Can diaphragm pacing improve gas exchange?
Insights from quadriplegic patients

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Running head: diaphragm pacing and gas exchange

One sentence summary: Diaphragm pacing reduces alveolo-arterial gradient and deadspace as compared to positive pressure ventilation in humans.

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Sir,

Diaphragm pacing as obtained by phrenic nerve stimulation through implanted electrodes is a valid alternative to positive pressure mechanical ventilation (PPV) in patients with high spinal cord injuries [1]. Diaphragm pacing allows such patients to be weaned from PPV, but to date the respective effects of diaphragm pacing and PPV on gas exchange have not been compared. PPV is known to reduce ventilation in the lung bases [2]. On the contrary, diaphragm pacing, like spontaneous breathing, should direct a larger proportion of the inspired volume to the lung bases. This should improve ventilation/perfusion matching. Would this be true, diaphragm pacing could become interesting to consider as an adjunct to PPV in patients with lung injury. Indeed, in this setting, preserving diaphragmatic activity during mechanical ventilation can improve arterial oxygenation [e.g.3]. This can however be difficult to achieve from a comfort point-of-view. In a proof-of-concept perspective, we compared blood gases and energy expenditure during PPV and diaphragm pacing in 10 quadriplegics.

Ten consecutive stable and well-nourished tracheotomized quadriplegic patients were studied (6 men, age 15-46, 21.9 ± 4.0 kg.m\(^{-2}\)). All had implanted phrenic nerve stimulators (Atrostim\(^{®}\), Atrotech, Tampere, Finland) since at least 6 months and were considered fully reconditioned. They were studied during planned routine visits, after approval of the ethics committee of the French learned society for intensive care medicine. They gave their informed consent. Measurements were performed at least 3 hours after a meal, with the tracheal cuff inflated. Oxygen consumption (V'O\(_2\)), carbon dioxide production (V'CO\(_2\)), and respiratory quotient were determined from O\(_2\) and CO\(_2\) measurements in inspired and expired gases (Deltatrac Metabolic Monitor\(^{™}\), Datex, Helsinki, Finland). Resting energy expenditure was calculated according to the Ben-Porat formula [4]. Arterial blood gases were analysed extemporaneously (Omni9, AVL, Shaffhausen, Switzerland). Tidal volume (V\(_T\)), respiratory
frequency ($f_R$) and ventilation ($V^E$) were measured using a portable differential pressure spirometer (Spiro+®, Saime, Savigny-le-temple, France). In each patient, a routine control of the stimulator was first performed. The patient was then switched to PPV and the home ventilator settings were adjusted to provide $f_R$ and $V_T$ as close as possible to that measured during diaphragm pacing. The metabolic measurements started 15-30 minutes later. They were repeated every 3 minutes, until metabolic steady state was achieved (less than 5% change in $V'O_2$, $V'CO_2$ and respiratory quotient). The patient was then switched back to diaphragm pacing and the measurements repeated according to the same sequence and criteria. The patients were studied in a semi-reclined posture in their bed, with no posture change between phrenic pacing and PPV. The instrument dead space was kept identical. Heart rate, blood pressure and body temperature were monitored. Of note, no inspiratory neck muscle use was observed during diaphragm pacing or PPV. The entire data set passed the Shapiro-Wilk test for normality and the results are therefore presented as mean ± SD. Comparisons were performed using the paired Student's t-test. Differences were considered significant for $P < 0.05$.

The breathing patterns during diaphragm pacing and PPV were similar (diaphragm pacing: $V_T$ 798 ± 274 mL; $f_R$ 13.6 ± 2.3; $V^E$: 10.5 ± 2.8 L; PPV: $V_T$ 710 ± 174 mL; $f_R$ 14.6 ± 2.1; $V^E$: 10.3 ± 2.8 L). No difference in blood pressure, heart rate, and temperature was observed. During diaphragm pacing, $PaO_2$ increased but without reaching statistical significance (Table 1) but there was a dramatic fall in the alveolar-arterial gradient ($PaO_2$)(diaphragm pacing: 11.4 ± 11.6 mmHg; PPV: 28.9 ± 14.1 mmHg, $P = 0.005$). Similarly, physiological deadspace (Bohr formula) was 0.48 ± 0.10 under PPV and 0.38 ± 0.11 under diaphragm pacing ($P = 0.023$). Diaphragm pacing was associated with an immediate rise in $V'O_2$ (PPV: 183.6 ± 27.4 mL.min$^{-1}$; diaphragm pacing: 207.8 ± 28.9 mL.min$^{-1}$; + 14.2%; $P < 10^{-4}$)(Figure1) and in $V'CO_2$ (PPV: 154.7 ± 24.4 mL.min$^{-1}$; diaphragm pacing: 173.6 ± 25.6 mL.min$^{-1}$; + 12.7%, $P < 10^{-4}$) without respiratory quotient change (PPV: 0.84 ± 0.04;
diaphragm pacing: 0.85 ± 0.02). In spite of the rise in V'CO₂, PaCO₂ during diaphragm pacing was not higher than during PPV, probably in line with the reduced deadspace. Resting energy expenditure was 3552.0 ± 536.6 kJ.day⁻¹ during PPV and 4051.9 ± 562.3 kJ.day⁻¹ during pacing (+21%, \( P < 10^{-4} \)).

From our observations, it appears that for a given level of ventilation diaphragm pacing improves gas exchange relative to PPV. This conclusion might not seem obvious in view of the nonsignificant rise in PaO₂ and the lack of change in PaCO₂ but it is nevertheless clearly warranted if one looks beyond these variables, as follows.

Regarding oxygenation, our most salient finding is the markedly reduced PA-aO₂ during diaphragm pacing. In the absence of diffusion abnormalities, this points at a reduced shunt effect that could result from diaphragm pacing directing a greater proportion of the inspired volume than PPV to the lower regions of the lungs, like does spontaneous breathing [2]. Consistent with this hypothesis, Di Marco et al. [5] observed better gas exchange in anesthetized dogs during diaphragm pacing as compared with intercostal pacing, at similar levels of ventilation. Diaphragm pacing could also have reopened collapsed or near-collapsed lung areas, frequently observed in quadriplegic patients.

Regarding carbon dioxyde elimination, we observed a 12% rise in V'CO₂ during diaphragm pacing. Because \( V'_E \) was identical during PPV and diaphragm pacing, this should have translated into a rise in PaCO₂. This did not occur, hence more efficient carbon dioxyde elimination during diaphragm pacing in line with the documented reduction in deadspace (Table 1).

The 12% rise in V'CO₂ during diaphragm pacing was the consequence of a 15% rise in V'O₂. In the absence of major stress and of obvious CO₂ storage issue (constant respiratory quotient), this is likely to represent the addition of the diaphragm pacing-related oxygen cost of breathing to basal metabolism. Yet data in the literature put respiratory V'O₂ closer to 5% of total V'O₂ in quadriplegics [6]. As most quadriplegics [7], our patients were overventilated
during diaphragm pacing and PPV (Table 1). Calculating what would have been a "normocapnic V'O₂" reduced our diaphragm V'O₂ values by 30%. In addition, diaphragm reconditioning by low-frequency stimulation may have shifted fibre composition toward highly oxidative type I fibres [8]. Whatever the mechanisms involved, the diaphragm pacing-related resting energy expenditure increase documented here should be taken into account in the nutritional management of these patients.

Beyond its clinical value in quadriplegics, diaphragm pacing has potential physiological advantages. It can improve cardiac performance through an increased abdominophragmatic pressure gradient [9]. Preliminary data indicate that it could protect the diaphragm against ventilator-induced injury [10, 11]. The present observations suggest that it can provide better gas exchange than PPV. We submit that these observations are a reasonable rationale to evaluate the effects of diaphragm pacing as an adjunct to PPV on gas exchange in mechanically ventilated patients suffering from acute lung disease. Animal data should be obtained first, keeping in mind that emerging minimally invasive techniques for temporary diaphragm pacing [12] should soon provide clinical feasibility. We anticipate that effects similar to those described when preserving spontaneous breathing during mechanical ventilation in patients with acute lung injury [e.g.3] should be observed. We also anticipate that this approach should make the equilibrium between preserved diaphragm activity and patient comfort easier to find.

References


Table 1. Breathing pattern, blood gases, and metabolic variables during positive pressure ventilation (PPV) and diaphragm pacing.

<table>
<thead>
<tr>
<th></th>
<th>Positive pressure ventilation (PPV)</th>
<th>Diaphragm pacing</th>
<th>P</th>
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<tbody>
<tr>
<td><strong>Breathing pattern</strong></td>
<td></td>
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<tr>
<td>VT (mL)</td>
<td>710 ± 174</td>
<td>798 ± 274</td>
<td>0.195</td>
</tr>
<tr>
<td>fR (breaths.min(^{-1}))</td>
<td>14.6 ± 2.1</td>
<td>13.6 ± 2.3</td>
<td>0.372</td>
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<tr>
<td>V'E (L.min(^{-1}))</td>
<td>10.3 ± 2.8</td>
<td>10.5 ± 2.8</td>
<td>0.826</td>
</tr>
<tr>
<td><strong>Gas exchange</strong></td>
<td></td>
<td></td>
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<tr>
<td>pH</td>
<td>7.50 ± 0.04</td>
<td>7.48 ± 0.04</td>
<td>0.236</td>
</tr>
<tr>
<td>PaO2 (mmHg)</td>
<td>93.1 ± 17.1</td>
<td>105.5 ± 15.5</td>
<td>0.061</td>
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<tr>
<td>PaCO2 (mmHg)</td>
<td>24.0 ± 5.5</td>
<td>26.3 ± 7.0</td>
<td>0.433</td>
</tr>
<tr>
<td>PA-aO2 (mmHg)</td>
<td>28.9 ± 14.1</td>
<td>11.4 ± 11.6</td>
<td>0.005</td>
</tr>
<tr>
<td>VD / VT</td>
<td>0.48 ± 0.10</td>
<td>0.38 ± 0.11</td>
<td>0.023</td>
</tr>
<tr>
<td><strong>Metabolism</strong></td>
<td></td>
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</tr>
<tr>
<td>V'O₂ (mL.min(^{-1}))</td>
<td>183.6 ± 27.4</td>
<td>207.8 ± 28.9</td>
<td>&lt; 10(^{-4})</td>
</tr>
<tr>
<td>V'CO₂ (mL.min(^{-1}))</td>
<td>154.7 ± 24.4</td>
<td>173.6 ± 25.6</td>
<td>&lt; 10(^{-4})</td>
</tr>
<tr>
<td>RQ</td>
<td>0.84 ± 0.04</td>
<td>0.85 ± 0.02</td>
<td>0.753</td>
</tr>
<tr>
<td>REE (kJ.day(^{-1}))</td>
<td>3552.00 ± 536.6</td>
<td>4051.94 ± 562.27</td>
<td>&lt; 10(^{-4})</td>
</tr>
</tbody>
</table>
VT, tidal volume; fR, breathing frequency; VE, ventilation; VD/VT, physiological deadspace (Bohr formula); VO2, oxygen consumption; VCO2, carbon dioxide production; RQ, respiratory quotient; REE, resting energy expenditure.