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Clinical paper

Helium ventilation for treatment of post-cardiac arrest syndrome: A safety and feasibility study☆,☆☆,★

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ABSTRACT

Aim: Besides supportive care, the only recommended treatment for comatose patients after cardiac arrest is target temperature management. Helium reduces ischaemic 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. We included 25 patients admitted after circulatory arrest, with a presenting rhythm of ventricular fibrillation or pulseless tachycardia, return of spontaneous circulation within 30 min and who were treated with hypothermia. Helium was administrated in a 1:1 mix with oxygen for 3 h. A safety committee reviewed all ventilation problems, complications and causes of mortality.
Results: Helium ventilation was started 4:59 ± 0:52 (mean ± SD) h after circulatory arrest. In one patient, helium ventilation was discontinued prematurely due to oxygenation problems. This was caused by pre-existing pulmonary oedema, and imposed limitations to PEEP and FiO_2 by the study protocol, rather than the use of 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 the use of helium occurred during the three hours of administration.

Introduction

Out of hospital cardiac arrest (OHCA) 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 outcome.[2,3] Circulatory arrest and subsequent return of circulation leads to ischaemia reperfusion injury of the whole body and is particularly injurious to the brain and myocardium.[4,5] Brain injury is the major cause of mortality and morbidity after cardiac arrest.[6] 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 target temperature management.[7–10] Despite this therapy, outcome results are disappointing and therapies to further reduce ischaemia reperfusion injury after OHCA are needed.

Helium reduces ischaemia reperfusion injury to the heart and the brain in animal models, suggesting that helium might be capable of reducing neurological and myocardial injury in patients after OHCA.[11–17] However no clinical studies in this field have been done yet. Recently we demonstrated that helium induces preconditioning in healthy volunteers, thereby protecting against endothelial

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☆☆ This study was performed at the Academic Medical Center, University of Amsterdam, Netherlands.
★ The study was registered with the Dutch Trial Registry (www.trialregister.nl), NTR2257, on 24 March 2010.
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dysfunction after regional forearm ischaemia.[18] Clinically, helium is used to ventilate both adults and children with severe obstructive pulmonary disease and helium inhalation is generally considered to be safe.[19] 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 OHCA.

Methods

This was an open-label single arm intervention study, performed in the mixed surgical and medical ICU of the Academic Medical Centre, Amsterdam, the Netherlands. The study was approved by the 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. Patients were included after obtaining informed consent from their legal representative.

Inclusion criteria were admissioned after witnessed OHCA, with the first registered rhythm being ventricular fibrillation (VF) or tachycardia (VT) and treatment with mild hypothermia (target temperature 33 °C). Return of spontaneous circulation (ROSC) had to occur within 30 min and helium ventilation had to be started within 6 h after cardiac arrest. Exclusion criteria were oxygenation problems (necessitating a FiO_2 > 50% and >10 cmH_2O positive end expiratory pressure [PEEP]), neurological deficits or severe disability before cardiac arrest, comorbidities with a life expectancy of less than 6 months and pregnancy. The described ventilation settings were limits during the study-protocol as well.

Study procedures

After inclusion, helium ventilation was initiated as soon as possible. Helium was administered using a heliox compatible Servo-I ventilator (Maquet, Netherlands), which was calibrated to accurately measure tidal volumes when using heliox. Helium was supplied from a pressurised cylinder containing 1780 L heliox (Heliox21, BOC Ltd., UK), as a 79/21 helium/oxygen mixture, and was mixed in the ventilator with oxygen to obtain an final gas mix of 50% helium and 50% oxygen. Helium ventilation was done in pressure control mode, which was the standard ventilation mode in our ICU, peak pressure was set to achieve a tidal volume of 6 ml/kg ideal body weight, with 5–10 cmH_2O of PEEP and the respiratory frequency was controlled to maintain a pCO_2 of 4.5–5.5 kPa and a pH of 7.35–7.45 (alpha-stat). A pO_2 of ≥10 kPa and a saturation of ≥95% were aimed for. After switching to helium, a setup period with repeated blood gas analyses was used to reach the target values for pCO_2 and pH. When these measurements were within the target values helium ventilation was continued for a 3-h period. Since the objective of this study was to investigate the safety and feasibility, and not the effectiveness, helium ventilation was stopped if the cylinder was empty before the end of the 3-h 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 haemodynamic 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 h. Serum samples for analysis of neuro specific enolase (NSE) levels were drawn 24 and 48 h after admission. NSE serum samples were centrifuged and stored at −80 °C until analysis by immunoassay (kit for ELECSYS, Roche).

Table 1
Baseline characteristics.

	Patients (25)
Male sex	20 (80%)
Age (years)	64.8 ± 12.1
BMI[a] (kg/m^2)	27.4 ± 4.8
SAPS II score[b]	53.6 ± 18.6
APACHE II score[c]	20.0 ± 8.6
Comorbidity cardiovascular disease	14 (56%)
Malignancy	4 (16%)
Cause of OHCA[d] Acute infarction	17 (68%)
Chronic infarction	4 (16%)
Structural heart disease	3 (12%)
Unknown	1 (4%)
Time to 1st shock (min)	8 ± 7
Time to ROSC[e] (min)	16 ± 7
CAG[f],	20 (80%)
PCI[g]	15 (60%)
IABP[h] or impella	9 (36%)
Inotropics or vasopressors	12 (48%)

[a] Body Mass Index.
[b] Simplified acute physiology score II.
[c] Acute physiology and chronic health evaluation II.
[d] Out-of-hospital cardiac arrest.
[e] Return of spontaneous circulation.
[f] Coronary angiography.
[g] Percutaneous coronary intervention.
[h] Intra-aortic balloon pump.

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).[20] 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 (FiO_2 50% and ≤10 cmH_2O 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 independent intensive care physician, anaesthesiologist and 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 that is used in similar studies.[21,22]

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.

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