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An appropriate inspiratory flow pattern can enhance CO$_2$ exchange facilitating protective ventilation of healthy lungs

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Short running title: CO$_2$ exchange enhanced by modified inspiratory flow
Summary

**Background:** In acute lung injury, CO$_2$ exchange is enhanced by prolonging the volume weighted mean time for fresh gas to mix with resident alveolar gas, denoted mean distribution time (MDT), and by increasing the flow rate immediately before inspiratory flow interruption, end-inspiratory flow (EIF). The objective was to study these effects in man without lung disease and to analyse the results with respect to lung-protective ventilation of healthy lungs.

**Methods:** During preparation for intracranial surgery, the lungs of eight subjects were ventilated with a computer-controlled ventilator, allowing breath-by-breath modification of the inspiratory flow pattern. The durations of inspiration (T$_I$) and post-inspiratory pause (T$_P$) were modified, as was the profile of the inspiratory flow wave (i.e. constant, increasing or decreasing). The single-breath test for CO$_2$ was used to quantify airway dead space (V$_{Daw}$) and CO$_2$ exchange.

**Results:** A long MDT and a high EIF augment CO$_2$ elimination by reducing V$_{Daw}$ and promoting mixing of tidal gas with resident alveolar gas. A heat and moisture exchanger had no other effect than enlarging V$_{Daw}$. A change of T$_I$ from 33 to 15% and of T$_P$ from 10 to 28%, leaving the time for expiration unchanged, would augment tidal elimination of CO$_2$ by 14%, allowing a 10% lower tidal volume.

**Conclusions:** In anaesthetised human subjects without lung disease, CO$_2$ exchange is enhanced by a long MDT and a high EIF. A short T$_I$ and a long T$_P$ allow significant reduction of tidal volume when lung-protective ventilation is required.

**Clinical trial registration:** NCT01686984

**Key words:** capnography; intermittent positive pressure ventilation; pulmonary gas exchange
**Introduction**

Seminal studies show increased survival among patients with acute respiratory distress syndrome (ARDS) ventilated with low tidal volume (V\textsubscript{T}).\textsuperscript{1,2} More recent studies show that low-V\textsubscript{T} ventilation may be protective against lung complications or organ failure in patients without prior lung disease, such as patients ventilated during major surgery.\textsuperscript{3-5} For large groups of ventilated patients, low V\textsubscript{T} has therefore been suggested as standard in several reviews and meta-analyses.\textsuperscript{6-10} Ventilation with reduced V\textsubscript{T} carries a risk of CO\textsubscript{2} retention. In this study, we explore how dead space can be reduced and CO\textsubscript{2} exchange enhanced simply by optimising the inspiratory flow pattern, thereby reducing the need for other interventions. These might include increasing respiratory rate (RR) or more complex remedies, such as using an active humidifier instead of a heat and moisture exchanger (HME) or flushing upper airways with fresh gas before inspiration.\textsuperscript{11-15}

Some patterns of inspiratory flow promote mixing of tidal and alveolar gas thereby reducing dead space.\textsuperscript{16-17} An adjustable inspiratory waveform was therefore introduced with the ServoVentilator 900 (Siemens-Elema AB, Solna, Sweden).\textsuperscript{18} Computer control of inspiratory flow and volumetric capnography allow detailed studies on how the inspiratory pattern affects dead space and CO\textsubscript{2} exchange.\textsuperscript{19-23} In large airways gas transport is convective, whereas diffusion predominates in the respiratory zone.\textsuperscript{24} During inspiration, the time allowed for such diffusion is essential for gas exchange.\textsuperscript{25} This time is represented by mean distribution time (MDT) which reflects the inspiratory time (T\textsubscript{I}), duration of post-inspiratory pause (T\textsubscript{P}), and profile of the inspiratory flow wave which can be constant, increasing or decreasing (Fig. 1). MDT is calculated as the volume-weighted mean time for fresh gas to mix with resident alveolar gas (Fig. 2). In healthy pigs, a prolonged MDT reduced airway dead space (V\textsubscript{Daw}) and increased CO\textsubscript{2} elimination.\textsuperscript{23} When flow rate immediately before
interruption of inspiration (end-inspiratory flow, EIF) was high, this also promoted CO₂ exchange in animal and human ARDS,¹⁹²¹ but the effect in healthy lungs on CO₂ exchange of increasing EIF or MDT has not previously been explored. The objectives of the present study were to quantify effects of inspiratory flow patterns on CO₂ exchange in humans without lung disease, and to analyse the results with respect to lung-protective ventilation of healthy lungs.
Methods

Eight subjects were studied after induction of anaesthesia and orotracheal intubation during preparation for elective intracranial surgery (Table 1). Lung disease and age <18 yr were exclusion criteria. The study was approved by the Institutional Review Board of the Regional Ethics Committee in Lund, Sweden (Dnr 2012/381), conducted in adherence to the declaration of Helsinki and registered with ClinicalTrials.gov (NCT01686984). Written informed consent was obtained from each subject.

Anaesthesia was induced with remifentanil (0.5 – 1 µg kg⁻¹ i.v.) followed by propofol (1.5 – 2 mg kg⁻¹ i.v.). Intubation was facilitated with rocuronium (0.5 mg kg⁻¹ i.v.). Anaesthesia was maintained with remifentanil (0.1 – 0.15 µg kg⁻¹ h⁻¹ i.v.) and propofol (4.0 – 6.7 mg kg⁻¹ h⁻¹ i.v.). Volume-controlled ventilation was delivered with a ServoVentilator 900C equipped with a mainstream CO₂ Analyzer 930 (Siemens-Elema AB, Solna, Sweden). Positive end-expiratory pressure (PEEP) was 5 cm H₂O and RR bpm. Ordinary breaths were delivered with constant flow, T₁ was 33% and Tᵢ 10%. Volumes and flow rates are expressed as measured at body temperature, standard barometric pressure, and gas saturated with water vapour (BTPS).

The ServoVentilator 900C was connected to a personal computer for instant and continuous ventilator control. Six sequences of 12 breaths were recorded. Breaths number 3, 6, 9 and 12 were modified with respect to T₁ (20 – 53%), Tᵢ (3 – 18%) and the profile of the inspiratory flow wave, which was square (constant flow) or triangular (increasing or decreasing flow rate). Vᵢ, PEEP and expiratory time were constant for all breaths. In total, 21 inspiratory flow patterns were studied (Fig. 1). An ordinary breath preceded each of the four modified breaths in a recording, and average values from
the four ordinary breaths served as the reference for the modified breaths in the same sequence. All breaths were analyzed with the single breath test for CO₂, as previously detailed.¹⁹

Subjects were studied in the supine position when end-tidal CO₂ concentration had stabilized. The six sequences were conducted with and without an HME between the CO₂ analyser and the subject (HCH 5708, Vital Signs Inc., Totowa, NJ, USA). When the HME was not used, tidal volume was reduced by the manufacturer-specified dead space contribution of the HME, 50 ml. Signals representing airway flow and fraction of CO₂ at the Y-piece of the ventilator tubing were sampled at 100 Hz. Each sequence was analyzed using Excel (Microsoft Corporation). Studied breaths were characterized by their MDT and EIF. The MDT refers to the volume-weighted mean time during which consecutive partitions of fresh inspired gas mixes by diffusion with resident alveolar gas (Fig. 2).¹⁹ The EIF is flow rate at the end of inspiration immediately before the post-inspiratory pause (Fig. 1).

Tidal CO₂ elimination (VTCO₂) and its variation attributable to changes in VDaw and alveolar CO₂ fraction (FACO₂) were determined (Fig. 3). The VDaw was calculated as previously described.²⁸ For VTCO₂, VDaw and FAÇO₂ the change relative to ordinary breaths was expressed as a percentage of the mean of the four ordinary breaths in the same recording sequence and denoted ΔVTCO₂%, ΔVDaw% and ΔFAÇO₂%, respectively. Static compliance of the respiratory system (C) was determined as VT divided by the difference between airway pressure at the end of post-inspiratory pause and PEEP. The effects of inspiratory flow pattern on ΔVTCO₂, ΔVDaw and ΔFAÇO₂ were expressed by applying multiple regressions with EIF, MDT and lnMDT as independent variables.¹⁹ ²¹
**Statistical analysis**

Results are presented as mean values (SD). Single or multiple regression analysis was performed using the Analysis ToolPak of Excel. Student’s paired two-tailed t-test was used to analyse differences between residuals. A $P$ value of <0.05 was considered to indicate statistical significance.
Results

For breaths with and without an HME, $V_{Daw}$ was 174 (19) and 113 (17) ml, respectively. The difference was 61.3 (7.3) ml. Internal volume of the HME was precisely measured *post hoc*. It was 53.2 ml measured at ambient temperature and barometric pressure, gas saturated with water vapour (ATPS) or 57.5 ml BTPS. Average MDT was lower with than without an HME, 0.74 (0.13) compared to 0.81 (0.14) s ($P<10^{-200}$). The HME did not affect how inspiratory patterns influenced $V_{T}CO_{2}$%, $V_{Daw}$% or $F_{A}CO_{2}$%.

In 32 breaths with EIF similar to the ordinary reference breaths, $\Delta V_{T}CO_{2}$ was in each subject correlated with MDT but significantly closer with $\ln$MDT. The following analysis therefore focuses on $\ln$MDT.

*Effects of mean distribution time and end-inspiratory flow on $V_{T}CO_{2}$, $V_{Daw}$ and $F_{A}CO_{2}$*

For all breaths, effects of MDT and EIF were analysed according to equation (1)

$$Y = a \times \ln$MDT + $b \times$ EIF + $c \quad (1)$$

where $Y$ represents $\Delta V_{T}CO_{2}$%, $\Delta V_{Daw}$% or $\Delta F_{A}CO_{2}$% (Table 2). Equation (1) was applied to all breaths of each individual subject.

For $\Delta V_{T}CO_{2}$% coefficient $a$ and $b$ differed significantly from zero, implying that $\Delta V_{T}CO_{2}$% was influenced by $\ln$MDT and EIF, $P<10^{-16}$ and $<10^{-9}$, respectively (Table 2, left columns). The coefficient $b$, representing the influence of EIF, was correlated significantly with individual values of compliance, as follows: $b = 0.26 \times C - 0.99$, ($P=0.03$).
For $\Delta V_{Daw} \%$, coefficients $a$ and $b$ (Table 2, middle columns) differed significantly from zero in each subject, implying that also $\Delta V_{Daw} \%$ was influenced by lnMDT and EIF ($P<0.02$).

For $\Delta F_{A CO_2} \%$, coefficient $a$ differed significantly from zero in all subjects ($P<0.001$), while $b$ did so in six out of eight subjects (Table 2, right columns). A composite analysis based on all breaths in all subjects showed that $\Delta F_{A CO_2} \%$ was influenced by both lnMDT ($P<10^{-57}$) and by EIF ($P<0.001$).

**Effects of alternative inspiratory flow patterns on $\Delta V_T CO_2$**

Table 2 details how inspiratory pattern influences CO$_2$ exchange. However, the coefficients in Table 2 do not clearly illustrate to what extent CO$_2$ elimination is influenced by different inspiratory patterns.

In order to make clinical consequences easier to comprehend, from the data in Table 2 $\Delta V_T CO_2 \%$ was recalculated for some patterns. These calculations are presented in Table 3 where the change of $V_T CO_2$ as a percentage of the value represented by ordinary unmodified breaths is given for these patterns. At ordinary $T_I$ and $T_P$, it was shown that the flow profile does not significantly affect CO$_2$ exchange (Table 3, left columns). At constant flow, with a prolonged $T_P$ and equally shortened $T_I$, $V_T CO_2$ would be augmented by 14% as a result of higher EIF and longer MDT and by 23% at increasing flow (middle columns). If total inspiratory time is prolonged at the expense of expiration, $V_T CO_2$ is further enhanced (right columns).
Discussion

In anaesthetised, mechanically ventilated patients with healthy lungs, we have demonstrated that a simple resetting of the inspiratory flow pattern of a ventilator with respect to $T_I$ and $T_P$, without increasing respiratory rate, can improve $CO_2$ elimination, allowing a lower tidal volume for lung protection.

Our system uniquely allows studies, in a short time, of $CO_2$ exchange with many inspiratory flow patterns. Modified breaths were compared to reference breaths in the same recording sequence to avoid problems related to steady state and to make observations specifically reflecting a varying inspiratory pattern.

The HME increased $V_{Daw}$ by 61 ml BTPS (i.e. 56.5 ml ATPS), 4 ml higher than its internal volume. The difference can be explained by the HME delaying entry of fresh gas to the respiratory zone, thereby shortening MDT. The HME did not have any other effect.

As in previous studies in patients with acute lung injury, longer MDT and higher EIF enhance $CO_2$ exchange. The effect of MDT on $\Delta V_T CO_2\%$ varied little between subjects (Table 2). Coefficient $a$ was 24% higher than in patients with acute lung injury ($P=0.006$) while coefficient $b$ reflecting the effect of EIF was 270% higher ($P<0.003$). Rather than MDT, $lnMDT$ is the relevant parameter because diffusion gradients decrease exponentially. During the post-inspiratory pause, movement of the fresh gas interface towards proximal airways with smaller total cross-sectional area most likely contributes to the non-linear effect of MDT. The positive effect of a high EIF on $CO_2$ exchange reflects conversion of kinetic energy to flow and pressure oscillations travelling down the
airways. The effect on $F_A CO_2$ shows, for the first time, that this phenomenon reaches into the alveolar space. The main effect of MDT is attributable to diffusion over the interface where fresh inhaled gas from conductive airways meets resident alveolar gas. The effect of EIF, in contrast, involves the whole pulmonary gas volume. The two different mechanisms may explain why EIF is efficient even when diffusion has slowed down during a post-inspiratory pause.

Variation in $V_{1CO_2}$, the loop area in Fig. 3, is attributable to $V_{Daw}$, affecting loop width, and $F_A CO_2$, with effect on loop height. An analysis showed that there was no difference in these two effects ($P=0.91$).

Although the effect of MDT was rather similar among our subjects, the effect of EIF varied more, and was less in subjects with low compliance. In patients with ARDS, in whom compliance is low, the effect of EIF was only about one-third of that observed in the present study. That coefficient $b$ for $\Delta F_A CO_2\%$ was not significant in two subjects illustrate the variable effect of EIF. The effect of MDT is more stable within and among populations. This is not surprising, because diffusion between fresh inhaled gas and resident alveolar gas is a relatively simple process compared with transmission of pressure and flow oscillations through the airways and into the alveolar zone. The latter process depends on distribution of elastance, resistance, and capacitance all along the airways and into the alveolar space.

To elucidate a potential clinical use of a modified inspiratory flow pattern, the coefficients in Table 2 were used to illustrate effects on CO$_2$ elimination for a number of alternate patterns (Table 3). At T$_i$ 33% and T$_p$ 10%, the flow profile was unimportant for CO$_2$ exchange. This reflects that with
increasing flow, positive effects of a higher EIF are balanced by negative effects of a shorter Tp. The opposite is true with decreasing flow. Shortening of T1 and prolongation of Tp importantly increased VT CO2, particularly with increasing flow. This reflects that when T1 is shortened, and Tp equally prolonged, MDT increases. This is because Tp is three times more important for MDT than T1, given that all fractions of gas entering the alveolar space benefit to the same extent from a longer Tp. In addition, a short T1 augments EIF. We illustrate that a further increased Tp boosts CO2 exchange, but if this excessively shortens T1, inspiratory peak pressures may be too high. If, in contrast, it is done at the expense of time for expiration, a higher auto-PEEP may develop. By prolonging Tp at a fixed VT and constant flow, CO2 elimination can be increased by ~15%. When a new steady state has been established after ~30 min, arterial and end-tidal PCO2 will have been reduced accordingly. However, it is often more important to reduce VT than arterial PCO2. An enhancement of CO2 elimination by 15% gives room for a VT reduction of ~10% because dead space takes its share of each breath. Furthermore, dead space reduction paves the way for a higher RR and a further reduction of VT, as has recently been emphasized. In early ARDS, reduction of VT by 1 ml (kg body weight)−1 might reduce mortality by 15%. When lung-protective ventilation is needed, ventilator resetting appears to be easier to accomplish than some alternatives (e.g. replacing the HME with an active humidifier or gas flushing of upper airways).

In recent studies, it has been emphasized that also in patients without ARDS high tidal volumes may induce lung injury. Examples are major abdominal surgery and heart surgery, particularly in obese patients. “Generalization of lung protective ventilation prophylactically to almost all mechanically ventilated patients beginning immediately following intubation” has been proposed. In organ donors, lung-protective ventilation improves lungs for transplantation. It has also been emphasised that lung-protective ventilation is by no means equivalent to low tidal volumes but rather a
combination of mechanical breath parameters. The authors of that review conclude: “Preventing rather than treating ARDS may be the way forward in dealing with this recalcitrant condition and would represent a paradigm shift in the way mechanical ventilation is currently practiced.”

The present study is limited to effects on CO₂ exchange. Anything that influences alveolar CO₂ tension will also, according to the alveolar gas equation, affect oxygen tension. Oxygen exchange will benefit from a pattern of inspiration that favours CO₂ exchange. During mechanical ventilation, oxygenation is upheld by oxygen enrichment of inhaled gas and by PEEP rather than by a specific degree of alveolar ventilation. This limits the interest in how oxygenation relates to patterns of inspiration.

Several studies indicate that the influence of the inspiratory flow pattern on CO₂ exchange is governed by some general principles. A field worth exploring is chronic obstructive lung disease in which large inhomogeneity of intrapulmonary gas mixing would in theory increase the influence of inspiratory flow patterns on gas exchange. The significant influence on gas exchange by EIF in the present study shows that distribution of inspired gas within resident alveolar gas depends not only on diffusion, as is often proposed. In addition, transmission of gas flow and pressure pulses through the airways play a role, and this is analogous to the physical phenomena enabling ventilation by high-frequency oscillation. The present study adds to our understanding of gas exchange in healthy lungs. It also produces new questions, for instance, about the potential importance of similar factors during heavy exercise when diffusion is hampered by high respiratory rates causing short periods for diffusive gas mixing.
In conclusion, the present study shows that in mechanically ventilated human subjects without lung disease, CO₂ exchange is enhanced by a long MDT and a high EIF. These factors reduce airway and alveolar dead space by moving the interface between inspired gas and resident alveolar gas orally and by enhancing gas mixing within the alveolar zone. During volume-controlled ventilation, this is accomplished by shortening inspiratory time and prolonging post-inspiratory pause. With a more efficient inspiratory pattern, tidal volume can be reduced, potentially in favour of less ventilation-induced lung injury.
Authors’ contributions

Study design: L.W.S., G.M., M.B., B.J.

Patient recruitment: L.W.S., M.B.

Data collection: L.W.S., S.A., M.C.

Data analysis: S.A., M.C., B.J.

Writing up the first draft of the paper: M.C., M.B.

Writing up the manuscript: L.W.S., G.M., S.A., B.J.
Declaration of interests

L.W.S: None declared.
G.M.: None declared.
S.A.: None declared.
M.C.: None declared.
M.B.: None declared.
B.J.: None declared.
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Tables

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<thead>
<tr>
<th>Subject</th>
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<th>Age (yr)</th>
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<th>Weight (kg)</th>
<th>BMI (kg m(^{-2}))</th>
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<th>Tidal volume with HME (ml)</th>
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**Table 1:** Characteristics of the subjects. HME, heat and moisture exchanger
Table 2. Coefficients for the equation $Y = a \times \ln\text{MDT} + b \times \text{EIF} + c$ where $Y$ is $\Delta V_{\text{T}CO_2\%}$, $\Delta V_{\text{Daw}\%}$, and $\Delta F_{\text{A}CO_2\%}$ respectively. $\Delta V_{\text{T}CO_2\%}$, $\Delta V_{\text{Daw}\%}$, and $\Delta F_{\text{A}CO_2\%}$ are the change of $\Delta V_{\text{T}CO_2}$, $\Delta V_{\text{Daw}}$, and $\Delta F_{\text{A}CO_2}$ respectively relative to ordinary breaths, expressed as a percentage of the mean of four ordinary breaths in the same recording sequence. EIF, end-inspiratory flow; MDT, mean distribution time.
Table 3. Mean values for each inspiratory pattern of EIF, MDT and lnMDT. The change of $V_{T}CO_2$ as a percentage of the value of ordinary unmodified breaths was calculated from these means and individual coefficients in Table 2. The flow profile of inspiration was increasing (Incr.), constant (Const.) or decreasing (Decr.). EIF, end-inspiratory flow; MDT, mean distribution time, $T_I$, duration of inspiration; $T_P$, post-inspiratory pause.

<table>
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<th>Flow profile</th>
<th>$T_I$ 33%, $T_P$ 10%</th>
<th>$T_I$ 15%, $T_P$ 28%</th>
<th>$T_I$ 15%, $T_P$ 35%</th>
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<td>MDT (s)</td>
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<td>-1 (0.5)</td>
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Legends to illustrations

Fig 1. The 21 types of breath delivered, all having different inspiratory flow patterns but identical tidal volumes. In each panel, the dark blue trace shows the pattern of ordinary breaths to which all other patterns were compared. (A) Breaths with ordinary insufflation at constant flow but with varying post-inspiratory pause. (B) Breaths with varying inspiratory time, all with an ordinary pause. (C) Breaths with varying inspiratory time-and pause time. (D) Breaths with varying inspiratory time and pause time all with similar mean distribution time. (E) Breaths with constant, increasing and decreasing flow profile, and also illustrating how end-inspiratory flow (EIF) was measured.

Fig 2. Flow rate (red line), and its integral volume (black line) against time. Initially, during inspiration, gas from airway dead space returns to the alveolar zone. When a volume of gas equal to airway dead space ($V_{Daw}$, grey area) has been inhaled, the first partition of fresh gas reaches the respiratory zone of the lung. Later consecutive partitions of fresh inspired gas (vertical lines) reach this zone. The first portion mixes by diffusion with resident alveolar gas during the distribution time $DT_1$, and the last portion has the distribution time $DT_n$. The volume weighted mean for alveolar gas distribution of portions 1 through $n$ is the mean distribution time, MDT. Calculation of MDT ceases at the start of expiration because no further mixing between inspired and resident alveolar gas takes place thereafter.
Fig 3. The single breath test for CO2. The red curve shows fraction of CO2 at the Y-piece (FCO2) plotted against expired volume (VE). The descending limb of the loop reflects the next inspiration. The orange area represents the volume of CO2 eliminated during the ordinary breath (VT CO2). The blue curve represents the expiratory limb of a breath with a prolonged pause. ΔVDaw shows how airway dead space (VDaw) was reduced by a volume represented by the difference between the vertical dotted red and blue lines. ΔFA CO2 shows how the level of the alveolar plateau increased. The reverse-hatched area indicates how ΔVT CO2 increased as a consequence of ΔVDaw and ΔFA CO2.