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A prolonged postinspiratory pause enhances CO_2 elimination by reducing airway dead space

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Summary

Background: CO_2 elimination per breath ($V_{CO_2,T}$) 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 $V_{CO_2,T}$ as a function of MDT in healthy pigs.

Methods: Ten healthy pigs were mechanically ventilated. Airway pressure, flow and partial pressure of CO_2 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, $V_{CO_2,T}$, and MDT after resetting were analyzed.

Results: V_{Daw} in percent of V_T decreased from 29 to 22%, SLOPE from 0·35 to 0·16 kPa per 100 ml as MDT increased from 0·51 to 1·39 s. Over the same MDT range, $V_{CO_2,T}$ 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 CO_2 can be done only after about 30 minutes, while the transient changes in $V_{CO_2,T}$ may give immediate information. MDT affects gas exchange to an important extent. Further studies in human subjects in health and in disease are needed.

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artificial respiration; breath tests; capnography; pulmonary gas exchange; swine

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 may 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 $PaCO_2$ 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 & Löfström, 1975; Dammann *et al.*, 1978; Al-Saady & Bennett, 1985; Markström *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 CO_2 (SBT-CO_2) (Uttman & Jonson, 2002). In the present study, we introduce the term 'mean distribution time'

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(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 CO_2 elimination per breath ($V_{CO_2,T}$) 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 H_2O. The baseline minute ventilation was adjusted to achieve $PaCO_2$ 4·5–5 kPa. A mainstream analyzer (CO_2 Analyzer 930, Siemens-Elema, Solna, Sweden) measured partial pressure of CO_2 in expired and inspired gas (P_{CO_2}). 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 CO_2 analyzer representing flow rate, airway pressure and P_{CO_2} 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 H_2O 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 ($\dot{V}_{aw}$). The expiratory flow signal was normalized by a correction factor so that expired volume equalled inspired volume. The correction factor obtained at T_P 10% was applied to all recordings. V_T was calculated by integration of expired $\dot{V}_{aw}$. Airway dead space distal to the CO_2 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 CO_2 analyzer (16 ml). $V_{CO_2,T}$ was calculated as the difference between expired volume of CO_2 and that re-inspired from the Y-piece and adjacent tubing, which corresponds to the area within the SBT-CO_2 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 $V_{CO_2,T}$. The effect on $V_{CO_2,T}$ caused by V_T variation was not an issue of this study and was accordingly corrected for. How $V_{CO_2,T}$ varies with V_T can be determined from the end-tidal alveolar slope and end-tidal P_{CO_2} in the SBT-CO_2 (Uttman & Jonson, 2002). $V_{CO_2,T}$ was normalized to the lowest V_T observed as was end-tidal P_{CO_2}.

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

$$MDT = \frac{\sum(\dot{V}_{aw} \cdot \Delta t \cdot t_{dist})}{\sum(\dot{V}_{aw} \cdot \Delta t)} = \frac{\sum(\dot{V}_{aw} \cdot t_{dist})}{\sum(\dot{V}_{aw})} \qquad (1)$$

where Δt 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.

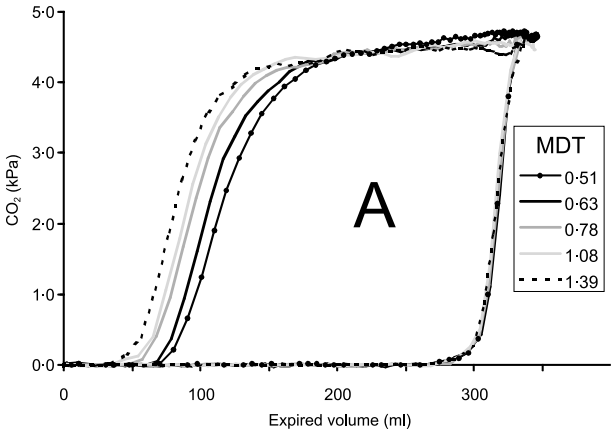

Figure 1 The single breath test for CO_2 in a representative animal at different mean distribution time (MDT). Longer MDT resulted in a left-hand shift of the sharp ascending expiratory limb of the loop. This corresponds to a decrease in airway dead space and an increase in tidal CO_2 elimination (area A). The slope of the alveolar plateau decreased with MDT.

Table 1 Consequences of postinspiratory pause.

T_P (%)	MDT (s) mean ± SD	V_{Daw} (% of V_T) mean ± SEM	$V_{CO_2,T}$ (ml) mean ± SEM	SLOPE (kPa per 100 ml) mean ± SEM	$P_{CO_2,ET}$ (kPa) mean ± SEM	$P_{plateau}$ (cm H_2O) mean ± SEM
0	0·51 ± 0·01	29 ± 1·0	8·0 ± 0·57	0·35 ± 0·04	4·8 ± 0·12	–
5	0·63 ± 0·01	27 ± 0·9	8·1 ± 0·56	0·26 ± 0·02	4·7 ± 0·13	15·1 ± 0·5
10	0·78 ± 0·01	25 ± 0·9	8·3 ± 0·59	0·24 ± 0·03	4·7 ± 0·12	14·8 ± 0·5
20	1·08 ± 0·02	24 ± 0·9	8·6 ± 0·60	0·14 ± 0·01	4·7 ± 0·12	14·7 ± 0·5
30	1·39 ± 0·02	22 ± 0·8	8·8 ± 0·60	0·16 ± 0·02	4·7 ± 0·14	15·0 ± 0·5

MDT, mean distribution time; V_{Daw}, airway dead space; $V_{CO_2,T}$, tidal CO_2 elimination; $P_{CO_2,ET}$, end-tidal P_{CO_2}; $P_{plateau}$, postinspiratory plateau pressure.

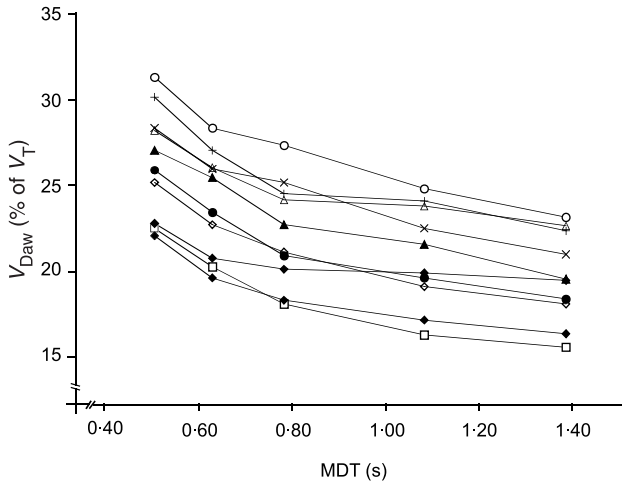

Figure 2 Airway dead space (V_{Daw}) as a function of mean distribution time (MDT) in each subject.

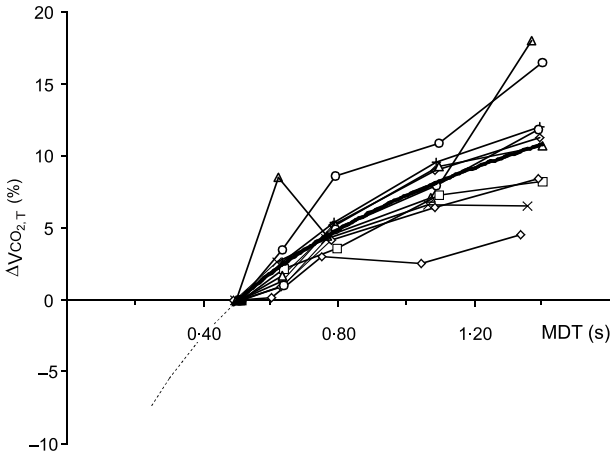

Figure 3 Tidal CO_2 elimination change ($\Delta V_{CO_2,T}$) as a function of mean distribution time (MDT). Individual curves (thin lines) and regression line (heavy line), with extrapolation (broken line).

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 (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-CO_2 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:

$$\Delta V_{CO_2,T} = 7·24 + 10·6\ln(\text{MDT}) \quad (r = 0·86, P < 0·001) \quad (2)$$

Discussion

At volume controlled ventilation with constant inspiratory flow, this study shows that a postinspiratory pause enhances CO_2 elimination by reducing V_{Daw}. The uniform results indicate that it is possible to detect even modest changes in V_{Daw} and CO_2 elimination. These changes follow immediately after resetting. In contrast, stabilization of $PaCO_2$ following a change in CO_2

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 H_2O. 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 CO_2 elimination reflected by equal $PaCO_2$ (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 & Löfström, 1975; Dammann *et al.*, 1978; Al-Saady & Bennett, 1985; Markström *et al.*, 2000). Such studies merit to be repeated with modern technique.

The effect of a longer T_P on V_{Daw} 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 V_{Daw} 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, T_P 0%), as shown in Fig. 3, $V_{CO_2,T}$ would in comparison to MDT 0·51 drop by about 7% and further increase dead space. This would enhance problems related to hypercapnia when V_T is restricted to 6 ml kg^{-1} (ARDS Network, 2000).

The effect of a longer T_P on SLOPE implies a more even P_{CO_2} 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 T_P was not so important so as to significantly reduce $V_{CO_2,T}$.

Our results agree with previous findings that a postinspiratory pause enhances CO_2 elimination (Fuleihan *et al.*, 1976; Dammann *et al.*, 1978; Lachmann *et al.*, 1982; Wolff *et al.*, 1989a; Mercat *et al.*, 2001). In the present study, we used the shortest possible tubing (compliance 0·45 ml per cm H_2O). 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 $V_{CO_2,T}$ 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 CO_2 can be done after about 30 min, while the transient changes in $V_{CO_2,T}$ 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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