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

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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 vol-

ume 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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CONTROLLED mechanical ventilation is frequently used in patients with critical lung disease such as acute lung injury and sometimes in acute respiratory insufficiency in chronic obstructive pulmonary disease. These groups are characterized by a very complex pathophysiology. Since the early 70s the optimal mode of mechanical ventilation in various critical lung diseases is a debated issue. For example, Reynolds treated infants with respiratory distress syndrome with pressure limited ventilation and inverse I:E ratio (1). An early study based upon mathematical simulation of various patterns of ventilation indicated that an optimal pattern depends on the patient's pathophysiology (2). During mechanical ventilation, modern monitoring technique allows automated analysis of both mechanics and CO₂ elimination, so as to illustrate the pathophysiology of the patient. The task of the physician or therapist is to combine this physiological profile with all available clinical information and on this basis decide about the mode of ventilation and exact ventilator setting. The physiological profile and all possible setting variations combine to an overwhelmingly complex system. In the

clinic, ventilators are not seldom reset on a trial and error basis. The result, particularly with respect to PaCO₂, cannot be judged until after 15–30 min (3). During that period a change of basic status of the patient may obscure the effect of resetting. Such strategies appear inefficient. An alternative strategy is to let the computer simulate an intended change of ventilator setting on the basis of information provided by the physiological profile. From the result of the simulation the physician could beforehand judge if the intentions should be carried through or if alternative settings should be analyzed. A prerequisite for the simulation would be that relevant physiological properties are expressed in mathematical terms.

The change in CO₂ elimination per minute (VCO₂) occurring after a change in alveolar ventilation will indicate the change in PaCO₂ at a new steady state (3). VCO₂ after resetting was therefore used as an index of changing CO₂ equilibrium.

This study should be regarded as an initial step in the development of systems for computer-aided ventilator resetting. One objective of the present study was to develop a technique for measurements based

upon a simple lung model. The main objective was to test the hypothesis that mechanical behavior and $\dot{V}_{CO_2}$ 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, Beerse, 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®, 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 (P_{vent}) and C_{CO₂} 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 post-inspiratory 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 (V_T). In order to keep $\dot{V}_{CO_2}$ constant we performed in each pig a an initial study sequence to examine how CO₂ elimination per breath ($\dot{V}_{CO_2,T}$) varied in relation to V_T , 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 30 s after resetting, covering 10 breaths were used to measure peak airway pressure (P_{peak}), postinspiratory quasi-static elastic recoil pressure ($P_{plateau}$) and $\dot{V}_{CO_2}$ which were compared to simulated data.

Data analysis

Data sampled during a study sequence were transferred to a spreadsheet (Microsoft® Excel 97, Microsoft Corp., Readmond, 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 ($\dot{V}'_{aw}$), 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 V_T equaled inspired V_T (7). Volume relative to end-expiratory volume (V) was calculated by integration of $\dot{V}'_{aw}$.

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 mono-compartment 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, CO_2 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 $P_{plateau}$. $V_{CO_2,T}$ and V_{CO_2} and their variation with V_T was determined from the single breath test for CO_2 (SBT- CO_2).

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

$P_{plateau}$ and post-expiratory quasi-static elastic recoil pressure ($P_{el,E}$) were read 0.3 s after flow cessation. This time corresponds to the duration of the postinspiratory pause at baseline ventilator setting. C was calculated as:

$$C = V_T / (P_{plateau} - P_{el,E}) \quad (1)$$

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

$$P_{tube} = R_{tube} \cdot V'_{aw} = (k_0 + k_1 \cdot |V'_{aw}|) \cdot V'_{aw} \quad (2)$$

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} :

$$P_{tr} = P_{vent} - P_{tube} \quad (3)$$

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 :

$$P_{res} = P_{tr} - V/C \quad (4)$$

G_I and G_E were calculated as V'_{aw}/P_{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:

$$G_E = g_0 + g_1 \cdot V \quad (5)$$

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

$V_{CO_2,T}$ reflects the difference between volume of CO_2 expired ($V_{CO_2,E}$) and the volume of CO_2 re-inspired at the start of inspiration ($V_{CO_2,I}$) (Fig. 1). $V_{CO_2,T}$ at current ventilation was calculated by integration of C_{CO_2} by volume over the respiratory cycle. To determine how $V_{CO_2,T}$ would vary in response to variations in V_T the SBT- CO_2 was further analyzed. The alveolar plateau of the CO_2 concentration during expiration ($C_{CO_2,A}$) was approximated according to . 6 applied over the last 40% of the volume expired (V_E):

$$C_{CO_2,A}(V_E) = f_0 + f_1 \cdot \ln(V_E) \quad (6)$$

Fig. 1. Upper panel: The single breath test for CO_2 shows expiratory CO_2 (heavy line) and inspiratory CO_2 (interrupted line) together delineating area A that corresponds to CO_2 elimination per breath ($V_{CO_2,T}$). Area B represents volume of CO_2 re-inspired from the Y-piece and ventilator tubing ($V_{CO_2,I}$). For calculation of how expired volume of CO_2 (area A + B, i.e. $V_{CO_2,E}$) varies with tidal volume (V_T) the alveolar plateau was described mathematically and extrapolated (crossed line, . 6). Lower panel: The heavy and crossed lines represent integration of the information in upper panel (. 7) yielding $V_{CO_2,E}$ as a function of volume. Thin and dotted lines represent $V_{CO_2,T}$ obtained by subtraction of $V_{CO_2,I}$ (. 8) from $V_{CO_2,E}$.

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

$V_{CO_2,E}$ at an alternative tidal volume ($V_{T,alt}$) was calculated:

$$V_{CO_2,E}(V_{T,alt}) = V_{CO_2,E}(V_T) + \int_{V_T}^{V_{T,alt}} C_{CO_2,A} dV_E \quad (7)$$

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

$V_{CO_2,I}$ at $V_{T,alt}$ was approximated:

$$V_{CO_2,I}(V_{T,alt}) = \frac{V_{CO_2,I}(V_T) \cdot C_{CO_2,ET}(V_{T,alt})}{C_{CO_2,ET}(V_T)} \quad (8)$$

$C_{CO_2,ET}$ is the end-tidal C_{CO_2} .

The parameters ($V_{CO_2,E}$, $V_{CO_2,I}$, $C_{CO_2,ET}$, f_0 , f_1 , C , G_1 , 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_I . 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

$$V'_{aw} = (P_{el} - P_{vent}) / (R_E + R_{tube}) \quad (9)$$

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 V_{CO_2} 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 V_{CO_2} . 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 CO_2 at an RR of 20 min^{-1} a V_T of on average $9.4 \pm 0.95 \text{ ml} \cdot \text{kg}^{-1}$ was required. This relates to a CO_2 production of $5.7 \pm 0.94 \text{ ml} \cdot \text{min} \cdot \text{kg}^{-1}$. The SBT- CO_2 showed a distinct increase of C_{CO_2} and a clearly delineated transition to the alveolar plateau (Fig. 1). The slope of the alveolar plateau at the end of V_T was in the range 0.09–0.26% per 100 ml. $V_{CO_2,I}$ was on average $8 \pm 1.3\%$ of $V_{CO_2,E}$.

Mid-tidal expiratory resistance ($R_{E,MID}$) was in each pig higher than inspiratory resistance (R_I). $R_{E,MID}$ correlated to R_I ($r^2 = 0.89$, $P < 0.01$) Fig. 2. Expiratory conductance decreased during expiration in 6 of 7 pigs, as indicated by a positive g_1 . The average resistance over the V_T is shown in Fig. 2. Compliance was $38 \pm 4.5 \text{ ml cm H}_2\text{O}^{-1}$.

In each case the simulation was in steady state already after 3 of the 6 simulated breaths as shown in a representative example (Fig. 3). Simulated P_{vent}/V , P_{tr}/V and P_{el}/V loops differed from loops calculated from measured flow and pressure, owing to simulation filtering (Fig. 4). The last simulated breath was compared to the average of 10 measured breaths before and after resetting. The difference was expressed as percent of the measured value (Fig. 5). The simula-

Fig. 2. Resistance. Illustration of the considered constant (6,7) inspiratory resistance (R_i) and the variable expiratory resistance (R_E) (. 5) as average and SEM of the 7 pigs.

tion of events before resetting, i.e. at RR 20, served as control of the process comprising measurements, modeling, parameterization and simulation. Then $\dot{V}CO_2$ showed nearly identity between simulated and measured values. At RR 20, P_{peak} and $P_{plateau}$ showed differences below 4% in each case ($P > 0.05$). Simulation of $\dot{V}CO_2$ 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 of $\dot{V}CO_2$ ($P = 0.003$ and $P < 0.001$, respectively). After resetting measured ranges of P_{peak} and $P_{plateau}$ were 12–25 cm H₂O and 11–24 cm H₂O, respectively. Out of simulated values 95% differed less than 1.0 cm H₂O from measured values. Simulated $P_{plateau}$ was marginally higher than measured at RR 25 and RR 30 ($P < 0.001$, $P = 0.025$, respectively). The

Fig. 3. Simulated pressure in the ventilator (P_{vent}) and elastic recoil pressure (P_{el}) illustrate that simulation reached a steady state after about 3 out of 6 breaths, as in this example.

precision of simulations of pressures after resetting, i.e. at RR 10, 15, 25 and 30, were not significantly different from those before resetting, at RR 20.

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

Table 1

Baseline characteristics of the animals.

	Pig 1	Pig 2	Pig 3	Pig 4	Pig 5	Pig 6	Pig 7	Average	SD
Weight, kg	33.0	32.2	29.2	29.9	27.1	31.0	33.5	30.8	2.3
V_T , mL · kg ⁻¹	10.1	10.1	9.4	9.7	7.4	9.1	10.0	9.4	0.95
$\dot{V}CO_2$, mL · kg ⁻¹ · min ⁻¹	6.7	6.0	5.3	6.1	3.8	5.8	6.4	5.7	0.94
V_{Daw} , mL	6.1	6.6	6.2	4.9	5.2	6.9	7.0	6.1	8.1
$\dot{V}CO_{2,i}$, mL CO ₂	0.9	0.8	0.8	0.8	0.6	0.8	0.9	0.8	0.09
$\dot{V}CO_{2,E}$, mL CO	12.1	10.5	8.7	10.1	5.9	9.9	11.7	9.8	2.09
$CCO_{2,A}$, % CO ₂	4.8	4.5	4.7	4.7	4.8	5.4	4.8	4.8	0.27
f_0 , % CO ₂	3.1	1.5	2.5	2.8	2.0	2.2	2.5	2.4	0.54
f_1 , % CO ₂	0.3	0.5	0.4	0.3	0.5	0.6	0.4	0.4	0.11
Compliance, mL · cm H ₂ O ⁻¹	4.2	3.4	3.4	3.2	4.0	4.1	4.3	3.8	4.5
R_i , cm H ₂ O · s · L ⁻¹	2.1	3.9	3.1	4.7	3.2	5.2	2.3	3.5	1.1
$R_{E,MID}$, cm H ₂ O · s · L ⁻¹	6.1	9.9	7.9	10.4	5.7	10.8	5.7	8.1	2.3
g_0 , L · s ⁻¹ · cm H ₂ O ⁻¹	0.14	0.10	0.11	0.08	0.11	0.09	0.19	0.12	0.036
g_1 , s ⁻¹ · cm H ₂ O ⁻¹	$1.5 \cdot 10^{-4}$	$1.5 \cdot 10^{-5}$	$1.3 \cdot 10^{-4}$	$8.2 \cdot 10^{-5}$	$5.2 \cdot 10^{-4}$	$1.1 \cdot 10^{-5}$	$-2.0 \cdot 10^{-3}$	$1.3 \cdot 10^{-4}$	$7.8 \cdot 10^{-4}$

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

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.

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

Fig. 5. Individual (◊) and average (—) errors in simulation of CO_2 elimination per minute (V_{CO_2}), 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 CO_2 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 CO_2 elimination and ventilator pressure after resetting. Tidal volume and respiratory rate are important factors determining mechanical behavior and CO_2 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 CO_2 elimination was based upon a complete breath, with the V_T and RR as only input parameters.

Among the comprehensive results of each simulation P_{peak} , P_{plateau} and V_{CO_2} 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_{CO_2} , which is based upon complete breaths is accurate. Modeling and parameterization are robust. As expected from these facts the simulation of V_{CO_2} 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 V_T 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 CO_2 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 CO_2 elimination will lead to reciprocal changes in PaCO_2 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 CO_2 elimination on gas mixing time must be studied in each subject remains to be investigated. If needed, the influence of gas mixing time on CO_2 elimination may be studied by changing RR, T_I 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 CO_2 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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