Explorations of the therapeutic potential of influencing metabolism during critical illness

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The effect of induced hypothermia on respiratory parameters in mechanically ventilated patients

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Short communication
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Abstract

Aim: Mild hypothermia is increasingly applied in the intensive care unit. Knowledge on the effects of hypothermia on respiratory parameters during mechanical ventilation is limited. In this retrospective study, we describe the effect of hypothermia on gas exchange in patients cooled for 24 hours after a cardiac arrest.

Methods: Respiratory parameters were derived from electronic patient files from 65 patients at the start and end of the hypothermic phase and at every centigrade increase in body temperature until normo-temperature, including tidal volume, positive end expiratory pressure (PEEP), plateau pressure, respiratory rate, exhaled CO₂ concentrations (etCO₂) and FIO₂. Static compliance was calculated as $V_T / (P_{plateau} – PEEP)$. Dead space ventilation was calculated as $(PaCO_2 – etCO_2) / PaCO_2$.

Results: During hypothermia, PaCO₂ decreased, at unchanged PaCO₂–etCO₂ gap and minute ventilation. During rewarming, PaCO₂ did not change, while etCO₂ increased at unchanged minute ventilation. Dead space ventilation did not change during hypothermia, but lowered during rewarming. During hypothermia, $PaO_2/FIO_2$ ratio increased at unchanged PEEP levels. Respiratory static compliance did not change during hypothermia, nor during rewarming.

Conclusion: Hypothermia possibly improves oxygenation and ventilation in mechanically ventilated patients. Results may accord with the hypothesis that reducing metabolism with applied hypothermia may be beneficial in patients with acute lung injury, in whom low minute ventilation results in severe hypercapnia.
Introduction

Induced hypothermia in patients after cardiac arrest improves neurological outcome (1). The protective effect occurs through reduction in cerebral CO₂ production and O₂ consumption, inhibition of the immune response and reduction of edema and epileptic activity (2;3). Induced hypothermia may also be beneficial in other causes of hypoxia–induced organ injury, such as traumatic brain injury, stroke, spinal cord injury, liver failure and asphyxial encephalopathy. Despite an increase in the application of induced mild hypothermia in critically ill patients, clinical observations on the effect of hypothermia on lung mechanics and gas exchange are mostly restricted to peri–operative settings (4;5), whereas knowledge on effects in survivors of a cardiac arrest are limited. Supposedly, the decrease in O₂ consumption induced by hypothermia (6) may increase arterial O₂ levels. However, impaired O₂ extraction in hypothermic tissues may offset a potential benefit in O₂ balance (7;8). A hypothermia–induced decrease in CO₂ production may be counteracted by decreased ventilation due to hypothermia–induced changes in compliance and resistance (9) or impaired gas exchange (5).

In this retrospective study, we describe the effect of induced hypothermia on respiratory parameters in survivors of a cardiac arrest, during the hypothermic period and during rewarming.

Methods

Patients admitted to the medical–surgical intensive care unit of our teaching hospital between July 2007 and August 2008 with a Glasgow Coma Scale ≤ 8 after a cardiac arrest, in whom mild hypothermia was induced, were evaluated. Hypothermia was induced by infusion of Ringers lactate (4°C, 100 ml/min) and by a cooling mattress (2). After achieving target temperature (32–34°C), hypothermia was maintained for 24 hours, after which patients were passively rewarmed. Further treatment included sedation, muscle relaxation in case of shivering and selective digestive tract decontamination (2). Patients were mechanically ventilated in a pressure controlled mode with an inspiratory to expiratory time of 1:2 and a ramp time of 0.25–0.50 seconds. Continuous exhaled (et) CO₂ was monitored with a mainstream etCO₂ module. Respiratory parameters were derived from the electronic patient data monitoring system, at maintenance phase after target temperature was reached (32–33°C), at the end of the maintenance phase (24hr later) and during rewarming at every centigrade increase until normo–temperature (37°C), including tidal volume, positive end expiratory pressure (PEEP), plateau pressure, respiratory rate, exhaled CO₂ concentrations (etCO₂) and FIO₂. Arterial blood gases were analyzed uncorrected for body temperature (alpha–stat management).
Static compliance was calculated as $V_t / P_{plateau} - PEEP$. Alveolar dead space ventilation was calculated as $(PaCO_2 - etCO_2) / PaCO_2$. During the hypothermic period, cumulative fluid balance was recorded. 

Data are mean (±SD) or median [IQR] as appropriate. Measurements at start of hypothermia vs. end hypothermia and start rewarming vs. end rewarming phase were analyzed using paired t–test (SPSS version 17, Illinois, USA).

**Results**

In total, 65 patients in whom hypothermia was induced were evaluated. Of these, 3 did not complete 24 hours of hypothermia, leaving 62 patients for analysis. Of these, 75% was male. Mean age was 63 (±12) years. Mean APACHE score was 24.7 (±1.3). Vasopressor therapy was given in 51 patients (82%).

**Hypothermic phase**

At the start of the hypothermic period, mean PaCO$_2$ was 5.5 (±1.1) kPa, decreasing to 5.1 (±0.9) kPa at the end of hypothermia, (p=0.02), while mean etCO$_2$ decreased non–significantly (3.8 (± 0.9) vs. 3.6 (±1.0) kPa, p=0.3, panel A). The PaCO$_2$–etCO$_2$ gap did not change (1.7 [–1.8 – 2.3] vs. 1.6 [1.2 – 2.2], p=0.6). Minute ventilation volume was also unchanged (11.3 ± 2.3 vs. 10.8 ± 3.2 L/min, panel B, p=0.9), as was the calculated dead space ventilation (32 ± 10 vs. 34 ± 12%, p=0.1).

During hypothermia, PaO$_2$/FiO$_2$ ratio increased from 233 [167 – 332] at the start of the hypothermic period to 268 [206 – 360] at the end of the hypothermic period (p=0.02), while PEEP levels did not change, panel C, p=0.9). The respiratory static compliance was low and did not change (27 [20.2 – 33.7] vs. 28 [22.0 – 35.8] mL/cmH$_2$O, panel D, p = 0.9)

**Rewarming phase**

During rewarming, PaCO$_2$ did not change (5.1 (± 1.0) vs. 5.4 (± 0.8) kPa, p=0.2) while etCO$_2$ increased from 3.6 (± 0.9) to 4.7 (± 1.1) kPa (p<0.0001, panel A), at unchanged minute volume ventilation (11.6 (± 2.9) vs. 11.6 (± 2.9) L/min, panel B, p=0.8). The calculated dead space ventilation lowered during rewarming (30 ± 14 vs. 18 ± 11%, p<0.0001).

With rewarming, PaO$_2$/FiO$_2$ ratio declined to 244 [188 – 304], p=0.001) (panel C). The respiratory static compliance did not change during rewarming (28 [20.6 – 33.7] vs. 26 [20.9 – 36.5] mL/cmH$_2$O, p = 0.1, panel D). Over the period of hypothermia and rewarming, cumulative fluid balances of all patients were positive, with a mean of 2.5 (± 1.6) L.
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**Discussion**

Mild hypothermia decreased PaCO$_2$ levels and increased PaO$_2$/FiO$_2$ ratio in cardiac arrest patients admitted to the ICU, despite fluid resuscitation. Static compliance was not changed by hypothermia.

In mechanically ventilated survivors of a cardiac arrest, hypothermia reduced arterial CO$_2$ pressure. The levels of etCO$_2$ were low at unchanged minute ventilation, which may suggest a reduction in CO$_2$ production as a consequence of reduced metabolism. Although CO$_2$ production was not measured, etCO$_2$ reflects the amount of CO$_2$ delivered to the lungs under stable conditions (10). It could be hypothesized that impaired pulmonary perfusion after cardiac arrest may have contributed to the decreased etCO$_2$ levels. However, as patients served as their own controls, measurements may not have been affected by a change in CO$_2$ delivery to the lungs. In line with this, hypothermia did not affect the PaCO$_2$-etCO$_2$ gap in our patients, as found before (5). As comparisons between start and end of the hypothermic period were done at the same temperature (32–33°C), an increase in solubility of CO$_2$ is unlikely to account for the observed decrease in pCO$_2$. Therefore, results may suggest that
hypothermia decreases CO₂ production in mechanically ventilated patients. However, we cannot exclude that changes in pulmonary perfusion over time may have contributed to the observed decrease. 

This finding may have clinical implications. Low tidal volume ventilation decreases mortality in ALI patients (11). Lowering tidal volume even further down to 4 ml/kg, results in further reduction of injury inflicted by the ventilator, albeit at the cost of extracorporeal CO₂ removal (12). Although mild hypercapnic acidosis may favorably influence the course of disease (13), unlimited acidosis is not acceptable. Also, larger tidal volumes are still applied in hypoxic and acidotic patients (14). Our results may serve to generate the hypothesis that induced hypothermia may benefit ALI patients mechanically ventilated with deviated tidal volumes to treat severe acidosis (15). In line with this, hypothermia reduced lung injury in experimental settings and reduced mortality in patients with severe lung injury when applied as a rescue therapy (16–18).

Respiratory compliance was not affected by 24 hours of hypothermia. A decrease in lung compliance has been found during short courses of profound hypothermia in the context of cardiopulmonary bypass (9), but this has not been reproduced in anesthetized patients not subjected to bypass (19). Our results extend these findings to the setting of prolonged hypothermia after a cardiac arrest.

Mild hypothermia improved oxygenation in this study, in line with some previous findings (4;6), but not with all (7). Fluid balances were positive in all patients, suggesting that improvement in oxygenation was not attributable to a decrease in hydrostatic pulmonary edema as a consequence of hypothermia–induced increase in dieresis (2). Rather, the improvement in arterial oxygenation may be a result of decreased O₂ consumption. Body temperature influences blood gas analysis. However, measurements during the hypothermic period were all taken at low body temperature. Therefore, increased solubility of oxygen at lower temperatures did not contribute to improvement in oxygenation during hypothermia (6), but may have contributed to a decline in PaO₂/FiO₂ ratio after rearming, albeit allowing for a lower PEEP level compared to start of hypothermia. There is an ongoing debate whether blood gases should be corrected for body temperature. Although it can be argued that corrected blood gases reflect a physically true situation, the alpha stat regimen has strong proponents for its use during hypothermia after a cardiac arrest, as correction of blood gases can lead to hypercapnia, cerebral vasodilatation and increased intracranial pressure (2). Therefore, uncorrected measurements may be considered clinically relevant. 

This study has limitations. Firstly, we were not able to obtain measurements before the induction of hypothermia, because a considerable part of the patients had a temperature already below 37°C on administration. Results apply only to induced hypothermia, not to effects of accidental hypothermia. Secondly, measuring O₂ delivery and CO₂ production were not part of the retrospective data set, rendering conclusions on metabolism speculative.
Data should be interpreted within the limits of the retrospective study design. Lastly, whether the observed effects are clinically relevant, cannot be dissected from our results. A normothermic control group is lacking, because induced hypothermia is part of standard patient care in our institution.

**Conclusion**

Mild induced hypothermia reduced CO₂ production and improved oxygenation in patients after cardiopulmonary resuscitation, without compromising compliance. Results may accord with the hypothesis that reducing metabolism with applied hypothermia may be a new therapy for critically ill patients with acute lung injury, in whom low minute ventilation results in severe hypercapnia.
References


