An appropriate inspiratory flow pattern can enhance CO₂ exchange, facilitating protective ventilation of healthy lungs

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Abstract

Background: In acute lung injury, CO₂ 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 human subjects 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 postinspiratory 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 CO₂ was used to quantify airway dead space (V_Daw) and CO₂ exchange.

Results: A long MDT and a high EIF augment CO₂ 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 CO₂ by 14%, allowing a 10% lower tidal volume.

Conclusions: In anaesthetized human subjects without lung disease, CO₂ 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

Seminal studies show increased survival among patients with acute respiratory distress syndrome (ARDS) ventilated with low tidal volume (V_T).¹ ² More recent studies show that low-V_T ventilation may be protective against lung complications or organ failure in patients without lung disease, such as patients ventilated during major surgery.³⁻⁴ For large groups of ventilated patients, low V_T has therefore been suggested as standard in several reviews and meta-analyses.⁵⁻¹⁰ Ventilation with reduced V_T carries a risk of CO₂ retention. In this study, we explore how dead space can be reduced and CO₂ exchange enhanced simply by optimizing 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...
**Editor’s key points**

- Effects of inspiratory flow patterns were quantified, on CO₂ exchange in humans without lung disease, to seek lung-protective ventilation of healthy lungs.
- Carbon dioxide exchange was enhanced by a long mean distribution time and a high end-inspiratory flow, and a short inspiration and a long postinspiratory pause allows significant reduction of tidal volume.

Some patterns of inspiratory flow promote mixing of tidal and alveolar gas, thereby reducing dead space. An adjustable inspiratory waveform was therefore introduced with the ServoVentilator 900 (Siemens-Elema AB, Solna, Sweden). Computer control of inspiratory flow and volumetric capnography allow detailed studies on how the inspiratory pattern affects the dead space and CO₂ exchange. In large airways gas transport is convective, whereas diffusion predominates in the respiratory zone. During inspiration, the time allowed for such diffusion is essential for gas exchange. This time is represented by the mean distribution time (MDT), which reflects the inspiratory time (Tᵢ), duration of postinspiratory pause (Tₚ), 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 (Vₑₑₑ) and increased CO₂ elimination. When flow rate immediately before interruption of inspiration (end-inspiratory flow, EIF) was high, this also promoted CO₂ exchange in animal and human ARDS, 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). PEEP was 5 cm H₂O and RR 16 bpm. Ordinary breaths were delivered with constant flow; Tᵢ was 33% and Tₚ 10%. Volumes and flow rates are expressed as measured at body temperature, standard barometric pressure, and gas saturated with water vapour (BTPS).

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**Fig 1.** The 21 types of breath delivered, all having different inspiratory flow patterns but identical tidal volumes. In each panel, the light 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 postinspiratory 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.
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 $T_I$ (20–53%), $T_P$ (3–18%), and the profile of the inspiratory flow wave, which was square (constant flow) or triangular (increasing or decreasing flow rate). The $V_T$, 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 analysed with the single breath test for CO2, as previously detailed.

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 the fraction of CO2 at the Y-piece of the ventilator tubing were sampled at 100 Hz. Each sequence was analysed 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). The EIF is flow rate at the end of inspiration, immediately before the postinspiratory pause (Fig. 1).

Tidal CO2 elimination ($V_{TCO2}$) and its variation attributable to changes in $V_{Daw}$ and alveolar CO2 fraction (FA$CO_2$) were determined (Fig. 3). The $V_{Daw}$ was calculated as previously described. For $V_{TCO2}$, $V_{Daw}$, and FA$CO_2$, 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 $\Delta V_{TCO2}$%, $\Delta V_{Daw}$%, and $\Delta F_{ACO2}$%, respectively. Static compliance of the respiratory system (C) was determined as $V_T$ divided by the difference between airway pressure at the end of the postinspiratory pause and PEEP. The effects of inspiratory flow pattern on $\Delta V_{TCO2}$, $\Delta V_{Daw}$, and $\Delta F_{ACO2}$ were expressed by applying multiple regressions with EIF, MDT, and lnMDT as independent variables.

Statistical analysis
Results are presented as mean values (SD). Single or multiple regression analysis was performed using the Analysis ToolPak of
For breaths with and without an HME, $V_{\text{Daw}}$ was 174 (19) and 113 (17) ml, respectively. The difference was 61.3 (7.3) ml. The internal volume of the HME was precisely measured (17) ml, respectively. The difference was 61.3 (7.3) ml. The 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.

In 32 breaths with EIF similar to the ordinary reference breaths, $\Delta V_{\text{TCO}_2}$ was in each subject correlated with MDT but significantly closer with lnMDT. The following analysis therefore focuses on lnMDT.

**Effects of mean distribution time and end-expiratory flow on $V_{\text{T-CO}_2}$, $V_{\text{Daw}}$, and $F_{\text{A-CO}_2}$**

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

$$Y = a \times \ln \text{MDT} + b \times \text{EIF} + c$$  \hspace{1cm} (1)

where $Y$ represents $\Delta V_{\text{TCO}_2}$, $\Delta V_{\text{Daw}}$, or $\Delta F_{\text{A-CO}_2}$ (Table 2). Equation (1) was applied to all breaths of each individual subject. For $\Delta V_{\text{TCO}_2}$, coefficient $a$ and $b$ differed significantly from zero, implying that $\Delta V_{\text{TCO}_2}$ was influenced by lnMDT and EIF, $P<10^{-15}$ and $P<10^{-4}$, respectively (Table 2, left columns). The coefficient $b$, representing the influence of EIF, was correlated significantly with individual values of compliance, as follows: $b=0.26C-0.99$ ($P=0.03$).

For $\Delta V_{\text{Daw}}$, coefficients $a$ and $b$ (Table 2, middle columns) differed significantly from zero in each subject, implying that $\Delta V_{\text{Daw}}$ also was influenced by lnMDT and EIF ($P<0.02$).

For $\Delta F_{\text{A-CO}_2}$, coefficient $a$ differed significantly from zero in all subjects ($P<0.001$), whereas $b$ did so in six out of eight subjects (Table 2, right columns). A composite analysis based on all breaths in all subjects showed that $\Delta F_{\text{A-CO}_2}$ was influenced by both lnMDT ($P<10^{-57}$) and by EIF ($P<0.001$).

**Effects of alternative inspiratory flow patterns on $\Delta V_{\text{TCO}_2}$**

Table 2 details how the inspiratory pattern influences CO2 exchange. However, the coefficients in Table 2 do not clearly illustrate to what extent CO2 elimination is influenced by different inspiratory patterns. In order to make clinical consequences easier to comprehend, from the data in Table 2 $\Delta V_{\text{TCO}_2}$ was recalculated for some patterns. These calculations are presented in Table 3, where the change of $\text{V}_{\text{TCO}_2}$ as a percentage of the value represented by ordinary unmodified breaths is given for these patterns. At ordinary $T_I$, and $T_E$, it was shown that the flow profile does not significantly affect CO2 exchange (Table 3, left columns). At constant flow, with a prolonged $T_I$ and equally shortened $T_E$, $\text{V}_{\text{TCO}_2}$ would be augmented by 14% as a result of higher EIF and longer MDT and by 23% at increasing flow (middle columns). If

![Fig 3 The single breath test for CO2. The blue curve shows the fraction of CO2 at the Y-piece ($F_{\text{CO}_2}$) plotted against expired volume ($V_{E}$). The descending limb of the loop reflects the next inspiration. The blue area represents the volume of CO2 eliminated during the ordinary breath ($V_{\text{TCO}_2}$). The green curve represents the expiratory limb of a breath with a prolonged pause. The red area shows how airway dead space ($V_{\text{Daw}}$) was reduced by a volume represented by the difference between the vertical dotted blue and green lines. The $\Delta F_{\text{A-CO}_2}$ shows how the level of the alveolar plateau increased. The reverse-hatched area indicates how $\Delta V_{\text{TCO}_2}$ increased as a consequence of $\Delta V_{\text{Daw}}$ and $\Delta F_{\text{A-CO}_2}$.

Table 2 Coefficients for the equation $Y=a\times\ln\text{MDT}+b\times\text{EIF}+c$, where $Y$ is $\Delta V_{\text{TCO}_2}$, $\Delta V_{\text{Daw}}$, and $\Delta F_{\text{A-CO}_2}$, respectively. $\Delta V_{\text{TCO}_2}$, $\Delta V_{\text{Daw}}$, and $\Delta F_{\text{A-CO}_2}$ are the changes of $V_{\text{TCO}_2}$, $V_{\text{Daw}}$, and $F_{\text{A-CO}_2}$ respectively relative to ordinary breaths, expressed as a percentage of the mean of the four ordinary breaths in the same recording sequence. EIF, end-inspiratory flow; MDT, mean distribution time.

<table>
<thead>
<tr>
<th>Subject</th>
<th>Coefficients for $\Delta V_{\text{TCO}_2}$%</th>
<th>Coefficients for $\Delta V_{\text{Daw}}$%</th>
<th>Coefficients for $\Delta F_{\text{A-CO}_2}$%</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>lnMDT (a)</td>
<td>EIF (litre s$^{-1}$) (b)</td>
<td>Constant (c)</td>
</tr>
<tr>
<td>1</td>
<td>18.2</td>
<td>17.3</td>
<td>-0.2</td>
</tr>
<tr>
<td>2</td>
<td>15.9</td>
<td>14.3</td>
<td>-2.9</td>
</tr>
<tr>
<td>3</td>
<td>14.2</td>
<td>8.7</td>
<td>-0.3</td>
</tr>
<tr>
<td>4</td>
<td>17.1</td>
<td>6.4</td>
<td>1.0</td>
</tr>
<tr>
<td>5</td>
<td>19.4</td>
<td>16.2</td>
<td>-0.1</td>
</tr>
<tr>
<td>6</td>
<td>18.4</td>
<td>14.0</td>
<td>-1.3</td>
</tr>
<tr>
<td>7</td>
<td>15.9</td>
<td>14.6</td>
<td>0.5</td>
</tr>
<tr>
<td>8</td>
<td>20.4</td>
<td>12.7</td>
<td>1.9</td>
</tr>
<tr>
<td>Mean</td>
<td>17.4</td>
<td>13.0</td>
<td>-0.2</td>
</tr>
<tr>
<td>sd</td>
<td>2.1</td>
<td>3.7</td>
<td>1.4</td>
</tr>
</tbody>
</table>
total inspiratory time is prolonged at the expense of expiration, $VTCO_2$ is further enhanced (right columns).

**Discussion**

In anaesthetized, 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 $T_e$, without increasing respiratory rate, can improve CO₂ elimination, allowing a lower tidal volume for lung protection.

Our system uniquely allows studies, in a short time, of CO₂ exchange with many inspiratory flow patterns. Modified breaths were compared with 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 enhanced CO₂ exchange.\(^1\) The effect of MDT on $\Delta VCO_2$ % varied little between subjects (Table 2). Coefficient a was 24% higher in patients with acute lung injury (P=0.006), whereas coefficient b, reflecting the effect of EIF, was 270% higher (P<0.003).\(^2\) Rather than MDT, lnMDT is the relevant parameter because diffusion gradients decrease exponentially.\(^9\) During the postinspiratory pause, movement of the fresh gas interface towards proximal airways with smaller total cross-sectional area most probably contributes to the non-linear effect of MDT. The positive effect of a high EIF on CO₂ exchange reflects conversion of kinetic energy to flow and pressure oscillations travelling down the airways.\(^21\) The effect on $FA_{CO_2}$ 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 postinspiratory pause.

Partial oscillations $VCO_2$, the loop area in Fig. 3, is attributable to $V_{Daw}$ affecting loop width, and $FA_{CO_2}$ 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.\(^5\) That coefficient b for $\Delta FA_{CO_2}$ % was not significant in two subjects illustrates 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.\(^29\)\(^30\)

To elucidate a potential clinical use of a modified inspiratory flow pattern, the coefficients in Table 2 were used to illustrate effects on CO₂ elimination for a number of alternative patterns (Table 3). At $T_i$ 33% and $T_e$ 10%, the flow profile was unimportant for CO₂ exchange. This reflects that with increasing flow, positive effects of a longer MDT are balanced by negative effects of a shorter $T_e$. The opposite is true with decreasing flow. Shortening of $T_i$ and prolongation of $T_e$ importantly increased $VTCO_2$, particularly with increasing flow. This reflects that when $T_i$ is shortened and $T_e$ equally prolonged, MDT increases. This is because $T_i$ is three times more important for MDT than $T_e$, given that all fractions of gas entering the alveolar space benefit to the same extent from a longer $T_e$.\(^21\) In addition, a short $T_i$ augments EIF. We illustrate that a further increase in $T_i$ boosts CO₂ exchange, but if this excessively shortens $T_e$, inspiratory peak pressures may be too high. If, in contrast, it is done at the expense of the time for expiration, a higher auto-PEEP may develop. By prolonging $T_e$ at a fixed $V_T$ 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 $PCO_2$ will have been reduced accordingly.\(^32\)\(^32\) However, it is often more important to reduce $V_T$ than arterial $PCO_2$. An enhancement of CO₂ elimination by 15% gives room for a $V_T$ 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 $V_T$, as has recently been emphasized.\(^33\) In early ARDS, reduction of $V_T$ by 1 ml (kg body weight)\(^{-1}\) might reduce mortality by 15%.\(^34\) 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.\(^3\)\(^4\)\(^5\)\(^10\)\(^10\) 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.\(^15\) In organ donors, lung-protective ventilation improves lungs for transplantation.\(^36\) It has also been emphasized that lung-protective ventilation is by no means equivalent to low tidal volumes but rather a combination of mechanical breath parameters.\(^5\) The authors of that review conclude: ‘Preventing rather that treating ARDS may be the way forward in dealing with

**Table 3** Mean values for each inspiratory pattern of EIF, MDT, and lnMDT. The change of $VTCO_2$ 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, constant, or decreasing. EIF, end-inspiratory flow; MDT, mean distribution time; $T_i$, duration of inspiration; $T_e$, postinspiratory pause.

<table>
<thead>
<tr>
<th>Flow profile</th>
<th>$T_i$, 33%, $T_e$, 10%</th>
<th>$T_i$, 15%, $T_e$, 28%</th>
<th>$T_i$, 15%, $T_e$, 35%</th>
</tr>
</thead>
<tbody>
<tr>
<td>EIF (ml s(^{-1}))</td>
<td>717</td>
<td>1576</td>
<td>1576</td>
</tr>
<tr>
<td>MDT (s)</td>
<td>0.59</td>
<td>1.16</td>
<td>1.42</td>
</tr>
<tr>
<td>lnMDT</td>
<td>−0.52</td>
<td>0.15</td>
<td>0.35</td>
</tr>
<tr>
<td>Change in $VTCO_2$ (%)</td>
<td>0 (1)</td>
<td>23 (3)</td>
<td>27 (3)</td>
</tr>
<tr>
<td>mean (sd)</td>
<td>−1 (0.5)</td>
<td>14 (2)</td>
<td>17 (2)</td>
</tr>
</tbody>
</table>

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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 the 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 the inspiratory time and prolonging the postinspiratory 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 of the first draft of the paper: M.C., M.B.
Writing the manuscript: L.W.S., G.M., S.A., B.J.

Declaration of interests
None declared.

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