Potential therapeutic strategies aimed at reducing the intensity of mechanical ventilation in ARDS
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Induced hypothermia improves ventilation in mechanically ventilated patients

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Submitted
Abstract

Objective: Previous retrospective studies suggest a reduction in minute ventilation needed for CO₂ elimination, when induced hypothermia (32-34°C) is applied in the Intensive Care Units (ICU). We hypothesized that induced hypothermia allows for improved gas exchange while maintaining protective ventilation settings in mechanically ventilated ICU patients.

Design: prospective observational cohort study

Setting: a mixed surgical- medical ICU of a university hospital

Patients: 56 patients admitted to the ICU and treated with induced hypothermia (32-34°C) for 24 hours and observed for 48 hours during protective mechanical ventilation

Interventions: Arterial blood gas were drawn three times, at the start and end of the hypothermic phase and after reaching normo-temperature. At the same time points respiratory data were collected from the electronic patient files. Dead space ventilation was calculated as (PaCO₂-etCO₂)/PaCO₂.

Measurements and main results: During hypothermia, median minute volume, tidal volume and respiratory rate did not change, while levels of PaCO₂ levels and exhaled CO₂ (etCO₂) decreased. Dead space ventilation, static compliance and P/F ratio also remained unchanged during hypothermia. Applied PEEP levels and plateau pressures could be decreased. After rewarming, P/F ratio and dead space ventilation decreased compared to end of hypothermic period, at unchanged minute volume, PEEP and PaCO₂ levels. Static compliance, plateau pressures, etCO₂ levels increased after rewarming.

Conclusions: Induced hypothermia improved ventilation in mechanically ventilated patients while maintaining lung protective ventilation settings and allowed for lower driving pressures and PEEP levels, providing a rationale to study whether induced hypothermia is a therapeutic option in patients in whom protective ventilation is hampered by severe respiratory acidosis.
**Introduction**

Induced hypothermia (32-34°C) is applied as a therapeutic intervention in Intensive Care Units (ICU) and in the operating room. The neurologic benefits are well described [1, 2], but clinical data on the effect of hypothermia on lung mechanics and gas exchange during mechanical ventilation are scarce. Retrospective data in ICU patients suggest a beneficial effect of hypothermia on gas exchange, with a decline of the partial CO$_2$ tension (PaCO$_2$), at unchanged minute ventilation [3], which may possibly be due to lowered CO$_2$ production.

Thereby, hypothermia may allow for reducing intensity of mechanical ventilation, with a reduction in applied driving pressures or tidal volumes needed for adequate ventilation. As both high pressure levels and high tidal volumes are associated with mortality during mechanical ventilation [4, 5], induced therapeutic hypothermia may be beneficial when protective mechanical ventilation is hampered by the need for application of potentially injurious ventilation settings to avoid severe acidosis. Effects of hypothermia on lung mechanics have not been described. In this study, we investigated the effect of induced hypothermia on lung mechanics and gas exchange in patients admitted after cardiac arrest. We hypothesized that induced hypothermia (32-34°C) allows for improved gas exchange while maintaining protective ventilation settings in mechanically ventilated ICU patients.

**Methods**

This prospective observational cohort study was approved by the local medical ethics committee of the Academic Medical Center, University of Amsterdam, the Netherlands and conducted in concordance with the principles of the declaration of Helsinki and good clinical practice. From January 2011 until October 2012, 56 cardiac arrest patients were included. All patients were admitted to a mixed surgical-medical intensive care unit (ICU) of a tertiary referral center in Amsterdam, the Netherlands after cardiopulmonary resuscitation and treated with induced hypothermia (32-34°C) for 24 hours. Patients were prospectively followed for 48 hours during which they were ventilated with tidal volumes of 6 ml/kg in a pressure controlled mode, which was switched to pressure support ventilation mode after stop of sedation. Ventilation was targeted to maintain normopH (7.35-7.45). Exclusion criteria were the presence of pulmonary fibrosis or inability to complete 24 hours of hypothermia according to treating physician. Other standard of care included administration of vasopressor therapy to target a blood pressure of at least
Induced hypothermia improves ventilation in mechanically ventilated patients. Patients received either anticoagulant medication as deemed appropriate or thrombosis prophylaxis. Patients were not fed during the hypothermic phase. In all patients an arterial blood gas was taken (alpha stat) and ventilation data were collected from the electronic patient files at the start (T=1) and end (T=2) of the hypothermic phase and after reaching normotemperature (T=3). Dead space ventilation was calculated as \((\text{PaCO}_2 - \text{etCO}_2)/\text{PaCO}_2\). Static compliance was calculated as tidal volume (mL) divided by plateau pressure minus peak end expiratory pressure (PEEP). When plateau pressures were not scored, peak pressures were used. Other data were collected from the patient data monitoring system or the Dutch National Intensive Care Evaluation [6]. Data were analyzed by a Friedman and Wilcoxon signed rank test, since the data are not normally distributed. Data are expressed as median ± range. P<0.05 was considered significant.

Table 1: Baseline characteristics of patients admitted at ICU after cardiac arrest.

<table>
<thead>
<tr>
<th></th>
<th>n=56</th>
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<tbody>
<tr>
<td>Gender (Male/Female)</td>
<td>41/15</td>
</tr>
<tr>
<td>Age (years)</td>
<td>62 ± 14</td>
</tr>
<tr>
<td>Length (cm)</td>
<td>177 ± 9</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>84 ± 19</td>
</tr>
<tr>
<td>Maximal leukocyte count</td>
<td>16.1 ± 8.1</td>
</tr>
<tr>
<td>SAPS II score</td>
<td>51 ± 16</td>
</tr>
<tr>
<td>APACHE III score</td>
<td>76 ± 33</td>
</tr>
</tbody>
</table>

**Previous medical history**

<table>
<thead>
<tr>
<th>Medical History</th>
<th>7 (13%)</th>
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<tbody>
<tr>
<td>Chronic cardiovascular insufficiency</td>
<td></td>
</tr>
<tr>
<td>Arrhythmia</td>
<td>20 (36%)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>9 (16%)</td>
</tr>
<tr>
<td>Chronic respiratory failure</td>
<td>4 (7%)</td>
</tr>
</tbody>
</table>

| Lowest mean blood pressure during first 24 hours of ICU admittance (mmHg) | 59 ± 9   |
| Number of patients requiring vasoactive medication during first 24 hours of ICU admittance | 48 (86%) |
| Number of patients with confirmed infection during first 24 hours of ICU admittance | 7 (13%)  |

Data expressed as mean ± SD or percentages
Results

Characteristics of patients are shown in table 1. A substantial part of patients required vasopressor therapy at the start of induced hypothermia. During hypothermia, median minute volume remained unchanged compared to baseline (10.5 ± 17.3 to 11.0 ± 20.1 L; P=0.9, figure 1), with unchanged tidal volume (5.5 ± 9.6 to 5.4 ± 9.8 mL/kg; P=0.23) and respiratory rate (24 ± 29 to 25 ± 28 breath/min; P=0.5), while levels of PaCO₂ levels (5.5 ± 5.8 to 4.8 ± 4.0 kPa; P=0.001) and exhaled CO₂ (etCO₂) (3.8 ± 4.1 to 3.6 ± 4.6 kPa; P=0.09) decreased. Dead space ventilation did not change during hypothermia compared to baseline (28.3 ± 53.6 to 28.8 ± 63.43 kPa; P=0.53). Applied PEEP levels could be decreased (7 ± 15 to 5 ± 13 cmH₂O; P=0.0001, figure 2), while P/F ratio remained unchanged (280 ± 754 to 268 ± 370 mmHg; P=0.6). Plateau pressures could be decreased (21 ± 31 to 21 ± 24 cmH₂O; P=0.039), whereas static compliance remained the same during hypothermia (33 ± 69 to 29 ± 89 cmH₂O; P=0.67).

After rewarming, P/F ratio decreased compared to end of hypothermic period (268 ± 370 to 207 ± 340 mmHg; P=0.0001) at unchanged PEEP levels (5 ± 13 to 5 ± 12 cmH₂O; P=0.4).
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Static compliance increased after rewarming (29 ± 89 to 46 ± 126 cmH₂O; P=0.0001), as well as plateau pressures (21 ± 24 to 19 ± 28 cmH₂O; P=0.004). After rewarming, some patients were weaned from ventilation, resulting in less data points for αT=2. Levels of PaCO² remained unchanged compared to end of hypothermic period (4.8 ± 4.0 to 4.8 ± 3.3 kPa; P=0.71), while etCO₂ levels increased (3.6 ± 4.3 to 4.4 ± 3.3 kPa; P=0.0001). Dead space ventilation decreased (28.8 ± 63.4 to 12.9 ± 40.3 kPa; P=0.0001), with an associated increase in tidal volume (5.4 ± 9.8 to 6.3 ± 12.8 mL/kg; P=0.0001; data not shown) and decreased respiratory rate (25 ± 28 to 23 ± 33 breath/min; P=0.038; data not shown). Minute volume remained unchanged (11.0 ± 20.1 to 12.0 ± 22.8 L; P=0.06).

Discussion

Therapeutic induced hypothermia for 24 hours improved ventilation in mechanically ventilated patients while maintaining lung protective ventilation settings and allowing for lower PEEP levels and peak pressures. Induced hypothermia reduced PaCO₂ levels, at unchanged minute ventilation. As hemodynamic parameters did not change over time, suggesting pulmonary perfusion remained unchanged, reduced CO₂ levels may be due
Induced hypothermia improves ventilation in mechanically ventilated patients to reduced CO₂ production during hypothermia. This improvement in ventilation during hypothermia is in line with retrospective data [3]. Thereby, driving pressures needed to generate a given minute volume ventilation were slightly lowered during hypothermia. The reduction in both PEEP levels and plateau pressures during hypothermia may be beneficial, since driving pressures are independently associated with mortality in patients with severe respiratory failure such as in ARDS [7-9]. Dead space ventilation did not vary during hypothermia, but did show a decrease after rewarming. This is mostly likely caused by the switch from controlled ventilation to spontaneous breathing [10]. Oxygenation, expressed as P/F ratio, declined after rewarming, which may be due to the fact that blood gases were measured alpha stat. Alternatively, the switch to spontaneous ventilation may have resulted in decreased oxygenation.

A limitation to our results is that it is not possible to differentiate between effects occurring over time following a cardiac arrest and induced hypothermia. Cardiopulmonary resuscitation after cardiac arrest results in an inflammatory state [11], which may have affected a change in ventilatory parameters over time. Nevertheless, ventilation settings changed after discontinuation of hypothermia, suggesting a causal effect. Furthermore, all patients were sedated, which also lower metabolism and CO₂ production. Thereby, it is not possible to dissect whether sedation or induced hypothermia contributed most to observed results. Whether induced hypothermia is beneficial by decreasing driving pressures and improving ventilation in patients in whom severe respiratory acidosis occurs as a result of respiratory failure remains to be determined.

Conclusions

Hypothermia improves ventilation in mechanically ventilated patients and allows for lower driving pressures and PEEP levels while maintaining lung protective ventilation settings. Results provide a rationale to study whether induced hypothermia is a therapeutic option in patients in whom protective ventilation is hampered by severe respiratory acidosis.
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