A prolonged postinspiratory pause enhances CO2 elimination by reducing airway dead space.

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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; Richecoeur 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., 1983; 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 & Lofstöm, 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 (Tₚ) 10% and positive end-expiratory pressure 6 cm H₂O. The baseline minute ventilation was adjusted to achieve PaCO₂ 1997). Signals from the ventilator and CO₂ analyzer represent the following elements: 10 normal breaths, 20 breaths of a different pattern of inspiration including the postinspiratory pause, and postinspiratory pause, MDT was calculated from all samples during a study sequence comprised 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 Vₚ (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 Vₚ and thereby in V_{CO₂,T}. The effect on V_{CO₂,T} caused by postinspiratory pause, MDT was calculated from all samples during a recording inspiration as:

\[
MDT = \frac{\sum (V_{aw} \cdot \Delta t \cdot t_{dist})}{\sum (V_{aw} \cdot \Delta t)} = \frac{\sum (V_{aw} \cdot t_{dist})}{\sum (V_{aw})}
\]

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.

**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 pattern of inspiration, 10 normal breaths. Tₚ was changed by manual switch of the Tₚ 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).

**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.
Table 1 Consequences of postinspiratory pause.

<table>
<thead>
<tr>
<th>$T_p$ (%)</th>
<th>MDT (s) mean ± SD</th>
<th>$V_{Daw}$ (% of $V_t$) mean ± SEM</th>
<th>$V_{CO_2,T}$ (ml) mean ± SEM</th>
<th>SLOPE (kPa per 100 ml) mean ± SEM</th>
<th>$P_{CO_2,ET}$ (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; $V_{CO_2,T}$, tidal CO₂ elimination; $P_{CO_2,ET}$, end-tidal $P_{CO_2}$; $P_{plateau}$, postinspiratory plateau pressure.

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 ($T_p$ 0%) and other values of MDT. Non-linear regression was used to establish the relationship between $V_{CO_2,T}$ 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 $T_p$ increased from 0 to 5% and remained at that level at longer $T_p$. The end-expiratory flow was 0 at $T_p$ 0% to $T_p$ 20% and increased to 0-05 ± 0.04 l s⁻¹ at $T_p$ 30%. Plateau pressure measured at the end of the postinspiratory pause showed only minor variations with $T_p$ (Table 1). For the different $T_p$ 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 $V_{CO_2,T}$ as illustrated in Fig. 1.

Longer MDT led to lower SLOPE and lower end-tidal $P_{CO_2}$ (ANOVA, $P<0.001$ for both) (Table 1). Effects on $V_{CO_2,T}$, related to changes of the alveolar plateau, were calculated from changes in the area below the alveolar plateau. When $T_p$ increased from 0 to 30%, the observed changes of the alveolar plateau did not influence $V_{CO_2,T}$ ($P>0.05$).

When $T_p$ increased from 0 to 30%, implying that MDT changed from 0.51 to 1.39 s, $V_{CO_2,T}$ in percent of the value at $T_p$ 0% increased as shown in Fig. 3. The change in $V_{CO_2,T}$ ($\Delta V_{CO_2,T}$) was expressed according as follows:

$$\Delta V_{CO_2,T} = 7.24 + 10.6 \ln(\text{MDT}) \quad (r = 0.86, P<0.001)$$

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 $P_{CO_2}$ following a change in CO₂
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 $T_P$ 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 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 $V_{CO2,T}$ for the increase in $V_T$, 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 $V_T$ 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 $V_{Daw}$ 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 $V_{CO2,T}$ 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.

Acknowledgments

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