Potential therapeutic strategies aimed at reducing the intensity of mechanical ventilation in ARDS
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Helium ventilation for treatment of post cardiac arrest syndrome: a safety and feasibility study

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Submitted
Abstract

Background: The only treatment available for comatose patients after cardiac arrest is induced hypothermia. Helium reduces ischemic injury in animal models, and might ameliorate neurological injury in patients after cardiac arrest. As no studies exist on the use of helium in patients after cardiac arrest we investigated whether this is safe and feasible.

Methods: The study was an open-label single arm intervention study, in a mixed-bed academic intensive care unit. 25 patients with a presenting rhythm of ventricular fibrillation or pulseless tachycardia, return of spontaneous circulation within 30 minutes and treatment with hypothermia after circulatory arrest were included. Helium was administrated in a 1:1 mix with oxygen for 3 hours. A safety committee reviewed all ventilation problems, complications and mortalities. Outcome and mortality data were compared with matched historical control patients.

Results: Helium ventilation was started 4:59±0:52 (mean ± SD) hours after circulatory arrest. In one patient, helium ventilation was discontinued prematurely due to oxygenation problems. This was caused by pre-existing pulmonary oedema, and there was no relation with helium ventilation. Sixteen (64%) patients had a favourable neurological outcome.

Conclusions: We found that helium ventilation is feasible and can be used safely in patients treated with hypothermia after cardiac arrest. No adverse events related to helium ventilation occurred during the three hours of ventilation. There was no difference in outcome between helium treated patients and matched controls.
Introduction

Out of hospital cardiac arrest is a major cause of morbidity and mortality, afflicting 335 per million per year in the Netherlands with an overall mortality of 81%1. Half of the patients admitted to the intensive care unit (ICU) leave the hospital with an unfavourable neurological outcome2-3. Circulatory arrest and subsequent return of circulation leads to ischaemia reperfusion injury of the whole body and is particularly injurious to the brain and myocardium4. Brain injury is the major cause of mortality and morbidity after cardiac arrest5. Therefore, patients admitted after cardiac arrest should receive treatment aimed at reducing brain injury as part of the post-resuscitation care. The only effective treatment currently available is mild hypothermia6-7. Despite this therapy, outcome results are disappointing and therapies to further reduce ischaemia reperfusion injury after cardiac arrest are needed.

The noble gas helium reduced ischaemia reperfusion injury in both in vitro and in vivo animal models, thereby reducing e.g. myocardial infarct size8-14. Inhalation of helium before, during or following a period of cerebral ischaemia also reduced the size of cerebral infarction in rats8-14. Helium might be capable of reducing neurological and myocardial injury in patients after cardiac arrest, but no clinical studies in this field have been done. Clinically, helium is used to ventilate both adults and children with severe obstructive pulmonary disease and helium inhalation is generally considered to be safe15. Recently we demonstrated that helium induces preconditioning in healthy volunteers, thereby protecting against endothelial dysfunction after regional forearm ischaemia16. Prior to investigating the use of helium as a therapeutic agent in neurological damaged patients, we performed a safety and feasibility study, investigating whether helium ventilation can safely be used in patients admitted to the ICU after cardiac arrest.

Methods

This was an open-label single arm intervention study, performed in the mixed surgical-medical ICU of a university hospital. The study was approved by the local medical ethics committee of the Academic Medical Centre (protocol number NL 30466.018.09) and was conducted in concordance with the principles of the declaration of Helsinki and good clinical practice. The study was registered with the Dutch Trial Registry (www.trialregister.nl) under NTR2257. Patients were included after obtaining informed consent from their legal representative.
Inclusion criteria were admission after witnessed out of hospital cardiac arrest (OHCA), with the first registered rhythm being ventricular fibrillation (VF) or tachycardia (VT) and treatment with mild hypothermia. Return of spontaneous circulation (ROSC) had to occur within 30 minutes and helium ventilation had to be started within 6 hours after cardiac arrest. Exclusion criteria were oxygenation problems (necessitating a FiO₂ >50% and >10 mmHg positive end expiratory pressure [PEEP]), neurological deficits or severe disability before cardiac arrest, and comorbidities with a life expectancy of less than 6 months. The described ventilation settings were limits during the study-protocol as well.

As a control group, propensity-score matched patients were selected from the PROPAC II study database. For every helium treated patient three controls were selected who met the same inclusion and exclusion criteria, including presenting rhythm, and a propensity score was calculated by logistic regression analysis using age, gender and duration of circulatory arrest as variables.

**Study procedures**

After inclusion, helium ventilation was initiated as soon as possible. Helium was administered from a pressurised cylinder containing 1780 L heliox (Heliox21, BOC Ltd, UK), as a 50/50 helium/oxygen mixture, using a heliox compatible Servo-I ventilator (Maquet, Netherlands). Helium ventilation was done in pressure control mode, peak pressure was set to achieve a tidal volume of 6 ml/kg ideal body weight, with 5-10 mmHg of PEEP and the respiratory frequency was controlled to maintain a pCO₂ of 4.5-5.5 kPa and a pH of 7.35-7.45 (alpha-stat). A pO₂ of ≥10 kPa and a saturation of ≥95% were aimed for. After switching to helium, a setup period with repeated blood gas analysis was used to reach the target values for pCO₂ and pH. When these measurements were within the normal limits helium ventilation was continued during a 3-hour period. Since the objective of this study was to investigate the safety and feasibility, and not the effectiveness, of helium ventilation, helium ventilation was stopped if the cylinder was empty before the end of the 3-hour period.

Data collected were age, gender, Body Mass Index (BMI), simplified acute physiology score II (SAPS II), acute physiology and chronic health evaluation score II (APACHE II), pre-existent cardiovascular disease or malignancy, cause of arrest, time until first shock, time to ROSC, the use of coronary angiography and percutaneous coronary interventions and the need for hemodynamic support at admission.
Serum samples for analysis of creatine kinase (CK), creatine kinase muscle-brain (CK-MB) and troponin-T were drawn at admission and at 6, 12, 18, 24, and 48 hours. Serum samples for analysis of neuro specific enolase (NSE) levels were drawn 24 and 48 hours after admission. NSE serum samples were centrifuged and stored at -20 until analysis by immunoassay (kit for ELECSYS, Roche).

Outcome was assessed by telephone interview of the patient or caregiver 30 days after admission. The Glasgow Outcome Scale (GOS) was used; poor outcome was defined as death or vegetative state (GOS 1-2). For matched control patients, outcome after one month and NSE levels 48 hours after admission to the ICU were available from the PROPAC II database.

Primary objective of the study was to investigate the safety and feasibility of helium administration in patients after cardiac arrest. Safety endpoints were the inability to adequately ventilate the patient using helium within the predetermined limits (FiO₂ 50% and ≤10 mmHg PEEP), and death related to helium. To determine the probability of an adverse event being related to helium treatment all serious adverse events were evaluated by an independent safety committee, consisting of an intensive care physician, an anaesthesiologist and a neurologist.

Secondary objectives were to investigate the effect of helium ventilation on outcome (GOS), brain injury (NSE) and cardiac injury (CK, CK-MB, and troponin-T).

**Statistics**

There is no data on the effectiveness or the occurrence of adverse events of helium treatment in patients after OHCA. Therefore, a formal sample size calculation could not be performed. We expected a mortality rate of approximately 50%, and therefore chose to include 25 patients, to be able to detect an increase in adverse events related to helium. This is also a sample size which is used in similar studies.

SPSS 19 (IBM, Armonk, New York, USA) was used for statistical analysis unless stated otherwise. Continuous data are presented as mean with standard deviation when normally distributed, and otherwise as median and interquartile range, while categorical data are presented as numbers with proportions. For comparison of outcome between cases and controls the odds ratio with 95% confidence interval was calculated using a conditional logistic regression analysis, using STATA 10.0 (StataCorp, CollegeStation, Texas, USA). Student’s t-test or Mann-Whitney U test was used for comparison of NSE values between cases and controls. Statistical significance was defined as p ≤ 0.05.
Results

Between April 2010 and October 2011, 106 patients admitted after OHCA were screened for eligibility, of which 64 patients were not eligible, 13 patients were eligible but were missed by the physician on call, in four patients study participation was refused by the legal representative, and finally 25 patients were included (fig. 1). Baseline characteristics of patients and matched controls are presented in table 1.

Figure 1: Flow schedule of patients

Helium ventilation was started 4:59±0:52 (mean ± SD) hours after arrest, and 21±13 (mean ± SD) minutes was used to reach target values for pCO₂ and pH. After that, helium ventilation was continued for a total of 3:10±39 (mean ± SD) hours. In six patients the treatment was stopped prematurely; in five patients the heliox cylinder was empty before completion of the 3 hour treatment protocol, due to high minute volumes needed and the duration of the adjustment period. In one patient, ventilation with helium was terminated prematurely. This patient had slight hypoxia at the time of inclusion due to pulmonary oedema following cardiac arrest, requiring 10 cmH₂O PEEP and a FiO₂ of 50%
to maintain an oxygen saturation (sO₂) of >90% and a PaO₂ of 8.4 kPa. Shortly after the initiation of helium ventilation, the sO₂ dropped to 84% and the PaO₂ to 7.1 kPa, and it was decided to discontinue the study protocol and switch back to a normal gas mixture. Only after increasing FiO₂ to 70% and PEEP to 12, oxygenation improved in this patient. These ventilation settings had to be maintained for several days. As the hypoxia was pre-existing and persisting, the safety committee concluded that the ventilation disorders were not caused by the short use of helium.

Table 1: Baseline characteristics of patients and matched controls.

<table>
<thead>
<tr>
<th></th>
<th>Patients (25)</th>
<th>Controls (75)</th>
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</thead>
<tbody>
<tr>
<td>Male sex</td>
<td>20 (80%)</td>
<td>61 (81%)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>64.8 ± 12.1</td>
<td>61.8 ± 13.2</td>
</tr>
<tr>
<td>BMI* (kg/m²)</td>
<td>27.4 ± 4.8</td>
<td></td>
</tr>
<tr>
<td>SAPS II score†</td>
<td>53.6 ± 18.6</td>
<td></td>
</tr>
<tr>
<td>APACHE II score‡</td>
<td>20.0 ± 8.6</td>
<td></td>
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<tr>
<td>Comorbidity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>14 (56%)</td>
<td>41 (55%)</td>
</tr>
<tr>
<td>Malignancy</td>
<td>4 (16%)</td>
<td>7 (9%)</td>
</tr>
<tr>
<td>Cause of OHCA§</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute Infarction</td>
<td>17 (68%)</td>
<td></td>
</tr>
<tr>
<td>Chronic Infarction</td>
<td>4 (16%)</td>
<td></td>
</tr>
<tr>
<td>Structural Heart Disease</td>
<td>3 (12%)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>1 (4%)</td>
<td></td>
</tr>
<tr>
<td>Time to 1st shock (min)</td>
<td>8 ± 7</td>
<td></td>
</tr>
<tr>
<td>Time to ROSC II (min)</td>
<td>16 ± 7</td>
<td>16 ± 8</td>
</tr>
<tr>
<td>CAG **</td>
<td>20 (80%)</td>
<td></td>
</tr>
<tr>
<td>PCI ††</td>
<td>15 (60%)</td>
<td></td>
</tr>
<tr>
<td>IABP ‡‡ or Impella</td>
<td>9 (36%)</td>
<td></td>
</tr>
<tr>
<td>Inotropics or vasopressors</td>
<td>12 (48%)</td>
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</tbody>
</table>

Data are mean ± SD or percentages.
* Body Mass Index, † Simplified Acute Physiology Score II, ‡ Acute Physiology and Chronic Health Evaluation II, § Out-of-Hospital Cardiac Arrest, II Return of spontaneous circulation, ** Coronary Angiography, †† Percutaneous Coronary Intervention, ‡‡ Intra-aortic Balloon Pump
Nine patients died within 30 days (36%); in all patients post-anoxic brain injury was the cause of death. None of these deaths were related to helium ventilation. At 30 days follow-up, the surviving 16 patients (64%) all had a favourable outcome, 13 patients (81%) resided at home, two patients (13%) in a rehabilitation centre and one patient was still hospitalized (6%).

In the propensity matched historic control group, 30-day mortality was 36% and 69% of the patients had a favourable outcome at one month follow-up. Compared to controls, the odds ratio (OR) for mortality was 0.87 (95% CI 0.31-2.4) in patients treated with helium; the OR for poor outcome was 1.3 (0.47-3.7).

Serum levels of CK, CK-MB, troponin-T and NSE of helium treated patients are presented in table 2. Helium treated patients had a mean NSE value of 44±51 µg/L at 24 hours, and 54±94 µg/L at 48 hours after arrest, compared to 33±55 µg/L for controls at 48 hours (p=0.22).

<table>
<thead>
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<th>Table 2: Laboratory data of helium patients.</th>
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<td>----------------------------</td>
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<tr>
<td>CK* (U/L)</td>
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<tr>
<td>CK-MB† (µg/L)</td>
</tr>
<tr>
<td>Troponin (µg/L)</td>
</tr>
<tr>
<td>NSE‡ (µg/L)</td>
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</table>

Data are mean ± SD.
* Creatinine Kinase, † Creatinine Kinase Muscle-Brain, ‡ Neurospecific Enolase

Discussion

This is the first study focusing on organ protective effects of helium in patients after cardiac arrest. We found that helium ventilation is feasible and can be used safely in patients treated with hypothermia after OHCA. No adverse events related to the helium ventilation occurred during the three hours of ventilation with this noble gas.

These results might open the door to a new treatment of brain injury following cardiac arrest. Helium might reduce the reperfusion injury, but in this small study, we found no indication for that. However, the study was not powered to study the ability of helium to
reduce organ injury and larger studies are needed to investigate the potential therapeutic value of helium in organ protection following ischemia reperfusion.

Although the mortality rate is lower than values normally reported in the literature for ICU patients admitted after cardiac arrest, this is probably due to the patient selection. We included patients who had a witnessed arrest, presented with VF or VT, and had a resuscitation time of thirty minutes or less, all factors that have a positive effect on outcome. When compared to matched historical controls, the helium treated patients had similar mortality rate and clinical outcome. NSE levels, used as marker for brain injury, were also comparable between treated patients and controls.

Comparison of our results to studies with helium or other noble gasses in patients after cardiac arrest is not possible, as this has never before been studied. Only animal studies have been performed showing conflicting results regarding neuroprotective properties of helium. In an in vitro model of traumatic brain injury helium had a protective effect, and in an in vivo rat model using MCA occlusion helium inhalation reduced infarct size. More positive effects in a MCA occlusion model were reported, but this protective effect was only seen when the animals were allowed to cool down in a flow chamber. The authors suggested that the protection was mediated by the induction of hypothermia. Finally, two studies in neonatal rats in which one common carotid artery was temporally occluded, demonstrated neuroprotection by helium. Other studies did not find a beneficial effect of helium on cerebral injury. In an in vitro model using oxygen glucose deprivation to induce brain injury helium provided no beneficial effect. Another study using a model of MCA occlusion found that helium only provided protection when given directly at the time of reperfusion, and in an inspired fraction of 70%. Until today, the exact underlying mechanisms mediating possible organ protective effects of helium are still unclear.

Other noble gasses have also been used as neuroprotective agents. In a pig model of cardiac arrest, xenon reduced brain injury. The neuroprotective effects of xenon are currently being investigated in ongoing clinical trials (NCT00934700, NCT00879892, ISRCTN75602528).

It is known that the results of animal studies investigating neuroprotection in different animal models are difficult to translate to the human situation. Many neuroprotective drugs have been studied in stroke patients, based on positive animal experiments, but no
effective drug has ever been found for humans²⁶,²⁷. A large difference with focal ischaemic stroke models is that in patients after OHCA the vasculature of the brain is intact and open. As soon as circulation is restored, neuroprotective agents can easily reach the brain cells and perform their actions.

We chose to start with a small study, which makes conclusions about possible effectiveness insignificant and might underestimate the side effects of helium ventilation. Especially longer periods of helium ventilation, which might be needed for an optimal treatment effect, could lead to more ventilation problems. This would be the logical topic to address in a subsequent study.

Second, the open-label use of helium inadvertently introduces a risk for bias, however by using endpoints that are not influenced by observer interpretation (mortality, vegetative state and laboratory assessments) the risk for observer bias was reduced.

Third, the setting of a single ICU of a university hospital limits extrapolation of the results. However, since the objective of the study was to investigate the safety and feasibility, we feel that these limitations are of minor concern at this stage. All patients were ventilated with 50% helium in order to give the same dosage. This also meant that all patients received 50% oxygen, regardless of their oxygenation status, which could lead to supranormal oxygen tensions in some patients. A high PaO₂ during or after cardiac arrest has been linked to an increase in mortality, and might influence a beneficial effect of helium²⁸-³⁰.

To summarize, we demonstrated for the first time that helium ventilation for three hours is safe and feasible in patients after OHCA. This might open the route for further studies investigating the effectiveness of this new organ protective treatment modality.
Reference list

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