \( CO2 \) at an RR of 20 min\(^{-1} \) a \( V_T \) of on average 9.4 ± 0.95 ml · kg\(^{-1} \) was required. This relates to a \( CO2 \) production of 5.7 ± 0.94 ml · min \(^{-1} \). The SBT-CO2 showed a distinct increase of \( VCO2 \) and \( VCO2 \) was approximated as described in .1 and .3. During expiration \( V'_{aw} \) was calculated as

\[ V'_{aw} = \frac{(P_{el} - P_{vent,E})}{(R_E + R_{tube})} \] (9)
tion of events before resetting, i.e. at RR 20, served as control of the process comprising measurements, modeling, parameterization and simulation. Then $\text{VCO}_2$ showed nearly identity between simulated and measured values. At RR 20, $P_{\text{peak}}$ and $P_{\text{plateau}}$ showed differences below 4% in each case ($P > 0.05$). Simulation of $\text{VCO}_2$ after resetting of RR and $V_T$ resulted in values which were not significantly different from measured values at reduced RR. However at RR 25 and particularly at RR 30 simulation resulted in an overestimation ($P = 0.003$ and $P < 0.001$, respectively). After resetting measured ranges of $P_{\text{peak}}$ and $P_{\text{plateau}}$ were 12–25 cm H$_2$O and 11–24 cm H$_2$O, respectively. Out of simulated values 95% differed less than 1.0 cm H$_2$O from measured values. Simulated $P_{\text{plateau}}$ was marginally higher than measured at RR 25 and RR 30 ($P = 0.001$, $P = 0.025$, respectively).

### Discussion

The present results contribute to the knowledge about respiratory physiology in pigs. Compliance, on average 1.2 ml/kg, was similar to data previously reported (6). No comparable data on resistance of the respiratory system have been found. Expiratory resistance higher than inspiratory and increasing toward the end of expiration is known in humans (7). This reflects that the resistive pressure drop in the airways reduces transbronchial pressure during expiration while the opposite is true during inspiration (7). An error in the

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**Table 1**

Baseline characteristics of the animals.

<table>
<thead>
<tr>
<th>Pig</th>
<th>Pig 2</th>
<th>Pig 3</th>
<th>Pig 4</th>
<th>Pig 5</th>
<th>Pig 6</th>
<th>Pig 7</th>
<th>Average</th>
<th>SD</th>
</tr>
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<tr>
<td>Weight, kg</td>
<td>33.0</td>
<td>32.2</td>
<td>29.2</td>
<td>29.9</td>
<td>27.1</td>
<td>31.0</td>
<td>33.5</td>
<td>30.8</td>
</tr>
<tr>
<td>$V_T$, mL</td>
<td>10.1</td>
<td>10.1</td>
<td>9.4</td>
<td>9.7</td>
<td>7.4</td>
<td>9.1</td>
<td>10.0</td>
<td>9.4</td>
</tr>
<tr>
<td>$V_{\text{CO}_2}$, mL</td>
<td>6.7</td>
<td>6.0</td>
<td>5.3</td>
<td>6.1</td>
<td>3.8</td>
<td>5.8</td>
<td>6.4</td>
<td>5.7</td>
</tr>
<tr>
<td>$V_{\text{CO}_2}$, mL CO$_2$</td>
<td>6.1</td>
<td>6.6</td>
<td>6.2</td>
<td>4.9</td>
<td>5.2</td>
<td>6.9</td>
<td>7.0</td>
<td>6.1</td>
</tr>
<tr>
<td>$V_{\text{CO}_2}$, mL CO$_2$</td>
<td>0.9</td>
<td>0.8</td>
<td>0.8</td>
<td>0.8</td>
<td>0.6</td>
<td>0.8</td>
<td>0.9</td>
<td>0.8</td>
</tr>
<tr>
<td>$t_0$, % CO$_2$</td>
<td>3.1</td>
<td>1.5</td>
<td>2.5</td>
<td>2.8</td>
<td>2.0</td>
<td>2.2</td>
<td>2.5</td>
<td>2.4</td>
</tr>
<tr>
<td>$t_1$, % CO$_2$</td>
<td>0.3</td>
<td>0.5</td>
<td>0.4</td>
<td>0.3</td>
<td>0.5</td>
<td>0.6</td>
<td>0.4</td>
<td>0.4</td>
</tr>
<tr>
<td>Compliance, mL·cm H$_2$O$^{-1}$</td>
<td>4.2</td>
<td>3.4</td>
<td>3.4</td>
<td>3.2</td>
<td>4.0</td>
<td>4.1</td>
<td>4.3</td>
<td>4.3</td>
</tr>
<tr>
<td>$R_I$, cm H$_2$O·s·L$^{-1}$</td>
<td>2.1</td>
<td>3.9</td>
<td>3.1</td>
<td>4.7</td>
<td>3.2</td>
<td>5.2</td>
<td>2.3</td>
<td>3.5</td>
</tr>
<tr>
<td>$R_{\text{EMD}}$, cm H$_2$O·s·L$^{-1}$</td>
<td>6.1</td>
<td>9.9</td>
<td>7.9</td>
<td>10.4</td>
<td>5.7</td>
<td>10.8</td>
<td>5.7</td>
<td>8.1</td>
</tr>
<tr>
<td>$g_0$, L·s$^{-1}$·cm H$_2$O$^{-1}$</td>
<td>0.14</td>
<td>0.10</td>
<td>0.11</td>
<td>0.08</td>
<td>0.11</td>
<td>0.09</td>
<td>0.19</td>
<td>0.12</td>
</tr>
<tr>
<td>$g_1$, s$^{-1}$·cm H$_2$O$^{-1}$</td>
<td>1.5·10$^{-4}$</td>
<td>1.5·10$^{-5}$</td>
<td>1.3·10$^{-4}$</td>
<td>8.2·10$^{-5}$</td>
<td>5.2·10$^{-4}$</td>
<td>1.1·10$^{-5}$</td>
<td>2.0·10$^{-3}$</td>
<td>1.3·10$^{-4}$</td>
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</tbody>
</table>
estimate of elastic recoil pressure at mid-$V_T$ leading to an overestimation of $R_I$ would lead to underestimation of $R_{E,MID}$ and vice versa. The close correlation between $R_I$ and $R_{E,MID}$ suggests that the linear elastic pressure volume relationship based upon measured values before and after an inspiration is valid. The model of mechanical behavior, which was defined prior to the study, is supported by internal coherence of the observations and principle agreement with previous data. Airway deadspace corrected for tube deadspace ($V_{Daw}$), on average 2.0 ml/kg body weight, appears larger than data reported in humans (13). The clearly delineated, nearly flat alveolar plateau of the SBT-CO$_2$ signifies that among lung units, which empty in sequence, ventilation/perfusion ratio ($V/Q$) is nearly even in healthy pigs. The classical SBT-CO$_2$

was complemented by its inspiratory limb so as to create a loop. This allows measurement of re-inspired CO$_2$ resident in the circuit proximal to the site where CO$_2$ is measured. Re-inspiration of about 8% of the expired volume of CO$_2$ reflects a deadspace in the Y-piece and, because of turbulence, in the adjacent tubings (5). The model for CO$_2$ elimination incorporates features allowing for uneven $V/Q$ leading to a sloping alveolar plateau, which probably is needed only in disease.

Previous authors have stressed that the physiological

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![Graph](image_url)

**Fig. 4.** Upper panel shows measured pressure in the ventilator ($P_{vent}$) during a breath and elastic recoil pressure ($P_{el}$) obtained by interpolation from data measured during pauses. Tracheal pressure ($P_{tr}$) was calculated from $P_{vent}$ by subtraction (-2-3). Lower panel illustrates the same pressures simulated.

**Fig. 5.** Individual (○) and average (---) errors in simulation of CO$_2$ elimination per minute ($V_{CO2}$), postinspiratory quasi-static plateau pressure ($P_{plateau}$) and peak airway pressure ($P_{peak}$) at different respiratory rates. A positive value corresponds to an overestimation.
effects of ventilator resetting are difficult or impossible to predict because of the complexity of the total system comprising ventilator and lungs (14, 15). In principle, such predictions may be performed if the properties of the total system can be described mathematically. Mechanics and CO₂ elimination can straightforwardly be described by simple mathematics. Furthermore, the parameters can be determined using a non-invasive fully automated technique as shown. In contrast, the effect of ventilator resetting on oxygenation is too complex to be modeled. Physiological parameters influencing oxygenation like cardiac output, right to left shunt and V/Q non-homogeneity can only be determined by invasive techniques. Accordingly, this study focussed on CO₂ elimination and ventilator pressure after resetting. Tidal volume and respiratory rate are important factors determining mechanical behavior and CO₂ elimination. These factors, which presently are in focus with respect to lung protective ventilation (16), were investigated in this first study of how simulations may be used to predict the results of alternative ventilator settings.

The simple model of lung physiology employed, allowed parameter estimation from normal breaths, only supplemented with a post-expiratory pause. The simple model also eased simulations. A model based upon a linear pressure volume curve without hysteresis and constant inspiratory resistance was applied. Studies in various mammals, healthy and diseased humans validate such a model as long as tidal volumes are not large (6, 7, 17–19). The model did not incorporate viscoelastic properties, as such properties are particularly difficult to measure (7, 20). Experimental validation is necessary to evaluate the adequacy of the simple model, the analysis leading to the physiological profile and the simulation program. The present study describes a method, illustrates its feasibility and serves as a first step in the validation that must be enlarged to lung disease and comprehensive variation in ventilator settings.

The method for simulation of mechanics was based upon calculation of events during small time intervals. This method allows simulation of any ventilator setting that can be described mathematically. The digital nature of the procedure made filters necessary in order to avoid oscillations originating from phase transitions. The method for simulation of CO₂ elimination was based upon a complete breath, with the VT and RR as only input parameters.

Among the comprehensive results of each simulation P_{peak}, P_{plateau} and V_{CO₂} were selected for presentation, as these are particularly relevant with respect to lung protective ventilation. Data on mean airway pressure and so-called auto-PEEP were not presented, as the settings studied in healthy pigs did not induce significant changes.

The differences between simulated and measured values at RR 20 reflect errors accumulated at measurements, modeling, parameterization and simulation. Measurement of V_{CO₂}, which is based upon complete breaths is accurate. Modeling and parameterization are robust. As expected from these facts the simulation of V_{CO₂} was precise at RR 20. The errors in P_{plateau} and P_{peak}, simulated at RR 20, were below 4% of measured values. This magnitude of errors is inherent to the methodological chain, from measurement to simulation. Simulation errors can not be expected to be less after resetting. After resetting to alternative values of RR and VT the errors of simulation were not significantly larger. The small random deviations between simulated and measured pressures after resetting of the ventilator imply that the model, the parameterization and simulation from a mechanical point of view was adequate in the present context.

The systematic overestimation of CO₂ elimination at RR 25 and 30 probably reflects that time for gas mixing in the respiratory zone becomes too short for establishment of diffusion equilibrium. A longer time for gas mixing leads to lower airway dead space because of movement towards the airway opening by diffusion of the interface between alveolar and airway gas (21, 22). This feature is not taken into account in the present simulation program. Errors of 3 and 5% of simulated CO₂ elimination will lead to reciprocal changes in PaCO₂ after an equilibration time of roughly 20 min (3). If such deviations are considered important, amendment of the model may be needed. Whether this can be accomplished according to some general rules or if the dependence of CO₂ elimination on gas mixing time must be studied in each subject remains to be investigated. If needed, the influence of gas mixing time on CO₂ elimination may be studied by changing RR, T₁ or post-inspiratory pause time at the time when other parameters are measured before simulation.

A novel technique based upon observations of physiology under essentially unperturbed ventilation allowed prediction of CO₂ elimination and airway pressure after resetting respiratory rate and minute ventilation in healthy pigs. In principle, it is feasible to predict effects of ventilator resetting on the basis of a physiological profile. Before systems can be applied clinically tests must be performed for a wide range of pathology and extended types of resetting. It is expected that a physiological model needs to be complemented.
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References

Address:
Leif Uttman
Department of Clinical Physiology
University Hospital
SE-221 85 Lund
Sweden
Fax: +46 46 151769
e-mail: leif.uttman@klinfys.lu.se