Effects of inspiratory pause on CO₂ elimination and arterial Pco₂ in acute lung injury

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Devaquet J, Jonson B, Niklason L, Si Larbi A-G, Uttman L, Aboab J, Brochard L. Effects of inspiratory pause on CO₂ elimination and arterial Pco₂ in acute lung injury. J Appl Physiol 105: 1944–1949, 2008. First published 18 September 2008; doi:10.1152/japplphysiol.90682.2008.—A high respiratory rate associated with the use of small tidal volumes, recommended for acute lung injury (ALI), shortens time for gas diffusion in the alveoli. This may decrease CO₂ elimination. We hypothesized that a postinspiratory pause could enhance CO₂ elimination and reduce PaCO₂ by reducing dead space in ALI. In 15 mechanically ventilated patients with ALI and hypercapnia, a 20% postinspiratory pause (Tp20) was applied during a period of 30 min between two ventilation periods with ALI and hypercapnia, a 20% postinspiratory pause (Tp0). Other parameters were kept unchanged. The single breath test for CO₂ was recorded every 5 min without postinspiratory pause (Tp0). Other parameters were kept unchanged. The single breath test for CO₂ was recorded every 5 min to measure tidal CO₂ elimination (VtCO₂), airway dead space (Vdaw), and slope of the alveolar plateau. PaCO₂, PEEP, and physiological and alveolar dead space (V̇Dphys, V̇Dalm) were determined at the end of each 30-min period. The postinspiratory pause, 0.7 ± 0.2 s, induced on average <0.5 cmH₂O of intrinsic positive end-expiratory pressure (PEEP). During Tp20, VtCO₂ increased immediately by 28 ± 10% (14 ± 5 ml per breath compared with 11 ± 4 ml on Tp0) and then decreased without reaching the initial value within 30 min. The addition of a postinspiratory pause significantly decreased VDaw by 14% and V̇Dphysys by 11% with no change in V̇Dalm. During Tp20, the slope of the alveolar plateau initially fell to 65 ± 10% of baseline value and continued to decrease. Tp20 induced a 10 ± 3% decrease in PaCO₂ at 30 min (from 55 ± 10 to 49 ± 9 mmHg, P < 0.001) with no significant variation in PaO₂. Postinspiratory pause has a significant influence on CO₂ elimination when small tidal volumes are used during mechanical ventilation for ALI.

AFTER TRANSPORT of inspired gas through conducting airways, gas mixing in the respiratory zone by diffusion is time dependent. Therefore, a pause following gas insufflation may enhance gas exchange. Mechanical ventilators allow setting of a postinspiratory pause time (Tp), often in percent of the breathing cycle. During mechanical ventilation, prolonged Tp has been shown to enhance CO₂ elimination (8, 10–12, 14, 21). In healthy pigs, a prolonged Tp increases CO₂ elimination per tidal breath (VtCO₂) by decreasing airway dead space (Vdaw) (20). It was suggested that a prolonged Tp increased the mean distribution time (MDT) of inspired gas, so as to allow more time for diffusion of CO₂ towards more central airways (7). MDT, further explained below, expresses the time available for enhanced diffusion between inhaled tidal volume and resident alveolar gas (2).

In pigs at health and with acute lung injury (ALI), Aström et al. recently found that a certain prolongation of MDT achieved with a longer Tp or with a longer inspiratory insufflation time had similar positive effects on CO₂ exchange (4). They noted that a prolonged Tp had a larger effect on MDT than a similar prolongation of inspiratory insufflation time.

Recently Aboab et al. showed that a longer Tp enhances CO₂ exchange evaluated from volumetric capnography in ALI and acute respiratory distress syndrome (ARDS) (2). Positive effects were observed both with regards to a reduced VDaw and an elevated alveolar plateau. In their study Tp was only changed for one breath at a time, and PaCO₂ was not measured. The question was left open if the beneficial effect of Tp was of temporary nature. In pigs, Aström et al. showed that a shortened MDT led to an increase in PaCO₂, that was nearly stable after 30 min. The study by Lessard et al. assessing CO₂ elimination in patients with ARDS was not controlled for the eventual increase in auto-positive end-expiratory pressure (PEEP) and hemodynamic effects induced by the extension of inspiratory time (12). Mercat et al. did so and found that in ARDS, an extended end-inspiratory pause led to lower PaCO₂, by reducing physiological dead space but did not lead to improved PaO₂ (14).

In this study, we hypothesized that in patients with ALI or ARDS ventilated with small tidal volume, a postinspiratory pause applied over a sufficient period of time would enhance CO₂ elimination and reduce PaCO₂ by reducing airway dead space and ventilation/perfusion nonhomogeneity at the alveolar level. By applying volumetric capnography during the whole study, we aimed at increased understanding about mechanisms behind effects of a prolonged Tp and dynamics of CO₂ exchange in ARDS.

PATIENTS AND METHODS

Material. Fifteen consecutive hypercapnic mechanically ventilated patients (Paco₂ ≥ 45 mmHg, Table 1), were studied within 48 h after they fulfilled criteria for ALI or ARDS (5).

Sedation was achieved by continuous infusion. Neuromuscular blockade was used in three patients. The level of sedation (modified Ramsay score ≥ 5) and the absence of respiratory effort on the flow-time curve during an end-expiratory pause of 6 s were checked before the beginning of the study. The patients were studied in semirecumbent position when stable with respect to ventilation, he-

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During the last period $T_p$ was reset to 0%. The periods were denoted $T_p0$ for the initial period and $T_p20$ for the second period with $T_p$ set to 20% for the second period. $T_p$ was changed to 20% for the second period. These changes were made to assess the effects of varying inspiratory pause on CO$_2$ elimination in patients with acute lung injury/acute respiratory distress syndrome (ALI/ARDS).

Before the study, it was ensured that the extended $T_p$ was reset from 0 to 20% of total breathing cycle duration did not increase intrinsic positive end expiratory pressure (IPPEEP) or chronic respiratory insufficiency with long-term oxygen therapy. High age of the patients and, as will be shown, high physiological dead space ($V_{Dphys,\%}$) indicate a group of patients with a poor prognosis, in accordance with a 53% mortality rate (15).

Patients were ventilated in volume-controlled mode with a constant airflow, pressure, and CO$_2$ were fed to the A/D converter of a personal computer and sampled at 100 Hz. Compliance of the ventilator tubing was 1.7 ml/cmH$_2$O. Tracheal tube, CO$_2$ analyzer, and heat and moisture exchanger dead space were measured in vitro (apparatus dead space volume was 86 ml if a heat and moisture exchanger was used, 41 ml for a heated humidifier). The Ethics Committee of French Intensive Care Society approved the protocol. Patients’ next of kin were informed of the study protocol and gave their consent.

During the initial period of 30 min, $T_p$ was set to 0%. $T_p$ was changed to 20% for the second period. During the last period $T_p$ was reset to 0%. The periods were denoted $T_p0_{init}$, $T_p20$, and $T_p0_{late}$, respectively. If needed, endotracheal suction was performed well before the beginning of the study. During the study, 10 patients were transferred to a spreadsheet for Excel 2002 (Microsoft, Redmond, WA, USA) and analyzed according to Utman and Jonson (19). The expiratory flow signal was normalized by a correction factor so that expired tidal volume equaled the inspired measured at normal breaths.

### Table 1. Characteristics of patients with acute lung injury/acute respiratory distress syndrome

<table>
<thead>
<tr>
<th>No</th>
<th>Age, y</th>
<th>SAPS II</th>
<th>Cause of ALI/ARDS</th>
<th>Underlying Disease</th>
<th>PaO$_2$/FiO$_2$, mmHg</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>78</td>
<td>37</td>
<td>Pneumonia</td>
<td>Ischemic cardiopathy</td>
<td>160</td>
<td>alive</td>
</tr>
<tr>
<td>2</td>
<td>78</td>
<td>74</td>
<td>Pneumonia</td>
<td>Ischemic cardiopathy</td>
<td>147</td>
<td>alive</td>
</tr>
<tr>
<td>3</td>
<td>38</td>
<td>22</td>
<td>Septic shock</td>
<td>Cirrhosis</td>
<td>121</td>
<td>alive</td>
</tr>
<tr>
<td>4</td>
<td>57</td>
<td>40</td>
<td>Septic shock</td>
<td>Alcoholism</td>
<td>146</td>
<td>dead</td>
</tr>
<tr>
<td>5</td>
<td>76</td>
<td>47</td>
<td>Pneumonia</td>
<td>Cachexy</td>
<td>174</td>
<td>dead</td>
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<tr>
<td>6</td>
<td>58</td>
<td>52</td>
<td>Pneumonia</td>
<td>Ischemic cardiopathy</td>
<td>97</td>
<td>alive</td>
</tr>
<tr>
<td>7</td>
<td>91</td>
<td>96</td>
<td>Pneumonia</td>
<td>Epilepsy</td>
<td>154</td>
<td>dead</td>
</tr>
<tr>
<td>8</td>
<td>81</td>
<td>57</td>
<td>Pneumonia</td>
<td>Hypertension</td>
<td>83</td>
<td>dead</td>
</tr>
<tr>
<td>9</td>
<td>82</td>
<td>99</td>
<td>Septic shock</td>
<td>Hypertension</td>
<td>248</td>
<td>alive</td>
</tr>
<tr>
<td>10</td>
<td>39</td>
<td>55</td>
<td>Inhalation</td>
<td>Cachexy</td>
<td>193</td>
<td>dead</td>
</tr>
<tr>
<td>11</td>
<td>50</td>
<td>57</td>
<td>Inhalation</td>
<td>Cirrhosis</td>
<td>92</td>
<td>dead</td>
</tr>
<tr>
<td>12</td>
<td>71</td>
<td>41</td>
<td>Pneumonia</td>
<td>Leukemia</td>
<td>146</td>
<td>dead</td>
</tr>
<tr>
<td>13</td>
<td>44</td>
<td>40</td>
<td>Pneumonia</td>
<td>Aortic dissection</td>
<td>101</td>
<td>alive</td>
</tr>
<tr>
<td>14</td>
<td>75</td>
<td>60</td>
<td>Tumor infiltration</td>
<td>Lymphoma</td>
<td>170</td>
<td>alive</td>
</tr>
<tr>
<td>15</td>
<td>86</td>
<td>33</td>
<td>Pneumonia</td>
<td>Atrial fibrillation</td>
<td>196</td>
<td>dead</td>
</tr>
</tbody>
</table>

Mean ± SD: 67±18; 51±18

### Table 2. Experimental parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>$T_p0_{init}$</th>
<th>$T_p20$</th>
<th>$T_p0_{late}$</th>
<th>Friedman Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>$V_T$, ml</td>
<td>489±63</td>
<td>502±63*</td>
<td>489±63</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>RR, min$^{-1}$</td>
<td>18±4</td>
<td>18±4</td>
<td>18±4</td>
<td></td>
</tr>
<tr>
<td>$Ti$, s</td>
<td>0.7±0.2</td>
<td>1.4±0.3</td>
<td>0.7±0.2</td>
<td></td>
</tr>
<tr>
<td>$Te$, s</td>
<td>3.0±0.6</td>
<td>2.3±0.5</td>
<td>3.0±0.6</td>
<td></td>
</tr>
<tr>
<td>Ppeak, cmH$_2$O</td>
<td>31.5±5.7</td>
<td>31.3±5.4</td>
<td>31.3±5.6</td>
<td>0.4</td>
</tr>
<tr>
<td>Pplat, cmH$_2$O</td>
<td>21.7±4.5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IPPEEP, cmH$_2$O</td>
<td>8.8±2.5</td>
<td>8.8±2.5</td>
<td>8.8±2.5</td>
<td></td>
</tr>
<tr>
<td>PEEPEtot, cmH$_2$O</td>
<td>9.1±2.5</td>
<td>9.5±2.6*</td>
<td>9.1±2.5</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>$V_{Dphy,%}$, % $V_T$</td>
<td>68.2±7.4</td>
<td>60.8±8.8*</td>
<td>67.6±7.6</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>$V_{Daw,%}$, % $V_T$</td>
<td>40.3±8.8</td>
<td>33.4±8.8*</td>
<td>40.4±8.7</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>$V_{Daw,%}$, ml</td>
<td>194±40</td>
<td>166±41*</td>
<td>195±39</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>$V_{Daw,%}$, % $V_T$</td>
<td>23.8±9.1</td>
<td>22.8±10.1</td>
<td>22.9±8.6</td>
<td>0.4</td>
</tr>
<tr>
<td>$FiO_2$</td>
<td>0.8±0.2</td>
<td>0.8±0.2</td>
<td>0.8±0.2</td>
<td></td>
</tr>
<tr>
<td>pH</td>
<td>7.27±0.07</td>
<td>7.31±0.08*</td>
<td>7.27±0.08</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>PaCO$_2$, mmHg</td>
<td>55±10</td>
<td>94±9*</td>
<td>55±10</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>PaO$_2$, mmHg</td>
<td>113±32</td>
<td>110±32</td>
<td>116±34</td>
<td>0.2</td>
</tr>
<tr>
<td>PaO$_2$/FiO$_2$, ratio</td>
<td>148±45</td>
<td>145±48</td>
<td>151±45</td>
<td>0.2</td>
</tr>
<tr>
<td>MAP, mmHg</td>
<td>69±7</td>
<td>73±11</td>
<td>70±6</td>
<td>0.6</td>
</tr>
</tbody>
</table>

Ventilatory and respiratory mechanical parameters, dead spaces, blood gas and hemodynamic parameters were taken at the end of each study period. Values are mean ± SD: $V_T$, tidal volume; RR, respiratory rate; $Ti$, inspiratory time including postinspiratory pause; $Te$, expiratory time; (Ti+$T_p$)/Tot, insufflation and postinspiration pause as percent of the breathing cycle; PEEPEtot, external positive end expiratory pressure; PEEPEpot, external positive end expiratory pressure + intrinsic positive end expiratory pressure; $V_{Dphy,\%}$, physiological dead space in percent of $V_T$; $V_{Daw,\%}$, alveolar dead space in percent of $V_T$; $FiO_2$, fraction of inspired oxygen; MAP, mean arterial pressure; HR, heart rate. *$P = 0.001$ $T_p20$ vs. $T_p0_{late}$ or $T_p0_{init}$. 

**EFFECTS OF INSPIRATORY PAUSE ON CO$_2$ ELIMINATION IN ALI**

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Upon adding the postinspiratory pause, the change during the very first eight breaths in \( V_{\text{tCO2}} \), Slope, MDT, and \( V_{\text{Daw}} \) are denoted in \( \Delta V_{\text{tCO2}}, \Delta \text{Slope}, \Delta \text{MDT}, \) and \( \Delta V_{\text{Daw}} \), respectively. The change of \( \text{PaCO}_2 \) between the ends of \( T_{\text{p0init}} \) and \( T_{\text{p20}} \) periods is denoted \( \Delta \text{PaCO}_2 \).

**Statistical methods.** Data are presented as mean and SD or SE as specified. Friedman’s nonparametric test was used to study the relationship between the quantitative variables at different periods. Differences at the level of \( P < 0.05 \) were considered statistically significant. For statistically significant differences, a Wilcoxon matched pairs signed-rank test was done to compare variables at \( T_{\text{p0init}} \) or \( T_{\text{p0late}} \) and \( T_{\text{p20}} \). Spearman correlation coefficient was used to compare \( \Delta \text{VtCO2}, \Delta \text{Slope}, \Delta \text{MDT}, \Delta V_{\text{Daw}}, \) and \( \Delta \text{PaCO}_2 \). Correlation coefficients were considered statistically significant at the 0.05 level, and linear regression was used to establish the relationship between \( \Delta V_{\text{Daw}} \) and \( \Delta \text{PaCO}_2 \).

**RESULTS**

**Ventilation and hemodynamics.** \( V_t \) was 489 ± 63 ml, corresponding to 7 ± 1 ml/kg of predicted body weight. Peak inspiratory flow rate was 0.7 ± 0.2 l/s. During \( T_{\text{p20}} \), airway pressure fell by 9.6 cmH\(_2\)O during the pause (from peak pressure to plateau pressure, Table 2). Then tube decompression led to an increase of \( V_t \), on average by 13 ± 6 ml (2.6%) (Table 2). \( V_{\text{Daw}} \) changed from 0.21 ± 0.07 s during \( T_{\text{p0init}} \) and \( T_{\text{p0late}} \) to 0.88 ± 0.24 s during \( T_{\text{p20}} \).

Mean airway pressure was 12.4 ± 2.7 cmH\(_2\)O at \( T_{\text{p0}} \) and 15.1 ± 2.9 cmH\(_2\)O at \( T_{\text{p20}} \) (\( P < 0.01 \)). Total PEEP increased by 0.4 cmH\(_2\)O on average during \( T_{\text{p20}} \) because of a slight but significant increase in intrinsic PEEP (Table 2). Resistance and compliance of the respiratory system at \( T_{\text{p20}} \) was 13.5 ± 2.8 cmH\(_2\)O \( \times \) 1\(^{-1}\) s\(^{-1}\) and 44.0 ± 11.4 ml/cmH\(_2\)O, respectively, yielding an average time constant of 0.59 s. The expiratory time for those 7 subjects who had a respiratory rate above 18 was 1.8 ± 0.2 s at \( T_{\text{p20}} \), i.e., about three time constants. Accordingly, expiration was long enough to allow near-cessation of expiratory flow and low values of auto-PEEP also during \( T_{\text{p20}} \) (Fig. 2). Hemodynamics remained constant during all periods (Table 2).

**\( \text{CO}_2 \) elimination and dead space.** During \( T_{\text{p20}} \), \( V_{\text{tCO2}} \) increased immediately by 28% (14 ± 5 ml) compared with baseline during \( T_{\text{p0init}} \), and then decreased without reaching baseline within the \( T_{\text{p20}} \) period (Fig. 3). During \( T_{\text{p0late}} \), \( V_{\text{tCO2}} \) first fell suddenly to below baseline and then returned to baseline. During the whole \( T_{\text{p20}} \), \( V_{\text{Daw}} \) was reduced by 28 ml (\( P < 0.0001 \), Table 2, Fig. 3). The decrease was 2.2 times higher than the increase in \( V_t \). During \( T_{\text{p0late}} \), \( V_{\text{Daw}} \) equaled that during \( T_{\text{p0init}} \) (Fig. 3). At the end of \( T_{\text{p20}} \), \( V_{\text{Dphys}} \) was 11 ± 4% lower than at \( T_{\text{p0init}} \), while \( V_{\text{Dalv}} \) was unchanged (Table 2).

During \( T_{\text{p20}} \), the slope of the alveolar plateau fell immediately to 65 ± 10% of baseline value (35 ± 19 vs. 53 ± 23 mmHg/l) and then slowly decreased further to 32 ± 17 mmHg/l (Figs. 3 and 4). During \( T_{\text{p20late}} \) the slope returned to baseline.

**Arterial blood gases.** During \( T_{\text{p20}} \), \( \text{PaCO}_2 \), fell by 10 ± 3% (from 55 ± 10 to 49 ± 9 mmHg; \( P < 0.0001 \)) (Fig. 5, Table 2). During \( T_{\text{p20late}} \), it returned to baseline. No significant change in \( \text{PaO}_2 \) was observed.

The change in \( \text{PaCO}_2 \) from baseline until end of \( T_{\text{p20}} \) (\( \Delta \text{PaCO}_2 \), mmHg) correlated with the immediate change in \( V_{\text{Daw}} \) when the pause was instituted (\( \Delta V_{\text{Daw}}, \text{ml} \) \( \rho = 0.60, P < 0.02 \)).

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[Diagram: Fig. 1. The single breath test for carbon dioxide (SBT-CO2) depicts partial pressure of CO\(_2\) at airway opening and \( \text{PaCO}_2 \) (horizontal dotted line) vs. volume. Area \( A \) within the loop represents amount of CO\(_2\) eliminated during breath (\( V_{\text{tCO2}} \)). Vertical interrupted line indicates airway dead space distal to CO\(_2\) sensor (\( V_{\text{Dalv}} \)). Area \( B \) reflects CO\(_2\) reinspired from y-piece and tubing and represents proximal airway dead space (\( V_{\text{Daw}} \)). Area \( C \) illustrates alveolar dead space. Alveolar plateau was characterized by equation \( \text{PCO}_2 = b + m(\ln V) \). Its slope was determined at its midpoint. Flow rate and its integral volume were then corrected for gas compression in tubing and adjusted to body temperature and pressure, saturated with water vapor (BTPS). Accordingly, tidal volume was measured as the volume really delivered to the patient, corrected for gas compression in tubing. An unforeseen problem, further discussed below, was that during \( T_{\text{p20}} \), the pressure drop at the end of inspiration caused redistribution from tubing to the lung. Therefore, \( V_t \) increased by about 13 ml or 2.6%. Partial pressure of CO\(_2\) at airway opening was calculated at actual barometric pressure.

Distribution and diffusion of tidal gas in the lung periphery starts at the moment when the interface between “fresh” inspired gas and “used” alveolar gas reaches the respiratory zone of the lung. It ends abruptly when the interface is pushed back into the airways at the start of expiration. Therefore, MDT is the interval from mean time of arrival of partitions of tidal volume in the respiratory zone until start of expiration. It expresses the time available for enhanced diffusion between inhaled tidal volume and resident alveolar gas, as mathematically described by Aboob et al. (2).

Further analysis was based upon the complete single breath test for CO\(_2\) (SBT-CO2), which is a loop comprising an expiratory and an inspiratory limb (6). \( V_{\text{tCO2}} \) corresponds to the area within the loop (Fig. 1).

Different parameters related to dead space (\( V_D \)) were calculated from the SBT-CO2. Mean values of 10 breaths were used. Physiologic dead space (\( V_{\text{Dphys}} \)) was calculated as follows:

\[
V_{\text{Dphys}} = \frac{(\text{PaCO}_2 \times V_t - \text{area } A)}{\text{PaCO}_2 - \text{Vt}} \times 100
\]

\( V_{\text{Dphys}} \) was calculated from signal recordings at the end of each period and simultaneous blood gas tests. Airway dead space distal to the CO\(_2\) sensor (\( V_{\text{Dalv}} \)) was calculated as the volume at which maximum slope of the SBT-CO2 was measured. Carbon dioxide reinspired from airway dead space proximal to the CO\(_2\) sensor (\( V_{\text{Daw,prox}} \)) corresponds to area \( C \) (Fig. 1).

\[
V_{\text{Daw,prox}} = \frac{\text{area } C}{\text{PaCO}_2 \times V_t} \times 100
\]

Alveolar dead space, \( V_{\text{Dalv}} \), was calculated as follows:

\[
V_{\text{Dalv}} = V_{\text{Dphys}} - (V_{\text{Daw,prox}} + V_{\text{Daw}})
\]

The slope of the alveolar plateau (\( \text{Slope} \)) was determined at the midpoint of the alveolar plateau from a logarithmic equation describing \( \text{PCO}_2 \) over volume (Fig. 1) (3).
No correlations were found between \( \text{PaCO}_2 \) and \( \text{V}_{\text{CO}_2} \), \( \text{Slope} \), or \( \text{MDT} \).

A comparison was made between 8 patients with respiratory rate \( \leq 18 \) and 7 patients with rates \( > 18 \). During \( \text{T}_20 \), in both groups, total PEEP increased by 0.4 cmH\(_2\)O, \( \text{PaCO}_2 \) decreased by 6 mmHg and \( \text{V}_{\text{Daw}} \) by 28 ml.

**DISCUSSION**

During volume-controlled ventilation with small tidal volume and constant inspiratory flow in hypercapnic patients with ALI or ARDS, this study shows that a 20% postinspiratory pause time leads to a 10% decrease in \( \text{PaCO}_2 \) after 30 min, secondary to enhanced \( \text{CO}_2 \) elimination. The main explanation of increased \( \text{CO}_2 \) elimination is lower \( \text{V}_{\text{Daw}} \).

Our results agree with previous findings that a postinspiratory pause enhances \( \text{CO}_2 \) elimination in healthy or surfactant-depleted animals \((4, 10, 11, 20)\) and with those obtained in surfactant-depleted pigs in which inspiration at pressure-controlled ventilation was prolonged \((13)\). They also agree with results in patients with ALI/ARDS \((2, 8, 12, 14)\).

The main effect of the postinspiratory pause on \( \text{CO}_2 \) elimination reflects an instantaneous and continuous reduction of \( \text{V}_{\text{Daw}} \) that was immediately abolished during \( \text{T}_0 \). According to the MDT concept, this reflects enhanced diffusion of \( \text{CO}_2 \) from alveoli towards airways during the pause. As the decrease of \( \text{V}_{\text{Daw}} \) was more than two times larger than the small increase in \( \text{V}_t \), the effect on \( \text{PaCO}_2 \) was about two-thirds caused by the change in \( \text{V}_{\text{Daw}} \). As further discussed below, the ultimate changes in \( \text{PaCO}_2 \) could not be estimated during the test periods of 30 min. During \( \text{T}_20 \), decompression of gas in the tubing during the pause reflects the product between \( (\text{P}_{\text{peak}} - \text{P}_{\text{plat}}) \) and tube compliance and was calculated to 16 ml. The increase in \( \text{V}_t \) during \( \text{T}_20 \) can accordingly be fully explained by gas decompression. The lower slope of the alveolar plateau during \( \text{T}_20 \) indicates that a more even alveolar ventilation-perfusion relationship may have contributed to enhanced \( \text{CO}_2 \) elimination. The slope of the alveolar plateau mainly reflects nonsynchronous emptying of lung compartments with different ventilation/perfusion ratios \((7)\). The immediate and nearly stable drop in slope during \( \text{T}_20 \) (Fig. 3) suggests more even alveolar ventilation due to diffusion within

\[
\text{DPaCO}_2 = 0.15\Delta\text{V}_{\text{Daw}} - 1.49
\]

![Fig. 2. Representative tracings from single breaths of airway flow, pressure (Paw), and partial pressure of CO2 at y-piece in mainstream CO2 analyzer, PCO2. Thin black lines represent postinspiratory pause time of 0% (Tp0), and thicker grey lines postinspiratory pause time of 20% (Tp20).](image)

![Fig. 3. Diamonds represent mean values for 15 patients at 5-min intervals throughout study. At 35 min the knob on the ventilator panel for setting Tp was reset from 0 to 20% to start Tp20. At 70 min Tp0late was started by turning knob back to 0%. Times for resetting are indicated with vertical interrupted lines. Data at 35 and 70 min represent first breaths during Tp20 and Tp0late. A: Tidal elimination of CO2 (VtCO2) against time. For 15 patients, diamonds and thin lines represent percent of mean value during Tp0init ± 2 SE. B: Airway dead space (V_{Daw}) against time in each subject, patients ventilated with heated humidifiers (continuous lines) or heat and moisture exchangers (broken lines). Diamonds show mean V_{Daw}. C: Slope of alveolar plateau against time. For 15 patients diamonds and thin lines represent percent of mean value during Tp0late ± 2 SE.](image)
At completely steady state, the change in PaCO₂ should equal body have been equilibrated, as discussed by Taskar et al. (17). However, the full effect on PaCO₂ of a change in efficient ventilation cannot be observed until CO₂ stores in the body (14). In their study we estimate that MDT doubled from about 0.6 s to 1.3 s at prolonged Tp, while MDT in ours increased more than four-fold, from 0.21 to 0.88. The lower change in PaCO₂ in Mercat’s study can be explained by the lower relative change in MDT, considering that the effect of variable MDT according to Aström et al. is nonlinear, i.e., more important towards lower MDT values.

At Tp20, shortening of expiration time from 80% to 60% led to a small but significant increase in intrinsic PEEP (<0.5 cmH₂O). PEEP tends to increase Vₐ and may hamper CO₂ elimination through hemodynamic effects. Increased PEEP increases in itself Vₐ due to airway distension (6, 18). Accordingly, the small increase in total PEEP might have attenuated the observed decrease in Vₐ and enhanced CO₂ elimination at Tp20. In spite of higher total PEEP at Tp20, peak pressure remained unchanged. This might indicate that some recruitment took place during Tp20. However, PaO₂ did not increase as was also observed in the study of Mercat et al. (14). One may speculate that positive effects of recruitment were balanced by negative effects caused by diversion of blood flow to collapsed lung, thereby increasing shunt. The two groups with respiratory rate (RR) ≤ 18 and RR > 18 showed equal response to a prolonged pause, which finding may reflect a low variation in RR in the present material.

In this experimental study, we aimed at unchanged tidal volume and used CO₂ turnover PaCO₂ as indicators of more efficient ventilation caused by a postinspiratory pause. In clinical practice, the utility of more efficient gas exchange would rather be to decrease tidal volume for enhanced lung protection. This could, depending on circumstances, be applied so as to either reduce peak pressure to limit barotrauma or to increase PEEP to stabilize lung recruitment. Notably, a postinspiratory pause is one of several options to lower VT. Another is an increase in respiratory rate. At high rates, MDT becomes shorter. Aström showed a steep decline in CO₂ exchange at}

the alveolar zone, which may have further contributed to enhanced CO₂ elimination during Tp20. In humans, equilibration through collateral channels may play a role in this. However, Uttman and Jonson made similar observations in healthy pigs, which do not have collaterals (20).

VtCO₂ at constant respiratory rate returned during Tp₀ₑᵣₑ to baseline as a sign of constant metabolic rate. Then, during Tp₂₀, VtCO₂ should, after the initial increase, return towards the baseline that represents metabolic rate. In patients without significant cardiopulmonary disease, when ventilation was decreased by 10%, a new steady state was established along a mono-exponential path with a time constant of ∼35 min (17). In the present study, the return towards baseline during Tp₂₀ was far from complete (Fig. 3). Initially during that period VtCO₂ fell rapidly and then very slowly. The reasonable explanation is that CO₂ stores in the body of this group of patients are large and distributed among compartments with very different time constants for equilibration of CO₂. Severe cardiopulmonary disease, increased extravascular liquid space, and poor circulation in peripheral edematous regions are likely causes of slow equilibration of CO₂. Similar conclusions have previously been drawn by Henneberg et al. (9).

During Tp₂₀, the fall in PaCO₂ of 10% is the result of enhanced CO₂ elimination as expressed by enhanced VtCO₂. However, the full effect on PaCO₂ of a change in efficient alveolar ventilation cannot be observed until CO₂ stores in the body have been equilibrated, as discussed by Taskar et al. (17). At completely steady state, the change in PaCO₂ should equal the change in initial effect on rate of CO₂ elimination, in this study represented by change in VtCO₂ by 28%. That VtCO₂ did not return to baseline indicates that a steady state was not achieved during Tp₂₀, as discussed. Accordingly, the observed change in PaCO₂ probably underestimates the full effect of a postinspiratory pause of 20%. To limit confounding factors due to spontaneous changes of metabolism and hemodynamic and other physiological parameters, the study periods were limited to 30 min as a compromise against a desirable steady state during each period. Aström et al. observed in pigs at health and with a model of ALI that after 30 min of ventilation with a different MDT, PaCO₂ changed by 0.75 of what was expected on the basis of immediate change in VtCO₂ (4). In the present study this fraction was only 10/28, i.e., 0.36. The difference may represent a much slower equilibration time in the gravely sick patient population. In the study of Mercat et al. PaCO₂ changed by only 5% when the pause was prolonged, although an equilibration time of 1 h left more time available for equilibration of CO₂ stores in the body (14). In their study we estimate that MDT doubled from about 0.6 s to 1.3 s at prolonged Tp, while MDT in ours increased more than four-fold, from 0.21 to 0.88. The lower change in PaCO₂ in Mercat’s study can be explained by the lower relative change in MDT, considering that the effect of variable MDT according to Aström et al. is nonlinear, i.e., more important towards lower MDT values.

Fig. 4. Single breath test for CO₂ from representative patient (no. 2), with and without pause, recorded at end of initial period of zero pause (Tp₀ᵣᵣₑ, continuous line), and after 10 and 30 min at Tp₂₀ (dotted and interrupted lines, respectively). At Tp₀ᵣᵣₑ airway dead space (Vₐₑₑₑₑ, vertical lines) was larger and slope of alveolar plateau steeper, while area within the loop representing VtCO₂ was smaller.

Fig. 5. Individual values and mean ± SE of PaCO₂ after mechanical ventilation with or without postinspiratory pause of 20% (Tp₀ᵣᵣₑₑ, Tp₂₀, and Tp₀ₑᵣₑ).
low MDT values (4). At high respiratory rates, it may therefore be important to use a pause to adequately prolong MDT.

**Conclusion.** Postinspiratory pause has a great influence on CO₂ exchange not only for breaths immediately following the effects of Tp are mostly due to diffusion of CO₂ into airways but also to a more homogenous ventilation/hypothesized. The effects of Tp are mostly due to diffusion of CO₂ into airways but also to a more homogenous ventilation/hypothesized. The effects of Tp are mostly due to diffusion of

**REFERENCES**

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**REFERENCES**


