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A prolonged postinspiratory pause enhances CO₂ elimination by reducing airway dead space
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Summary
Background: CO₂ elimination per breath \((V_{CO₂,T})\) depends primarily on tidal volume \((V_T)\). The time course of flow during inspiration influences distribution and diffusive mixing of \(V_T\) and is therefore a secondary factor determining gas exchange. To study the effect of a postinspiratory pause we defined ‘mean distribution time’ (MDT) as the mean time given to inspired gas for distribution and diffusive mixing within the lungs. The objective was to quantify changes in airway dead space \((V_{Daw})\), slope of the alveolar plateau (SLOPE) and \(V_{CO₂,T}\) as a function of MDT in healthy pigs.

Methods: Ten healthy pigs were mechanically ventilated. Airway pressure, flow and partial pressure of CO₂ were recorded during resetting of the postinspiratory pause from 10% (baseline) to, in random order, 0, 5, 20 and 30% of the respiratory cycle. The immediate changes in \(V_{Daw}\), SLOPE, \(V_{CO₂,T}\), and MDT after resetting were analyzed.

Results: \(V_{Daw}\) in percent of \(V_T\) decreased from 29 to 22%, SLOPE from 0Æ35 to 0Æ16 kPa per 100 ml as MDT increased from 0Æ51 to 1Æ39 s. Over the same MDT range, \(V_{CO₂,T}\) increased by 10%. All these changes were statistically significant.

Conclusion: MDT allows comparison of different patterns of inspiration on \(V_{Daw}\) and gas exchange. Estimation of the effects of an altered ventilator setting on exchange of CO₂ can be done only after about 30 minutes, while the transient changes in \(V_{CO₂,T}\) may give immediate information. MDT affects gas exchange to an important extent. Further studies in human subjects in health and in disease are needed.

Introduction
A low tidal volume \((V_T)\) appears to be a crucial factor for lung protective ventilation in the acute respiratory distress syndrome. When low \(V_T\) is used to provide lung protective ventilation, respiratory acidosis can be partly balanced by an increased respiratory rate (RR) (ARDS Network, 2000). In itself, a low \(V_T\) leads to increased dead space fraction. A short duration of inspiration that follows from an increased RR may then further compromise gas exchange by uneven distribution and inadequate mixing of \(V_T\) in the alveolar space. Different means to reduce dead space have been suggested. For instance, replacement of passive humidifiers with active ones, tracheal gas insufflation and aspiration of dead space implies that the interface between ‘fresh and old’ gas is moved distally already at the beginning of inspiration (Jonson et al., 1990; De Robertis et al., 1999; Richiocoeur et al., 1999). Furthermore, a ventilator setting that facilitates diffusion may reduce dead space by allowing this interface to move proximally before the end of inspiration. Accordingly, the dead space related to the airways represents function as well as anatomy. Rather than the term ‘anatomical dead space’ we prefer the term airway dead space that should be read as ‘functional airway dead space’. Several studies in health or in disease show a decrease in dead space or PaCO₂ when using a postinspiratory pause (Fuleihan et al., 1976; Dammann et al., 1978; Lachmann et al., 1982; Wolff et al., 1989a; Mercat et al., 2001). However, positive effects of inspiratory patterns intended to improve gas exchange have not always been observed (Johansson, 1975; Johansson & Lofström, 1975; Dammann et al., 1978; Al-Saady & Bennett, 1985; Markstrom et al., 2000). Partly diverging results may reflect methodological limitations. Recently, a known method allowing high accuracy of dead space determination in intensive care was further refined (Beydon et al., 2002). A method to compensate for inevitable changes in \(V_T\) can be based on mathematical modelling of the alveolar plateau in the single breath test for CO₂ (SBT-CO₂) (Uttman & Jonson, 2002). In the present study, we introduce the term ‘mean distribution time’.
(MDT), which is the mean time given to inspired gas for distribution and diffusive mixing within the lungs. MDT was varied by changing the duration of the postinspiratory pause at volume controlled ventilation with constant flow. The objective was to quantify changes in airway dead space ($V_{Daw}$), slope of the alveolar plateau (SLOPE) and CO2 elimination per breath ($V_{CO2,T}$) as a function of MDT in healthy pigs.

**Methods**

**Materials**

The local Ethics Board of Animal Research approved the experimental protocol. Ten pigs of the Swedish native breed, mean weight 29·5 kg (23·0–33·5), were fasted overnight with free access to water. Seven of these animals were the same as in (Uttman & Jonson, 2002). The animals were premedicated with azaperon (7 mg kg$^{-1}$), anaesthetized with ketamin (5 mg kg$^{-1}$), intubated with a 7·0 mm ID tracheal tube and connected to a ventilator (ServoVentilator 900C, Siemens-Elema, Solna, Sweden). Ventilation was volume controlled with a square inspiratory flow pattern. At baseline setting RR was 20 min$^{-1}$, inspiratory time 33%, postinspiratory pause time ($T_p$) 10% and positive end-expiratory pressure 6 cm H2O. The baseline minute ventilation was adjusted to achieve PaCO$_2$ 4·5–5 kPa. A mainstream analyzer (CO2 Analyzer 930, Siemens-Elema, Solna, Sweden) measured partial pressure of CO2 in expired and inspired gas (P$_{CO2}$. Anaesthesia was maintained by continuous infusion of ketamin (17 mg kg$^{-1}$ h$^{-1}$), midazolam (1·7 mg kg$^{-1}$ h$^{-1}$) and pancuronium bromide (0·5 mg kg$^{-1}$ h$^{-1}$). The ventilator/computer system used for data recording has previously been described (Svantesson et al., 1997). Signals from the ventilator and CO2 analyzer representing flow rate, airway pressure and P$_{CO2}$ were sampled by a personal computer at the frequency of 50 Hz. Compliance of the tracheal tube and ventilator tubing was measured in vitro. There were no dropouts among the animals.

**Protocol**

After preparation of the animals a stabilization period of 30 min was allowed. A recruitment manoeuvre was performed by inflating the lungs with a pressure of 35 cm H2O for 10 s to eliminate atelectasis and standardize lung volume history and conditions among the animals. The system was tested for leakage. A continuous record of a study sequence comprised the following elements: 10 normal breaths, 20 breaths of a different $T_p$, 10 normal breaths. $T_p$ was changed by manual switch of the $T_p$ control of the ventilator from 10 to 0, 5, 20 and 30% of the respiratory cycle, in randomized order.

**Data analysis**

Data sampled during a study sequence were transferred to a spreadsheet for analysis (Excel 97, Microsoft Corp., WA, USA). Measured flow rate was corrected for the compliance in the tubing in order to obtain airway flow rate ($V_{aw}$). The expiratory flow signal was normalized by a correction factor so that expired volume equaled inspired volume. The correction factor obtained at $T_p$ 10% was applied to all recordings. $V_T$ was calculated by integration of expired $V_{aw}$. Airway dead space distal to the CO2 sensor was determined according to an algorithm of (Wolff & Brunner, 1984) that was modified to correct for a sloping alveolar plateau (Åström et al., 2000) in accordance with principles previously described (Wolff et al., 1989b). Airway dead space distal to the tip of the tracheal tube ($V_{Daw}$) was calculated by subtracting the dead space volume of the tracheal tube and CO2 analyzer (16 ml). $V_{CO2,T}$ was calculated as the difference between expired volume of CO2 and that re-inspired from the Y-piece and adjacent tubing, which corresponds to the area within the SBT-CO2 loop (Fig. 1) (Uttman & Jonson, 2002). From an equation describing the alveolar plateau its SLOPE was calculated at the volume halfway between $V_{Daw}$ and $V_T$ (Beydon et al., 2002). Technical limitations and flux of gas from tubing to the subject in the first phase of a postinspiratory pause caused small variations in $V_T$ and thereby in $V_{CO2,T}$. The effect on $V_{CO2,T}$ caused by $V_T$ variation was not an issue of this study and was accordingly corrected for. How $V_{CO2,T}$ varies with $V_T$ can be determined from the end-tidal alveolar slope and end-tidal P$_{CO2}$ in the SBT-CO2 (Uttman & Jonson, 2002). $V_{CO2,T}$ was normalized to the lowest $V_T$ observed as was end-tidal P$_{CO2}$.

For a certain pattern of inspiration including the postinspiratory pause, MDT was calculated from all samples during a recorded inspiration as:

$$MDT = \frac{\sum (V_{aw} \cdot \Delta t \cdot t_{dist})}{\sum (V_{aw} \cdot \Delta t)} = \frac{\sum (V_{aw} \cdot t_{dist})}{\sum (V_{aw})} \quad (1)$$

where $\Delta t$ is the sampling interval (0·02 s) and $t_{dist}$ is the time left for distribution of the particular gas sample until start of expiration.

**Figure 1** The single breath test for CO2 in a representative animal at different mean distribution time (MDT). Longer MDT resulted in a left-hand shift of the sharp ascending expiratory limb of the loop. This corresponds to a decrease in airway dead space and an increase in tidal CO2 elimination (area A). The slope of the alveolar plateau decreased with MDT.
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Table 1 Consequences of postinspiratory pause.

<table>
<thead>
<tr>
<th>Tp (%)</th>
<th>MDT (s) mean ± SD</th>
<th>V_daw (% of V_t) mean ± SEM</th>
<th>V_CO₂,T (ml) mean ± SEM</th>
<th>SLOPE (kPa per 100 ml) mean ± SEM</th>
<th>P_CO₂,ET (kPa) mean ± SEM</th>
<th>P_plateau (cm H₂O) mean ± SEM</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0·51 ± 0·01</td>
<td>29 ± 1·0</td>
<td>8·0 ± 0·57</td>
<td>0·35 ± 0·04</td>
<td>4·8 ± 0·12</td>
<td>—</td>
</tr>
<tr>
<td>5</td>
<td>0·63 ± 0·01</td>
<td>27 ± 0·9</td>
<td>8·1 ± 0·56</td>
<td>0·26 ± 0·02</td>
<td>4·7 ± 0·13</td>
<td>15·1 ± 0·5</td>
</tr>
<tr>
<td>10</td>
<td>0·78 ± 0·01</td>
<td>25 ± 0·9</td>
<td>8·3 ± 0·59</td>
<td>0·24 ± 0·03</td>
<td>4·7 ± 0·12</td>
<td>14·7 ± 0·5</td>
</tr>
<tr>
<td>20</td>
<td>1·08 ± 0·02</td>
<td>24 ± 0·9</td>
<td>8·6 ± 0·60</td>
<td>0·14 ± 0·01</td>
<td>4·7 ± 0·12</td>
<td>14·7 ± 0·5</td>
</tr>
<tr>
<td>30</td>
<td>1·39 ± 0·02</td>
<td>22 ± 0·8</td>
<td>8·8 ± 0·60</td>
<td>0·16 ± 0·02</td>
<td>4·7 ± 0·14</td>
<td>15·0 ± 0·5</td>
</tr>
</tbody>
</table>

MDT, mean distribution time; V_daw, airway dead space; V_CO₂,T, tidal CO₂ elimination; P_CO₂,ET, end-tidal P_CO₂; P_plateau, postinspiratory plateau pressure.

Figure 2 Airway dead space (V_daw) as a function of mean distribution time (MDT) in each subject.

Figure 3 Tidal CO₂ elimination change (ΔV_CO₂,T) as a function of mean distribution time (MDT). Individual curves (thin lines) and regression line (heavy line), with extrapolation (broken line).

Statistical methods

Data are presented as mean ± SD. Two-way ANOVA was used to study variations of different parameters with MDT. Student’s paired two-tailed t-test was used to analyze differences among parameters observed at MDT 0·51 s (Tp 0%) and other values of MDT. Non-linear regression was used to establish the relationship between V_CO₂,T and MDT.

Results

V_t was 286 ± 42 ml, corresponding to 9·7 ± 1·0 ml kg⁻¹. V_t increased with on average 4 ml when Tp increased from 0 to 5% and remained at that level at longer Tp. The end-expiratory flow was 0 at Tp 0% to Tp 20% and increased to 0·05 ± 0·04 l s⁻¹ at Tp 30%. Plateau pressure measured at the end of the postinspiratory pause showed only minor variations with Tp (Table 1). For the different Tp MDT varied from 0·51 to 1·39 s with a coefficient of variation between animals of less than 2% (Table 1). Figure 1 shows the SBT-CO₂ for the different MDT in a representative animal. As appears from Fig. 2, V_daw decreases non-linearly with MDT in each animal. The decrease in V_daw resulted in an increase in V_CO₂,T as illustrated in Fig. 1.

Longer MDT led to lower SLOPE and lower end-tidal P_CO₂ (ANOVA, P<0·001 for both) (Table 1). Effects on V_CO₂,T, related to changes of the alveolar plateau, were calculated from changes in the area below the alveolar plateau. When Tp increased from 0 to 30%, the observed changes of the alveolar plateau did not influence V_CO₂,T (P>0·05).

When Tp increased from 0 to 30%, implying that MDT changed from 0·51 to 1·39 s, V_CO₂,T in percent of the value at Tp 0% increased as shown in Fig. 3. The change in V_CO₂,T (ΔV_CO₂,T) was expressed according as follows:

\[ \Delta V_{CO₂,T} = 7·24 + 10·6 \ln(MDT) \] (t = 0·86, P<0·001) (2)

Discussion

At volume controlled ventilation with constant inspiratory flow, this study shows that a postinspiratory pause enhances CO₂ elimination by reducing V_daw. The uniform results indicate that it is possible to detect even modest changes in V_daw and CO₂ elimination. These changes follow immediately after resetting. In contrast, stabilization of PaCO₂ following a change in CO₂...
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elimination takes several minutes (Farhi & Rahn 1955; Taskar et al., 1995) and may be obscured by physiological instability. The determination of MDT according to Eq. (1) was robust as indicated by low scatter (Table 1). As this study has its focus on methodological and conceptual development it has several limitations. Healthy pigs do not have collateral ventilation (Woolcock & Macklem, 1971). Furthermore, as airway resistance is low, different lung units probably fill and empty nearly synchronously. Obviously, the results cannot be applied on humans in whom collateral ventilation may equilibrate ventilation non-homogeneity. This may be particularly important in obstructive lung disease. The end-expiratory flow indicated the presence of auto-PEEP at Tp 30%. An estimate based on previous observations of expiratory resistance in healthy pigs (Uttman & Jonson, 2002) suggests that auto-PEEP was less than 0·5 cm H₂O. That auto-PEEP was unimportant was further supported by the nearly constant postinspiratory plateau pressure (Table 1). If benefits of a prolonged MDT are obtained by prolongation of inspiration at the expense of expiratory time, a deleterious degree of auto-PEEP may result, particularly in the presence of airway obstruction. A more favourable approach may then be to prolong MDT by changing the flow wave pattern of inspiration. However, we only studied constant inspiratory flow. Pressure controlled ventilation, which particularly in Scandinavia is frequently used, results in a decelerating inspiratory flow. When airway resistance varies within the lung such a flow rate leads to a more even ventilation (Jansson & Jonson, 1972). One rational of decelerating flow is, indeed, to prolong MDT and to promote even gas distribution and diffusion. Obviously, the limitations of this study merit further studies with different flow patterns in humans with different nature of lung pathology.

MDT was conceived with the prospect that it is applicable to all patterns of inspiration. The algorithm of MDT (Eq. 1) dictates that any symmetrical inspiratory waveform will have the same MDT, provided that inspiratory time is constant. The validity of this assumption is supported by that ventilation with square and sine inspiratory waveforms give rise to the same CO₂ elimination reflected by equal PaCO₂ (Dammann et al., 1978). Notably, a decelerating or accelerating inspiratory flow pattern will have longer and shorter MDT, respectively, compared to symmetrical flow waveforms. Different waveforms have been studied in humans with indistinct results (Johansson, 1975; Johansson & Lofstrom, 1975; Dammann et al., 1978; Al-Saadly & Bennett, 1985; Markstrom et al., 2000). Such studies merit to be repeated with modern technique.

The effect of a longer Tp on VDaw indicates a movement in the proximal direction of the ’distal boundary of dead space’ (Bowes et al., 1985). As the total airway cross-section area decreases rapidly with each bronchial generation in the cranial direction (Weibel, 1963), the rate of this movement must be expected to decline in a non-linear fashion, as was found (Fig. 2). The rational of using a logarithmic equation is based on this concept. When MDT is falling towards zero no time is available for diffusion, which is a prerequisite for exchange of gas within the respiratory zone. On the other hand, after a long time for gas distribution the interface between alveolar gas and fresh gas would by diffusion have reached a level in the airways at which the fast drop in total cross-section area would render diffusion more and more inefficient.

The variation in VDaw we observed corresponds to about 0·7 ml kg⁻¹ body weight, which is not trivial with respect to lung protective strategies. In the clinic, it might be desirable to use high RR. If we allow ourselves to extrapolate MDT to 0·25 s (RR 40, Tp 0%), as shown in Fig. 3, VCO₂,T would in comparison to MDT 0·51 drop by about 7% and further increase dead space. This would enhance problems related to hypercapnia when Vt is restricted to 6 ml kg⁻¹ (ARDS Network, 2000).

The effect of a longer Tp on SLOPE implies a more even PCO₂ in lung units, which empty non-synchronously. This can either be due to equilibration between parallel units caused by pendelluft or by equilibration along longitudinally oriented units in terms of distal and more proximal alveoli (Fletcher, 1980). In principle, one cannot from external global observations differentiate between these models (West, 1971). One can only speculate that low peripheral resistance in healthy pigs might prevent significant uneven ventilation between parallel lung units. Time-dependent equilibration between proximal and more distal alveoli offers a more likely explanation. Anyway, the more even alveolar concentration reflected by a lower SLOPE after a long Tp was not so important so as to significantly reduce VCO₂,T.

Our results agree with previous findings that a postinspiratory pause enhances CO₂ elimination (Fuleihan et al., 1976; Dammann et al., 1978; Lachmann et al., 1982; Wolff et al., 1989a; Mercret et al., 2001). In the present study, we used the shortest possible tubing (compliance 0·45 ml per cm H₂O). In spite of that, about 4 ml was re-distributed from the tubing to the lungs when a postinspiratory pause was applied. If we had not corrected VCO₂,T for the increase in Vt, effects of a postinspiratory pause in itself would have been overestimated. In the clinic, both longer tubing and a larger drop in airway pressure at transition to the pause may cause larger Vt variation. In comparison to previous studies, the methodological development is considered to increase the validity and accuracy of the results, which increased the ability to quantify changes in dead space related to modest changes in MDT.

In conclusion, the concept MDT was introduced to allow comparison of different patterns of inspiration with respect to VDaw and gas exchange. Estimation of the effects of an altered ventilator setting on exchange of CO₂ can be done after about 30 min, while the transient changes in VCO₂,T may give immediate information. MDT affects gas exchange to such an extent that it may be of importance for optimisation of ventilator setting. Further studies on human subjects in health and in disease are needed.

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