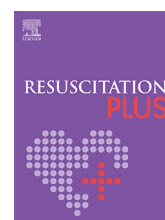


Available online at www.sciencedirect.com

Resuscitation Plus

journal homepage: www.elsevier.com/locate/resuscitation-plus

Protocol paper

CardioPulmonary resuscitation with Argon (CPAr): A protocol for a randomised controlled multicentre clinical trial



Giuseppe Ristagno^{a,b,*}, Lidia Staszewsky^c, Giulia Merigo^{a,b}, Aurora Magliocca^a, Alberto Cucino^d, Jennifer Meessen^c, Francesca Fumagalli^c, Matteo Pozzi^{e,f}, Alessandro Galazzi^g, Claudio Sandroni^{h,i}, Marco Meneguzzi^j, Anna Marangone^j, Chiara Robba^{k,l}, Erik Roman-Pognuz^m, Giovanni Salatiⁿ, Edoardo Picetti^o, Deborah Novelli^c, Giacomo Bellani^{d,p}, Mauro Panigada^b, Lars Wik^{q,r,s}, Silvio Garattini^t, Giuseppe Foti^{e,f}, Massimo Antonelli^{h,i}, Elisa Zanier^c, Giacomo Grasselli^{a,b}, Roberto Latini^c, CPAr Study group[#]

Abstract

Aims: The CardioPulmonary resuscitation with Argon (CPAr) trial evaluates the clinical neuroprotective efficacy and safety of post-resuscitation ventilation with a 70/30 argon/oxygen (Ar/O₂) gas mixture compared to standard care ventilation with 30% O₂ in unconscious adults resuscitated from out-of-hospital cardiac arrest (OHCA).

Methods: CPAr is an allocation-concealed, single-blinded, multi-centre, phase II, pre-marketing, randomised controlled trial (RCT). The study aims to recruit 120 patients across tertiary intensive care units (ICUs) in Italy. Eligible participants are unconscious adult OHCA survivors with a shockable presenting rhythm. Upon ICU admission, patients are individually randomised in a 1:1 ratio to receive either 4-h ventilation with 70/30 Ar/O₂ via an experimental ventilator, or standard ICU ventilation with 30% O₂. All patients receive guideline-based post-resuscitation care. Inclusion is conducted under a deferred consent model, with consent obtained from patients or legal representatives once clinically appropriate.

The primary clinical efficacy outcome is serum neuron-specific enolase (NSE) concentration at 48 h, as a surrogate marker of neurological injury. Secondary outcomes include markers of myocardial and multiorgan injury, neuroimaging signs of brain injury, survival, and neurological recovery (Cerebral Performance Category, CPC) up to 6 months. Safety outcomes include the incidence, timing, and duration of O₂ desaturation requiring discontinuation of Ar, and haemodynamic adverse events. Patients are followed up to 6 months, with outcome assessment at ICU/hospital discharge, 1- and 6-months post-CA. A centralized plasma and serum biobank will support future mechanistic analyses.

Conclusion: CPAr trial is the first RCT to assess the efficacy and safety of Ar ventilation in humans following OHCA and may inform future neuroprotective strategies in post-resuscitation care.

Trial registration: EudraCT-No.: 2018-003047-32; CTIS code: 2024-516864-27-00; [ClinicalTrials.gov](https://clinicaltrials.gov) identifier: NCT05482945.

Keywords: Cardiac arrest, Argon, Neuroprotection, Inhaled gases, Clinical trial protocol

* Corresponding author at: Department of Pathophysiology and Transplantation, University of Milan, Italy, Department of Anaesthesiology, Intensive Care and Emergency, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy, Via Della Commenda 16, 20122 Milan, Italy.

E-mail address: gristag@gmail.com (G. Ristagno).

[#] The members of the 'CPAr Study group Collaborators' are listed in Acknowledgments section at the end of the article.

<https://doi.org/10.1016/j.resplu.2025.101096>

Received 27 July 2025; Received in revised form 5 September 2025; Accepted 7 September 2025

Introduction

Argon (Ar), the most abundant noble gas in the atmosphere, comprising 0.93 % of air, has long been considered chemically inert.^{1,2} However, accumulating evidence has challenged this notion, demonstrating that Ar is not an inert gas but may exert biological effects.³ Indeed, preclinical studies have shown that Ar inhalation can reduce neurological and myocardial damage following hypoxic-ischemic insults, including cardiac arrest (CA).^{4,5} These effects have been observed using inspiratory Ar concentrations ranging from 20 % to 80 % in oxygen (O₂). Overall, Ar exposure resulted in reduced infarct size, less cell death, and faster neurological recovery in animals.^{6–13} A recent systematic review summarised data from 60 experimental studies and confirmed Ar ability to improve cell survival, reduce neuroinflammation, and enhance neurological and functional recovery, across various models and ischaemic injuries.⁵ Despite safety not being a primary endpoint, no studies reported adverse outcomes after Ar inhalation.^{6–11,13,15–20}

Since the 1960s, Ar has also been used in clinical research to measure lung volumes,^{21–23} estimate cardiac output,^{24,25} and assess myocardial blood flow.²⁶ Although these exposures were brief, they did not suggest adverse effects. Longer exposures under normoxic and hyperbaric conditions, such as in diving studies, have further anticipated its safety in humans.^{27,28}

Ar appears to exert its protective effect through anti-apoptotic mechanisms, modulating the molecular pathways involved in cell survival. It prevents cell death by upregulating the extracellular signal-regulated kinase 1/2 and phosphatidylinositol 3-kinase-AKT pathways and activates the toll-like receptor 2 and 4, which reduce caspase-3 activity stimulating downstream effectors, involved in the production of pro-inflammatory cytokines, growth factors, and cell survival.^{4,5} Ar also possesses O₂ like properties, which could partially restore mitochondrial respiratory enzyme activity.

Particularly promising results have emerged from CA animal studies, in which post-resuscitation ventilation with Ar/O₂ mixtures improved neurological outcomes and reduced brain injury.^{4–14} To date, seven preclinical studies have tested Ar ventilation after CA, five in rats^{6,8–11} and two in swine.^{7,13} All demonstrated better neurological recovery and less brain damage with Ar ventilation compared to controls. In rats, a 70/30-Ar/O₂ mixture administered for 1 h post-resuscitation improved both functional and histological outcomes.^{8,9} Swine models confirmed a dose-dependent effect across different no-flow durations and Ar concentrations, with benefits observed in neurologic scores, circulating biomarkers of brain injury, and brain histology.¹³ A trend toward myocardial preservation was also noted.^{7,13}

The CardioPulmonary resuscitation with Argon (CPAr) trial is the first study evaluating the efficacy and safety of Ar ventilation in adult unconscious patients resuscitated from out-of-hospital cardiac arrest (OHCA) and admitted to intensive care units (ICUs).

Methods

CPAr is a non-profit, investigator-initiated, allocation-concealed, single-blinded, multi-centre, phase II, pre-marketing superiority randomized controlled trial (RCT).

The study protocol was developed by the trial investigators of the Steering Committee in accordance with national legislations, the declaration of Helsinki²⁹ and the International Council for Harmonisation (ICH) guideline for good clinical practice. This protocol manuscript was written in concordance with the SPIRIT 2025 for RCTs (checklist in the [Supplementary Materials](#)).³⁰ Administrative details are in [Table 1](#).

Ethical approval was obtained from the Agenzia Italiana del Farmaco and the Regional Ethics Committee “Lombardia 3” (approval. 0027585-04/03/2025-AIFA-AIFA_USC-P). The trial is currently recruiting across seven tertiary ICUs in Italy, with two additional sites in the process of initiating recruitment. A full list of participating centres is available at clinicaltrials.gov (NCT05482945).

CPAr was initially designed as a phase I–II study, to assess the safety of post-resuscitation Ar treatment. Primary endpoints in the initial protocol (V2.0_05/12/2020, [Supplementary Materials](#)) included O₂ saturation and treatment-related haemodynamic events, while secondary endpoints evaluated Ar-related biological activity. Following the enrolment of the first 30 patients across three phase I–certified ICUs, safety data were reviewed by the Data Safety Monitoring Board (DSMB). The DSMB concluded that the data provided exhaustive evidence of the treatment safety and unanimously recommended continuation of the study as a phase II trial, maintaining the study protocol in all its aspects. Hence, the protocol was amended to the current version (V4.0_16/10/2024, [Supplementary Materials](#)) to increase the sample size to 120 patients, with a focus on evaluating the efficacy of Ar treatment, while continuing to monitor safety as a secondary outcome.

The first patient was recruited on 30 May 2022, and the enrolment phase is expected to last four years, followed by another 6-month of follow-up. The trial will be reported in accordance with the CONSORT guidelines for RCTs.³¹

Trial objectives

The primary objective is to evaluate the efficacy of a 4-hr post-resuscitation ventilation using a 70/30-Ar/O₂ gas mixture, delivered via an experimental ventilator, in reducing neurological injury, as measured by serum neuron-specific enolase (NSE) levels, in unconscious adult patients resuscitated from OHCA.

Secondary objectives include: assessing the effects of Ar ventilation on myocardial injury, multiorgan function, survival, and neurological outcome; and providing information on the safety of the experimental Ar ventilation.

Eligibility criteria

Consecutive unconscious adult patients resuscitated from OHCA with a presenting shockable rhythm and admitted to one of the participating ICUs are screened for study eligibility. Inclusion and exclusion criteria, detailed in [Fig. 1](#), are verified by the attending physician and confirmed by the local investigator.

The eligibility criteria are intentionally stringent, reflecting the initial study design as a phase 1–2 safety trial of a treatment never administered to humans. To minimize confounding factors in the assessment of Ar's safety, enrolment is restricted to patients with shockable rhythms and limited CPR duration, representing a population more likely to achieve favourable outcomes. In accordance with national regulatory requirements, women under the age of 50 years

Table 1 – Administrative information.

Title	CardioPulmonary resuscitation with Argon (CPAr): A prospective multicentre randomised interventional phase II trial protocol
Trial registration	EudraCT-No.: 2018-003047-32; CTIS code: 2024-516864-27-00; ClinicalTrial.gov Identifier: NCT05482945
Protocol version	Version 4.0 – 16 October 2024
Funding	Italian Ministry of Health, Ricerca Finalizzata, grant agreement No. RF-2019-12371416; Società Italiana Acetilene e Derivati S.I.A.D., spa, Bergamo, Italy
Author details	Giuseppe Ristagno,^{a,b} Lidia Staszewsky,^c Giulia Merigo,^{a,b} Aurora Magliocca,^a Alberto Cucino,^d Jennifer Meessen,^c Francesca Fumagalli,^c Matteo Pozzi,^{e,f} Alessandro Galazzi,^g Claudio Sandroni,^{h,i} Marco Meneguzzi,^j Anna Marangone,^j Chiara Robba,^{k,l} Erik Roman-Pognuz,^m Giovanni Salati,ⁿ Edoardo Picetti,^o Deborah Novelli,^c Giacomo Bellani,^{d,p} Mauro Panigada,^b Lars Wik,^{q,r,s} Silvio Garattini,^t Giuseppe Foti,^{e,f} Massimo Antonelli,^{h,i} Elisa Zanier,^c Giacomo Grasselli,^a Roberto Latini.^c ^a Department of Pathophysiology and Transplantation, University of Milan, Milan, Italy ^b Department of Anaesthesiology, Intensive Care and Emergency, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy ^c Department of Acute Brain and Cardiovascular Injury, Istituto di Ricerche Farmacologiche Mario Negri IRCCS, Milan, Italy ^d Anaesthesia and Intensive Care 1, Santa Chiara Hospital, Azienda Provinciale per i Servizi Sanitari (APSS), Trento, Italy ^e School of Medicine and Surgery, University of Milano Bicocca, Monza, Italy ^f Department of Emergency and Intensive Care, Fondazione IRCSS San Gerardo dei Tintori, Monza, Italy ^g Department of Medicine and Surgery, LUM University, Casamassima (Bari), Italy ^h Department of Intensive Care, Emergency Medicine and Anaesthesiology, Fondazione Policlinico Universitario "Agostino Gemelli"-IRCCS, Rome, Italy ⁱ Institute of Anaesthesiology and Intensive Care Medicine, Università Cattolica del Sacro Cuore, Rome, Italy ^j Department of Anaesthesia and Intensive Care, Pordenone Hospital, Azienda Sanitaria Friuli Occidentale, Italy ^k IRCCS Policlinico San Martino, Genoa, Italy ^l Department of Surgical Sciences and Integrated Diagnostics, University of Genoa, Genoa, Italy ^m Department of Medical Science, University of Trieste, Trieste, Italy ⁿ UOC Anestesia e Rianimazione, IRCCS Arcispedale Santa Maria Nuova, Reggio Emilia, Italy ^o Department of Anaesthesia and Intensive Care, Parma University Hospital, Parma, Italy ^p Centre for Medical Sciences, University of Trento, Trento, Italy ^q Norwegian National Advisory Unit on Prehospital Emergency Medicine, Division of Prehospital Care, Oslo University Hospital, Oslo, Norway ^r Air Ambulance Department, Doctor Respond Car 119, Division of Prehospital Care, Oslo University Hospital, Oslo, Norway ^s Department of Anaesthesiology, Division of Emergency Medicine, Oslo University Hospital, Oslo, Norway ^t Istituto di Ricerche Farmacologiche Mario Negri IRCCS, Milan, Italy
Steering Committee	Giuseppe Ristagno, Roberto Latini, Giuseppe Foti, Alberto Cucino, Giacomo Grasselli, Francesca Fumagalli, Lars Wik, Aurora Magliocca, Silvio Garattini, Elisa Zanier
Data Safety Monitoring Board (DSMB)	Aldo Pietro Maggioni,^u Federico Semeraro,^v Gianni Tognoni^w (chair) ^u Centro Studi ANMCO, Florence, Italy ^v Ospedale Maggiore – AUSL di Bologna, Italy ^w Centro Nazionale di Coordinamento dei Comitati Etici (CNCCE), Italy
Event Committee	Andrea Finzi,^x Roberto Fumagalli,^{y,z} Antonio Pesenti,^{aa} ^x Istituto di Ricerche Farmacologiche Mario Negri IRCCS, Milan, Italy ^y Department of Anaesthesiology, ASST Grande Ospedale Metropolitano Niguarda, Milan, Italy ^z School of Medicine and Surgery, University of Milano Bicocca, Monza, Italy ^{aa} Department of Pathophysiology and Transplantation, University of Milan, Milan, Italy
Name and contact information for the trial sponsor	Istituto di Ricerche Farmacologiche Mario Negri IRCCS, Milan, Italy Via Mario Negri 2, 20156, Milan, Italy
Role of Sponsor	Sponsor has provided support for data collection, management and analysis, ethical submission, data agreement transfers with all participating centres, clinical monitoring of the participating centres, and plasma biobanking.

are excluded to avoid enrolling potentially fertile individuals, given the unknown effects of Ar exposure on pregnancy and newborn outcomes.

Study interventions

Upon ICU admission, unconscious patients receive standard post-CA care following the European Resuscitation Council/European Society of Intensive Care Medicine international guidelines and local protocols.^{32–34} Eligible patients are then randomised to receive one of the following 4-hr interventions: ventilation with a gas mixture of 70/30-Ar/O₂ using an experimental ventilator (Bellavista 1000 IMT, Switzerland) (*interventional arm*); or ventilation with an inspiratory oxygen fraction (FiO₂) of 30 % using the standard ventilators available at enrolling ICUs (*control arm*). Ventilation mode and other settings, aside from the specific study intervention, are left to the discretion of the treating clinicians based on local practices and clinical judgment. The study design is outlined in Fig. 1, and the participant timeline is reported in Fig. 2.

Due to the fixed FiO₂ used in both study arms, only patients who demonstrate adequate arterial oxygenation (SaO₂ ≥ 94 %) on 30 % FiO₂ prior to randomisation are eligible for enrolment. If, during Ar ventilation, a desaturation event occurs, defined as peripheral oxygen saturation (SpO₂) < 90 % (and recruitment manoeuvres fail to restore adequate oxygenation), the Ar mixture is discontinued and FiO₂ is increased. Once SpO₂ stability is regained on 30 % FiO₂, Ar ventilation may resume to conclude the 4-hr treatment, with the total time exposure not exceeding 8-hr post-resuscitation. SpO₂ evo-

lution is closely monitored in both groups for comparative safety analysis.

Patients in the interventional group are ventilated using an experimental ventilator certified for use with Ar/O₂ mixtures in the context of this pre-marketing clinical investigation. The gas mixture is supplied from certified tanks (SIAD S.p.A.-UNI EN ISO 9001:2015).

The selection of the 70/30-Ar/O₂ mixture is based on extensive preclinical evidence demonstrating neuroprotective effects associated with high Ar concentrations without any signs of toxicity.^{6–10,16–19,35–42} We conducted a dose-comparison study in a swine CA model, comparing 50 % vs. 70 % Ar in O₂, which showed a clear dose-dependent neuroprotective effect.¹³ Additionally, the safety of the 4-hr 70/30-Ar/O₂ ventilation using the experimental Bellavista ventilator was confirmed in healthy anaesthetised pigs, with no significant changes noted in cardiac, neurologic, hepatic, renal, respiratory, and haematologic parameters.⁴³ From a toxicological standpoint, Ar is regarded as safe for human exposure.^{21–28,44–46}

The control arm, employing ventilation with 30 % FiO₂ in air, was selected to isolate the effect of Ar while keeping O₂ concentrations consistent across groups.

Other than the fixed FiO₂ setting, no limitations are imposed on concomitant treatments or interventions during the study period. To avoid potential interactions with other investigational therapies, patients enrolled in CPAr are not permitted to participate in other interventional trials during their study inclusion period (i.e. up to completion of the 6-month follow-up).

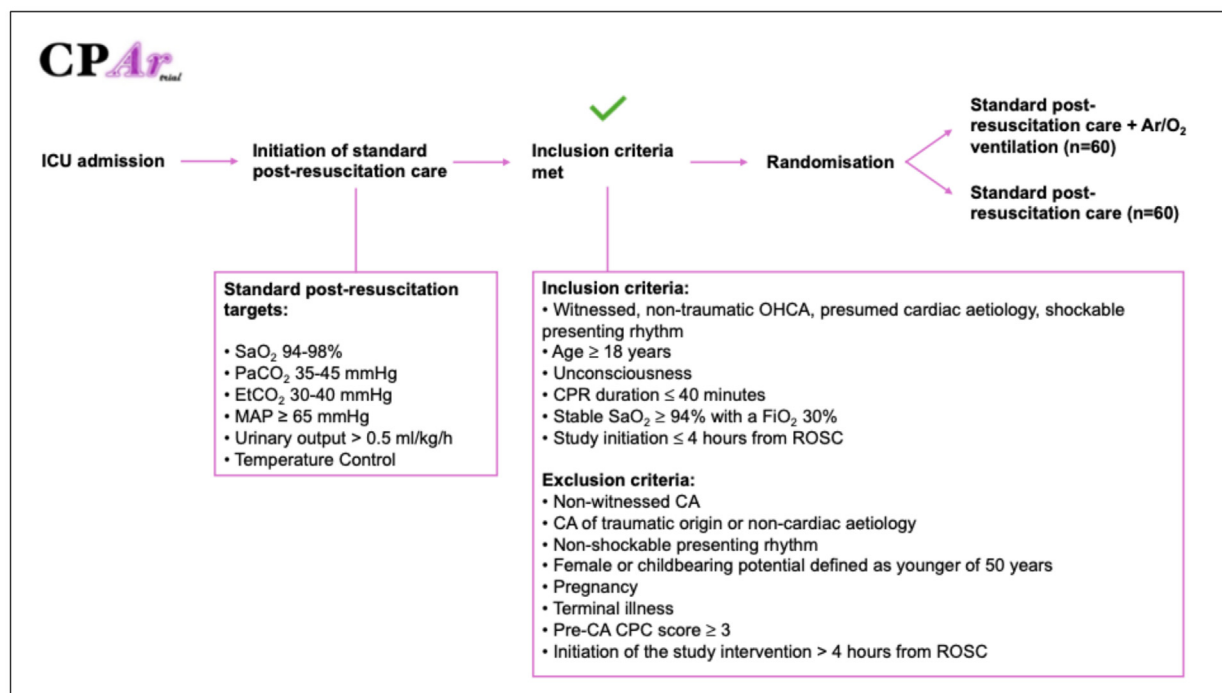


Fig. 1 – Inclusion and randomization flow diagram. CA, cardiac arrest; CPC, cerebral performance category score; CPR, cardiopulmonary resuscitation; EtCO₂, end-tidal carbon dioxide; FiO₂, inspiratory oxygen fraction; MAP, mean arterial pressure; PaCO₂, arterial partial pressure of carbon dioxide; OHCA, out-of-hospital cardiac arrest; ROSC, return of spontaneous circulation; SaO₂, arterial oxygen saturation.

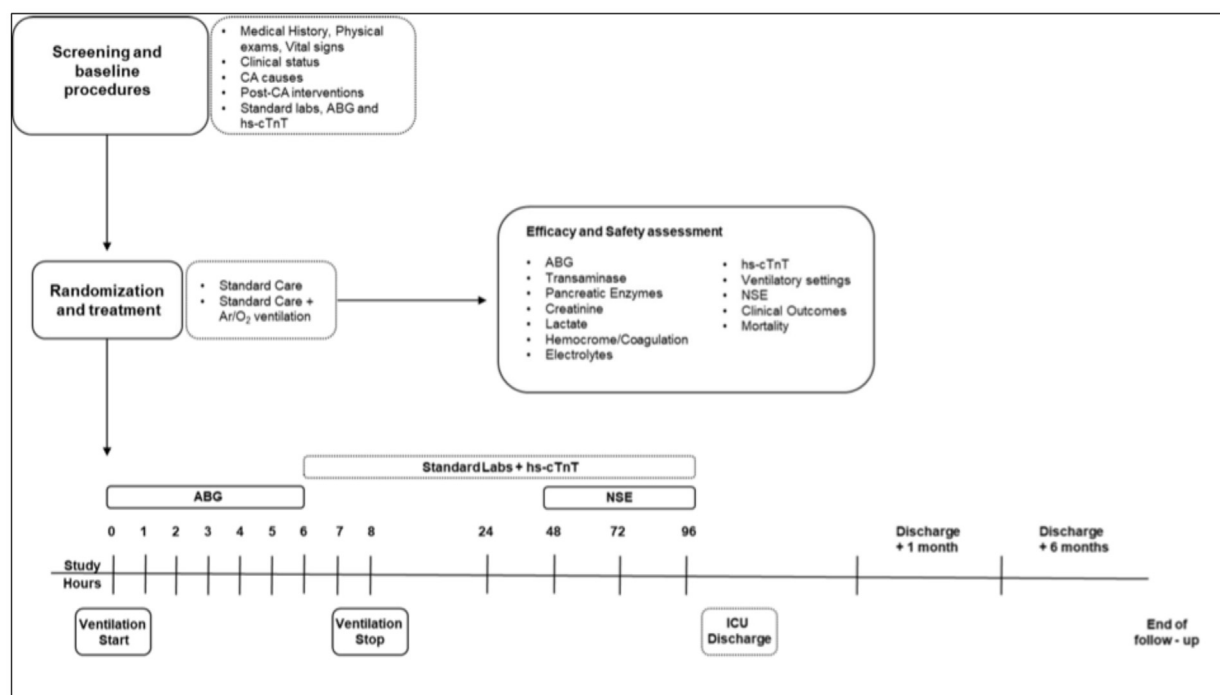


Fig. 2 – Study flow diagram. ABG, arterial blood gas; CA, cardiac arrest; hs-cTnT, high sensitivity cardiac troponin T; ICU, intensive care unit; NSE, neuron-specific enolase.

Trial outcomes

The primary clinical outcome is the serum concentration of NSE at 48 h post-CA, used as a surrogate marker for neuronal injury to assess the neuroprotective effect of Ar ventilation.

Secondary clinical outcomes are grouped as follows:

- A) Activity outcomes: circulating biomarkers of organ preservation, including levels of high-sensitivity cardiac troponin T, liver transaminases, pancreatic enzymes, creatinine, haemochrome, and coagulation markers (i.e. prothrombin time, international normalized ratio, activated partial thromboplastin time, fibrinogen, D-dimer) measured at 6, 24, 48, 72, and 96 h post-CA and NSE at 48, 72, and 96 h post-CA; cerebral magnetic resonance imaging between days 5–7 post-CA in patients who remain comatose; survival and neurological recovery, assessed using the cerebral performance category (CPC) score at ICU discharge, hospital discharge, 1 and 6 months post-CA.
- B) Safety outcomes: incidence, timing, and duration of Ar ventilation interruptions due to O₂ desaturation; incidence of haemodynamic adverse events potentially attributable to Ar, such as arterial hypotension unresponsive to fluids and/or vasoactive drugs.
- C) Explorative outcome: establishment of a representative biobank of serial plasma and serum samples for future analyses of circulating biomarkers of organ damage and inflammation, such as neurofilament light chain, interleukin-6, and kynurenic pathway metabolites.

Participant recruitment and randomisation

Upon ICU admission, eligible patients are randomly allocated 1:1 to either the intervention or control arm, via a centrally generated randomisation plan, managed by trial coordinator. More specifically, a block randomisation with variable block size and stratified by centre is adopted. Randomisation is performed directly by the site investigator using a secure web-based case report form (eCRF) Research Electronic Data Capture—REDCap software.

Blinding

Due to the visible differences in ventilator type and the use of Ar/O₂ tanks, ICU personnel cannot be blinded to group assignment. However, outcome assessors remain blinded to treatment allocation. Patients also remain unaware of their group assignment until completion of the follow-up.

Consent, data collection and follow-up

Because CPAr includes unconscious patients in a time-critical emergency setting, enrolment is conducted under a deferred consent model, in accordance with European (REGULATION (EU) No 536/2014 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC) and national legislation (“Linee di Indirizzo per la raccolta del consenso informato alla partecipazione a sperimentazioni cliniche”, Appendix 2, Centro Coordinamento Nazionale dei Comitati Etici – CCNCE, Agenzia Italiana del Farmaco – AIFA) and approved by the ethics committee. Once consciousness is regained, patients are briefed about their

inclusion in the trial and asked to provide written informed consent for the use of personal data and biological samples. For patients who are unable to provide consent, it is sought from a legally authorised representative. Patients can withdraw consent at any time during the study. A patient is considered discontinued from the study and her/his data removed, only if she/he withdraws the consent.

Patients are intensively monitored during the 4-hr intervention for adverse events, including hourly arterial blood gas analysis and haemodynamic measurements. Neuroprognostication is performed at 72–96 h after CA, with survival and CPC score documented at ICU and hospital discharge. Follow-up includes telephone interviews at 1- and 6-months post-CA. Table 2 summarises the data collection at key timepoints.

Data collected at ICU admission include: demographics; cause and characteristics of the OHCA (i.e., witnessed/non-witnessed; bystander CPR; time to CPR, time to return of spontaneous circulation (ROSC); number of defibrillations; adrenaline doses); post-ROSC interventions (i.e., coronary angiography; percutaneous coronary intervention, haemodynamic support (i.e. use of vasoactive drugs or mechanical support such as intra-aortic balloon counter pulsation), temperature control); pre-existing pathological conditions; Sequential Organ Failure Assessment (SOFA) score.

Subsequent data are recorded throughout the ICU stay, as part of routine post-CA care. Blood sampling is performed at ICU admission and at 6, 24, 48, 72, and 96 h later. Blood samples for the biobank are processed and centrally stored at the Sponsor's certified biobank (ISO 90001:2015).

The eCRF system is designed with predefined data ranges and logic checks to ensure high data quality. Database management and quality control are overseen by the Sponsor, which complies with all the technical obligations of a certified clinical research organization. All procedures conform to applicable data protection laws, under the supervision of the data protection officer.

All participating sites are provided with comprehensive study materials; prior to site activation, training is conducted for local investigators, research nurses, and ICU staff to ensure full understanding of the need for this study, protocol adherence, correct implementation of procedures, and the importance for active recruitment. Pre-enrolment training on the use of the experimental ventilator is mandatory and coordinated by the site principal investigator.

Sample size and statistical analyses

The primary outcome is the severity of neurological injury, assessed by NSE concentration at 48 h after CA. Based on prior cohort studies, the expected mean NSE concentration at 48 h is approximately $17 \pm 20 \mu\text{g/L}$.^{47–49} In addition, in previous small RCTs,^{48–51} post-ROSC ventilatory treatments resulted in >50 % decrease of NSE values at 48 h. Thus, thirty-nine patients in each arm would provide a power of 80 %, with the significance set at 0.05, to detect a 50 % difference in NSE. Accounting for potential attrition due to early death or loss to follow-up, the target enrolment was increased by 50 %. Thus, the total sample size is set at 120 patients.

The primary statistical analysis will be conducted on an intention-to-treat (ITT) basis, including all patients randomised to either intervention or control.

Baseline characteristics and other relevant variables will be summarised using descriptive statistics. The primary outcome, NSE concentration, will be evaluated using the Mann–Whitney test. If, despite randomization, any imbalances in baseline characteristics are identified between the two treatment groups, linear regression models

including the treatment group and the relevant baseline characteristics will be employed to adjust for these differences.

The secondary efficacy outcomes will be analysed in a similar way to the primary outcome. For survival analyses, the Cox proportional hazard model will be used to determine time-to-event hazard ratios and 95 % confidence intervals.

To evaluate safety outcomes, the incidence, timing, and duration of interruptions in Ar ventilation due to O₂ desaturation will be summarised using descriptive statistics and compared to the SpO₂ evolution in the control arm. Haemodynamic adverse events will be compared between groups using descriptive approaches, reporting incidence and severity.

No per-protocol analysis will be performed, as no crossover between study arms is anticipated. No imputation will be performed for missing outcome data; analyses will be based on available data only.

Harms

The collection, assessment and reporting of safety data are conducted in accordance with the Regulation (EU) No 536/2014 of the European Parliament and of the Council (16/04/2014) on clinical trials on medicinal products for human use.

All enrolled patients are closely monitored for the occurrence of adverse events (AEs) throughout the study period. Monitoring includes clinical observations and laboratory investigations, with AEs evaluated for seriousness, severity, and causal relationship to the investigational treatment. The results of this assessment inform safety reporting to investigators, independent event committees (EC), and regulatory authorities. An AE which leads to death, is life-threatening, causes in persistent or significant disability or incapacity, requires hospitalisation or prolongation of current hospitalisation, is classified as serious SAE. Given the critical condition of patients resuscitated from CA and admitted to ICU, a range of untoward medical events is anticipated as part of standard care. On this basis, only SAEs that are possibly, probably, or definitely related to the trial intervention, and are not already collected as clinical outcomes (i.e. death),^{52,53} are recorded as reportable events.

Each participating site is also responsible for collecting data on any device deficiencies and adverse device effects (ADEs) related to the experimental ventilator. This includes both serious and non-serious ADEs, in accordance with Regulation (EU) 2017/745 on medical devices. Those meeting the criteria for seriousness are categorised as serious ADEs (SADEs).

The EC conducts blinded external reviews of reported AEs and ventilator metrics to determine whether events are attributable to the device or to the Ar/O₂ gas mixture.

Monitoring

The trial is externally monitored by the Sponsor's monitoring office. Source data verification is performed according to a monitoring plan made available to the trial monitors. Monitoring visits are conducted at each participating centre in compliance with national regulatory requirements, to ensure protection of patients' rights and safety, adherence to the trial protocol, accuracy and completeness of data collection, proper documentation, reporting of outcomes, management and storage of blood samples. Findings from each visit are documented in a monitoring report.

The independent DSMB oversees the interim analyses for safety, futility, and efficacy, allowing the EC and Steering Committee to remain blinded to study outcomes. During the initial phase (phase

Table 2 – Schedule of enrolment, interventions, and assessments.

Study Period											
	Screening	Baseline	Hourly (first 5 h)	6 h	24 h	48 h	72 h	96 h	ICU/Hospital discharge	Follow-up 1-month	Follow-up 6-months
Informed consent									X		
Subject identification	X										
Eligibility	X										
Demographic		X									
Cause of OHCA		X									
Characteristics of OHCA		X									
Medical history		X									
Study intervention		X	X	X	X	X	X	X	X		
Clinical exam		X			X	X	X	X			
Vital signs		X	X	X	X	X	X	X			
ABG		X	X	X	X	X	X	X			
Ventilatory settings		X	X	X							
SAPS II score					X						
SOFA score						X	X	X			
Lactate		X	X	X	X	X	X	X			
hs-cTnT		X		X	X	X	X	X			
Creatinine		X		X	X	X	X	X			
Transaminase		X		X	X	X	X	X			
Pancreatic enzymes		X		X	X	X	X	X			
Electrolytes		X		X	X	X	X	X			
Haemachrome		X		X	X	X	X	X			
Coagulation		X		X	X	X	X	X			
Biobank blood samples		X		X	X	X	X	X			
NSE						X	X	X			
cMRI								Xa			
SSEP						Xa	Xa	Xa			
EEG						Xa	Xa	Xa			
CPC score									X	X	X
Survival									X	X	X

CA: cardiac arrest; SAPSII: simplified acute physiology score; SOFA: sequential organ failure assessment; OHCA: out-of-hospital cardiac arrest; ABG: arterial blood gas; hs-cTnT: high sensitivity cardiac troponin T; NSE: neuron-specific enolase; cMRI: cerebral magnetic resonance imaging; SSEP: somatosensory evoked potential; EEG, electroencephalography; CPC: cerebral performance category; Xa: specific time point or when clinically relevant according to local practice and ERC/ESICM guidelines.

I–II) of the trial, to ensure patient safety, the DSMB performed continuous monitoring of O₂ desaturation and haemodynamic events (i.e. evaluating data for each 8 patients randomised), assessing any significant differences in safety outcomes between the treatment and control groups to inform potential stopping decisions. An independent statistician, who had full database access, reported these data to the DSMB. Following each analysis, the DSMB issued formal recommendations, and a report was sent to the Steering Committee. No additional interim analyses are planned till the end of the enrolment period. The members of the DSMB have been appointed by the Steering Committee of the CPAr trial, to include medical and biostatistical competences, as well as expertise in clinical trials. The DSMB members are individuals free of competing financial, scientific, or regulatory conflicts of interest (more details on DSMB composition, roles, evaluating process and reporting can be found in [Table 1](#) and in the DSMB charter attached as [Supplementary Materials](#)).

Confidentiality

Pseudonymised data are collected on the eCRF, while transcoding registries are kept at local sites. Statistical analysis will be performed on fully anonymised data. The DSMB and regulatory authorities have access to the database for oversight purposes.

Ancillary and post-trial care

The sponsor provides a clinical trial insurance, compliant with local laws and regulatory requirements, covering any patients' harm directly attributable to trial participation.

Patient and public involvement, data availability, dissemination policy and authorship

No patients were directly involved in setting the research questions, determining the outcome measures, or designing the study protocol. However, patient and public involvement was facilitated through national press releases advertising the study. This approach allows readers to assess the relevance and usefulness of the study for end users and helps boost recruitment.

A fully anonymised dataset generated during this study will be available from the corresponding author upon reasonable request.

At the end of the outcome assessment collection, data will be analysed within three months and presented to all investigators before publication. Results will be: disseminated among healthcare professionals, patients, and policymakers; presented at national and international scientific conferences; and communicated through press releases. The main manuscript will be submitted to one of the major peer-reviewed clinical journals as open access publication.

Conclusion

Preclinical studies have consistently demonstrated the neuroprotective potential of Ar ventilation following CA. However, to date, Ar ventilation has not been tested in clinical settings involving patients resuscitated from OHCA.

The CPAr trial is a phase II and pre-marketing RCT designed to assess both the efficacy and safety of Ar inhalation in this patient population. A total of 120 unconscious resuscitated OHCA patients will be randomised to receive either 4-hr ventilation with 70/30 Ar/O₂ or 30 % O₂, alongside standard post-resuscitation care.

This trial aims to provide the first clinical evidence of Ar as a neuroprotective intervention in the context of post-CA brain injury. The

study findings could help to establish Ar ventilation as a therapeutic option in post-CA care and may pave the way for the refinement of Ar administration protocols, larger-scale RCTs, and exploration of Ar neuroprotective effects in other acute neurological conditions. Indeed, the numerous secondary outcomes and measures are exploratory in nature and intended to generate preliminary data to inform future trials. While the eligibility criteria of the trial approach prioritise safety, they inevitably limit the generalisability of the findings, particularly regarding gender representation, as women < 50-year are excluded. Nevertheless, since the average age for cardiac arrest is typically around 68 years (range 58–74),⁵⁴ the impact of this exclusion criterion on the applicability of the results is likely modest.

If proven effective, Ar ventilation has the potential to significantly improve neurological outcomes in a population with persistently high morbidity and mortality, contributing valuable insights into post-resuscitation management and critical care.

CRedit authorship contribution statement

Giuseppe Ristagno: Writing – review & editing, Writing – original draft, Investigation, Funding acquisition, Conceptualization. **Lidia Staszewsky:** Writing – original draft, Methodology, Conceptualization. **Giulia Merigo:** Project administration, Investigation. **Aurora Magliocca:** Writing – review & editing, Investigation. **Alberto Cucino:** Writing – original draft, Investigation, Conceptualization. **Jennifer Meessen:** Writing – review & editing, Project administration, Methodology, Formal analysis. **Francesca Fumagalli:** Writing – review & editing, Conceptualization. **Matteo Pozzi:** Writing – review & editing, Investigation. **Alessandro Galazzi:** Writing – review & editing, Investigation. **Claudio Sandroni:** Writing – review & editing, Investigation. **Marco Meneguzzi:** Writing – review & editing, Investigation. **Anna Marangone:** Writing – review & editing, Investigation. **Chiara Robba:** Writing – review & editing, Investigation. **Erik Roman-Pognuz:** Writing – review & editing, Investigation. **Giovanni Salati:** Writing – review & editing, Investigation. **Edoardo Picetti:** Writing – review & editing, Investigation. **Deborah Novelli:** Writing – review & editing, Supervision, Methodology. **Giacomo Bel-lani:** Writing – review & editing, Investigation. **Mauro Panigada:** Writing – review & editing, Investigation. **Lars Wik:** Writing – original draft, Methodology, Conceptualization. **Silvio Garattini:** Writing – review & editing, Conceptualization. **Giuseppe Foti:** Writing – review & editing, Investigation. **Massimo Antonelli:** Writing – review & editing, Methodology. **Elisa Zanier:** Writing – review & editing, Project administration. **Giacomo Grasselli:** Writing – review & editing, Investigation. **Roberto Latini:** Writing – original draft, Methodology, Investigation, Funding acquisition, Conceptualization. **Aldo Pietro Maggioni:** . **Federico Semeraro:** . **Gianni Tognoni:** . **Andrea Finzi:** . **Roberto Fumagalli:** . **Antonio Pesenti:** . **Enrico Nicolis:** . **Martina Colombo:** . **Claudia Fracasso:** . **Marco Gobbi:** . **Gaia Giussani:** . **Nicoletta Hellmann:** . **Sara Monfrini:** . **Silvia Maria Balosso:** . **Luciano Carlucci:** . **Antonella Vasami:** . **Silvana Castaldi:** . **Anna Preti:** . **Linda Ferrarini:** . **Giulia Antonelli Libretti:** . **Paola Roselli:** . **Chiara Abbruzzese:** . **Nicola Bottino:** . **Alessandra Rosati:** . **Ivan Silvestri:** . **Ilaria Mariani:** . **Marco Normanno:** . **Emanuele Rezoagli:** . **Paolo De Santis:** . **Nadia Todesco:** . **Tommaso Pellis:** . **Vincenzo Sagnelli:** . **Nicolo' Patroniti:** . **Denise Battaglini:** . **Francesca Gualdi:** . **Paola Manzoni:** . **Maurizio Migliari:** . **Silvia Grossi:** . **Susanna Manstretta:** . **Eleonora Bal-**

zani: . Elisabetta Macchini: . Giulia Colussi: . Lorenzo Gamberini: . Guido Tavazzi: . Simone Savastano: .

Funding

CPAr trial is funded by the Italian Ministry of Health, Ricerca Finalizzata, grant agreement No. RF-2019-12371416 and Società Italiana Acetilene e Derivati S.I.A.D., spa, Bergamo, Italy.

Declaration of competing interest

GR is member of the editorial board of Resuscitation Plus; AM is associate editor of Resuscitation Plus. All other authors declare no conflict.

Acknowledgments

Members of the CPAr Study Group:

Data Safety Monitoring Board: Aldo Pietro Maggioni^u, Federico Semeraro^v, Gianni Tognoni^w.

Event Committee: Andrea Finzi^x, Roberto Fumagalli^{y,z}, Antonio Pesenti^{aa}

Data management and analysis team: Enrico Nicolis^x, Martina Colombo^x, Claudia Fracasso^x, Marco Gobbi^x.

Clinical Monitoring team: Gaia Giussani^x, Nicoletta Hellmann^x, Sara Monfrini^x.

Pharmacovigilance team: Silvia Maria Balosso^x, Luciano Carlucci^x

Clinical trial assistance: Antonella Vasami^x

Quality control management for phase I trial: Silvana Castaldi^{ab,ac}, Anna Preti^{ac}

Site investigators: Linda Ferrarini^{ad}, Giulia Antonelli Libretti^{ad}, Paola Roselli^{ad}, Chiara Abbruzzese^{ad}, Nicola Bottino^{ad}, Alessandra Rosati^{aa,ad}, Ivan Silvestri^{aa,ad}, Ilaria Mariani^{ae}, Marco Normanno^{ae}, Emanuele Rezoagli^{z,ae}, Paolo De Santis^{af}, Nadia Todesco^{ag}, Tommaso Pellis^{ag}, Vincenzo Sagnelli^{ag}, Nicolo' Patroniti^{ah,ai}, Denise Battaglini^{ah,ai}, Francesca Gualdi^{ai}, Paola Manzoni^{aj}, Maurizio Miglian^{aj}, Silvia Grossi^{ak}, Susanna Manstretta^{al}, Eleonora Balzani^{al}, Elisabetta Macchini^{am}, Giulia Colussi^{am}, Lorenzo Gamberini^v, Guido Tavazzi^{an}, ^{ao}, Simone Savastano^{ap}

^u ANMCO Research Centre, Heart Care Foundation, Florence, Italy.

^v Department of Anaesthesia, Intensive Care and Prehospital Emergency, Ospedale Maggiore Carlo Alberto Pizzardi, Bologna, Italy.

^w Centro Nazionale di Coordinamento dei Comitati Etici (CNCCE), Italy.

^x Istituto di Ricerche Farmacologiche Mario Negri IRCCS, Milan, Italy.

^y Department of Anaesthesiology, ASST Grande Ospedale Metropolitano Niguarda, Milan, Italy.

^z School of Medicine and Surgery, University of Milano Bicocca, Monza, Italy.

^{aa} Department of Pathophysiology and Transplantation, University of Milan, Milan, Italy.

^{ab} Department of Biomedical Sciences for Health, University of Milan, Milan, Italy.

^{ac} Quality Units, Fondazione Ca' Granda Policlinico di Milano, Milan, Italy.

^{ad} Department of Emergency, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy.

^{ae} Department of Emergency and Intensive Care, Fondazione IRCCS San Gerardo Dei Tintori, Monza, Italy.

^{af} Department of Intensive Care, Emergency Medicine and Anaesthesiology, Fondazione Policlinico Universitario "Agostino Gemelli"-IRCCS, Rome, Italy.

^{ag} Department of Anaesthesia and Intensive Care, Pordenone Hospital, Azienda Sanitaria Friuli Occidentale, Italy.

^{ah} IRCCS Policlinico San Martino, Genova.

^{ai} Dipartimento di Scienze Chirurgiche Diagnostiche Integrate, Università di Genova, Italy.

^{aj} Agenzia Regionale Emergenza Urgenza – AREU, Milan, Italy.

^{ak} Department of Anaesthesia and Intensive Care, Parma University Hospital, Parma, Italy.

^{al} Anaesthesia and Intensive Care 1, Santa Chiara Hospital, Azienda Provinciale per i Servizi Sanitari (APSS), Trento, Italy.

^{am} Department of Medical Science, University of Trieste, Trieste, Italy.

^{an} Department of Clinical-Surgical, Diagnostic and Paediatric Sciences, University of Pavia, Pavia, Italy.

^{ao} Intensive Care, Fondazione Policlinico San Matteo Hospital IRCCS, Pavia, Italy.

^{ap} Division of Cardiology, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy

Appendix A. Supplementary material

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.resplu.2025.101096>.

Author details

CPAr Study group[#] ^aDepartment of Pathophysiology and Transplantation, University of Milan, Milan, Italy ^bDepartment of Anaesthesiology, Intensive Care and Emergency, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy ^cDepartment of Acute Brain and Cardiovascular Injury, Istituto di Ricerche Farmacologiche Mario Negri IRCCS, Milan, Italy ^dAnaesthesia and Intensive Care 1, Santa Chiara Hospital, Azienda Provinciale per i Servizi Sanitari (APSS), Trento, Italy ^eSchool of Medicine and Surgery, University of Milano Bicocca, Monza, Italy ^fDepartment of Emergency and Intensive Care, Fondazione IRCCS San Gerardo dei Tintori, Monza, Italy ^gDepartment of Medicine and Surgery, LUM University, Casamassima, Bari, Italy ^hDepartment of Intensive Care, Emergency Medicine and Anaesthesiology, Fondazione Policlinico Universitario "Agostino Gemelli"-IRCCS, Rome, Italy ⁱInstitute of Anaesthesiology and Intensive Care Medicine, Università Cattolica del Sacro Cuore, Rome, Italy ^jDepartment of Anaesthesia and Intensive Care, Pordenone Hospital, Azienda Sanitaria Friuli Occidentale, Italy ^kIRCCS Policlinico San Martino, Genoa, Italy ^lDepartment of Surgical Sciences and Integrated Diagnostics, University of Genoa, Genoa, Italy ^mDepartment of Medical Science, University of Trieste, Trieste, Italy ⁿUOC Anestesia e Rianimazione, IRCCS Arcispedale Santa Maria Nuova, Reggio Emilia, Italy ^oDepartment of Anaesthesia and Intensive Care, Parma University Hospital, Parma, Italy ^pCentre for

Medical Sciences, University of Trento, Trento, Italy ⁹Norwegian National Advisory Unit on Prehospital Emergency Medicine, Division of Prehospital Care, Oslo University Hospital, Oslo, Norway ¹⁰Air Ambulance Department, Doctor Respond Car 119, Division of Prehospital Care, Oslo University Hospital, Oslo, Norway ¹¹Department of Anaesthesiology, Division of Emergency Medicine, Oslo University Hospital, Oslo, Norway ¹²Istituto di Ricerche Farmacologiche Mario Negri IRCCS, Milan, Italy

REFERENCES

- Roberts MW, Mathiesen KA, Ho HS, et al. Cardiopulmonary responses to intravenous infusion of soluble and relatively insoluble gases. *Surg Endosc* 1997;11:1341–1336.
- Ulbrich F, Goebel U. The molecular pathway of argon-mediated neuroprotection. *Int J MolSci* 2016;17:E1816.
- Soldatov PE, D'iachenko AI, Pavlov BN, et al. Survival of laboratory animals in argon-containing hypoxic gaseous environments. *Aviakosm Ekol Med* 1998;32:33–7.
- Nespoli F, Redaelli S, Ruggeri L, et al. A complete review of preclinical and clinical uses of the noble gas argon: evidence of safety and protection. *Ann Card Anaesth* 2019;22:122–35.
- Merigo G, Florio G, Madotto F, et al. Treatment with inhaled Argon: a systematic review of pre-clinical and clinical studies with meta-analysis on neuroprotective effect. *EBioMedicine* 2024;103:10514.
- Brücken A, Kurnaz P, Bleilevens C, et al. Dose dependent neuroprotection of the noble gas argon after cardiac arrest in rats is not mediated by K(ATP)-channel opening. *Resuscitation* 2014;85:826–32.
- Ristagno G, Fumagalli F, Russo I, et al. Postresuscitation treatment with argon improves early neurological recovery in a porcine model of cardiac arrest. *Shock* 2014;41:72–8.
- Brücken A, Kurnaz P, Bleilevens C, et al. Delayed argon administration provides robust protection against cardiac arrest-induced neurological damage. *Neurocrit Care* 2015;22:112–20.
- Brücken A, Cizen A, Fera C, et al. Argon reduces neurohistopathological damage and preserves functional recovery after cardiac arrest in rats. *Br J Anaesth* 2013;110:i106–12.
- Zuercher P, Sprunge D, Grandgirard D, et al. A randomized trial of the effects of the noble gases helium and argon on neuroprotection in a rodent cardiac arrest model. *BMC Neurol* 2016;16:43.
- Brücken A, Bleilevens C, Föhr P, et al. Influence of argon on temperature modulation and neurological outcome in hypothermia treated rats following cardiac arrest. *Resuscitation* 2017;117:32–9.
- Moro F, Fossi F, Magliocca A, et al. Efficacy of acute administration of inhaled argon on traumatic brain injury in mice. *Br J Anaesth* 2021;126:256–64.
- Fumagalli F, Olivari D, Boccardo A, et al. Ventilation with argon improves survival with good neurological recovery after prolonged untreated cardiac arrest in pigs. *J Am Heart Assoc* 2020;9:e016494.
- Motta F, De Giorgio D, Cerrato M, et al. Postresuscitation ventilation with a mixture of argon and hydrogen reduces brain injury after cardiac arrest in a pig model. *J Am Heart Assoc* 2024;13:e033367.
- David HN, Haelewyn B, Degoulet M, et al. Ex vivo and in vivo neuroprotection induced by argon when given after an excitotoxic or ischemic insult. *PLoS One* 2012;7:e30934.
- Alderliesten T, Favie LMA, Neijzen RW, et al. Neuroprotection by argon ventilation after perinatal asphyxia: a safety study in newborn piglets. *PLoS One* 2014;9:e113575.
- Broad KD, Fierens I, Fleiss B, et al. Inhaled 45–50% argon augments hypothermic brain protection in a piglet model of perinatal asphyxia. *Neurobiol Dis* 2016;87:29–38.
- Ryang Y-M, Fahlenkamp AV, Rossaint R, et al. Neuroprotective effects of argon in an in vivo model of transient middle cerebral artery occlusion in rats. *Crit Care Med* 2011;39:1448–53.
- Pagel PS, Krolikowski JG, Shim YH, et al. Noble gases without anesthetic properties protect myocardium against infarction by activating prosurvival signaling kinases and inhibiting mitochondrial permeability transition in vivo. *Anesth Analg* 2007;105:562–9.
- Martens A, Ordies S, Vanaudenaerde BM, et al. A porcine ex vivo lung perfusion model with maximal argon exposure to attenuate ischemia-reperfusion injury. *Med Gas Res* 2017;7:28–36.
- Black AM, Hahn CE, Maynard P, et al. Measurement of lung volume by multiple indicator dilution. Differences in apparent volumes of distribution of oxygen, nitrogen and argon. *Br J Anaesth* 1984;56:289–98.
- Ozanne GM, Zinn SE, Fairley HB. Measurement of functional residual capacity during mechanical ventilation by simultaneous exchange of two insoluble gases. *Anesthesiology* 1981;54:413–47.
- McCarthy DS, Spencer R, Greene R, et al. Measurement of “closing volume” as a simple and sensitive test for early detection of small airway disease. *Am J Med* 1972;52:747–53.
- Heneghan CPH, Branthwaite MA. Non-invasive measurement of cardiac output during anaesthesia. An evaluation of the soluble gas uptake method. *Br J Anaesth* 1981;53:351–5.
- Bonde-Petersen F, Norsk P, Suzuki Y. A comparison between freon and acetylene rebreathing for measuring cardiac output. *Aviat Space Environ Med* 1980;51:1214–21.
- Kotzerke J, Glatting G, van den Hoff J, Höher M, et al. Validation of myocardial blood flow estimation with nitrogen-13 ammonia PET by the argon inert gas technique in humans. *Eur J Nucl Med* 2001;28:340–5.
- Behnke AR, Yorabrough OD. Respiratory resistance, oil-water solubility and mental effects of argon compared with helium and nitrogen. *Am J Physiol* 1939;126:409–15.
- Fowler B, Ackles KN. Narcotic effects in man of breathing 80-20 argon-oxygen and air under hyperbaric conditions. *Aerosp Med* 1972;43:1219–24.
- World Medical Association. World medical association declaration of Helsinki: ethical principles for medical research involving human subjects. *JAMA* 2013;310:2191–214.
- Chan A, Boutron I, Hopewell S, et al. SPIRIT 2025 statement: updated guideline for protocols of randomised trials. *BMJ* 2025;389:e081477.
- Hopewell S, Chan A, Collins GS, et al. CONSORT 2025 statement: updated guideline for reporting randomised trials. *BMJ* 2025;389:e081123.
- Nolan JP, Sandroni C, Böttiger BW, et al. European Resuscitation Council and European Society of Intensive Care Medicine Guidelines 2021: post-resuscitation care. *Resuscitation* 2021;161:220–69.
- Nolan JP, Sandroni C, Andersen LW, et al. ERC-ESICM guidelines on temperature control after cardiac arrest in adults. *Resuscitation* 2022;172:229–36.
- Merigo G, Madotto F, Magliocca A, et al. Adherence to post-cardiac arrest care guidelines and impact on survival and neurological outcome. *Ann Intensive Care* 2025;15:88.
- Höllig A, Weinandy A, Liu J, et al. Beneficial properties of argon after experimental subarachnoid hemorrhage: early treatment reduces mortality and influences hippocampal protein expression. *Crit Care Med* 2016;44:e520–9.
- Zhuang L, Yang T, Zhao H, et al. The protective profile of argon, helium, and xenon in a model of neonatal asphyxia in rats. *Crit Care Med* 2012;40:1724–30.
- Fahlenkamp AV, Coburn M, De Prada A, et al. Expression analysis following argon treatment in an in vivo model of transient middle cerebral artery occlusion in rats. *Med Gas Res* 2014;4:11.
- Ulbrich F, Schallner N, Coburn M, et al. Argon inhalation attenuates retinal apoptosis after ischemia/reperfusion injury in a time- and dose-dependent manner in rats. *PLoS One* 2014;9:e115984.

39. Ulbrich F, Kaufmann KB, Coburn M, et al. Neuroprotective effects of Argon are mediated via an ERK-1/2 dependent regulation of heme-oxygenase-1 in retinal ganglion cells. *J Neurochem* 2015;134:717–27.
40. Balon N, Kriem B, Dousset E, et al. Opposing effects of narcotic gases and pressure on the striatal dopamine release in rats. *Brain Res* 2002;947:218–24.
41. Balon N, Risso JJ, Blanc F, et al. Striatal dopamine release and biphasic pattern of locomotor and motor activity under gas narcosis. *Life Sci* 2003;72:2731–40.
42. Abraini JH, Kriem B, Balon N, et al. Gamma-aminobutyric acid neuropharmacological investigations on narcosis produced by nitrogen, argon, or nitrous oxide. *Anesth Analg* 2003;96:746–9.
43. Cucino A, Ruggeri L, Olivari D, et al. Safety of ventilation with an argon oxygen gas mixture. *Brit J Anaesth* 2018;122:e31–2.
44. Horrigan DJ, Wells CH, Guest MM. Tissue gas and blood analyses of human subjects breathing 80% argon and 20% oxygen. *Aviat Space Environ Med* 1979;50:357–62.
45. Mielck F, Stephan H, Weyland A, et al. Effects of one minimum alveolar anesthetic concentration sevoflurane on cerebral metabolism, blood flow, and CO₂ reactivity in cardiac patients. *Anesth Analg* 1999;89:364–9.
46. Grüne F, Kazmaier S, Hoeks SE, et al. Argon does not affect cerebral circulation or metabolism in male humans. *PLoS One* 2017;12:e0171962.
47. Vaahersalo J, Hiltunen P, Tiainen M, et al. Therapeutic hypothermia after out-of-hospital cardiac arrest in Finnish intensive care units: the FINNRESUSCI study. *Intensive Care Med* 2013;39:826–37.
48. Jakkula P, Reinikainen M, Hästbacka J, et al. Targeting low- or high-normal Carbon dioxide, Oxygen, and Mean arterial pressure After Cardiac Arrest and REsuscitation: study protocol for a randomized pilot trial. *Trials* 2017;18:507.
49. Jakkula P, Pettilä V, Skrifvars MB, et al. Targeting low-normal or high-normal mean arterial pressure after cardiac arrest and resuscitation: a randomised pilot trial. *Intensive Care Med* 2018;44:2091–101.
50. Kuisma M, Boyd J, Voipio V, et al. Comparison of 30 and the 100% inspired oxygen concentrations during early post-resuscitation period: a randomised controlled pilot study. *Resuscitation* 2006;69:199–206.
51. Eastwood GM, Schneider AG, Suzuki S, et al. Targeted therapeutic mild hypercapnia after cardiac arrest: a phase II multi-centre randomised controlled trial (the CCC trial). *Resuscitation* 2016;104:83–90.
52. Gräsner JT, Wnent J, Lefering R, et al. European registry of cardiac arrest study THREE (EuReCa- THREE) - EMS response time influence on outcome in Europe. *Resuscitation* 2025;7:110704.
53. Neumar RW, Nolan JP, Adrie C, et al. Post-cardiac arrest syndrome: epidemiology, pathophysiology, treatment, and prognostication. A consensus statement from the International Liaison Committee on Resuscitation (American Heart Association, Australian and New Zealand Council on Resuscitation, European Resuscitation Council, Heart and Stroke Foundation of Canada, Inter American Heart Foundation, Resuscitation Council of Asia, and the Resuscitation Council of Southern Africa); the American Heart Association Emergency Cardiovascular Care Committee; the Council on Cardiovascular Surgery and Anesthesia; the Council on Cardiopulmonary, Perioperative, and Critical Care; the Council on Clinical Cardiology; and the Stroke Council. *Circulation*, 118. p. 83–2452.
54. Gräsner JT, Wnent J, Lefering R, et al. European registry of cardiac arrest study THREE (EuReCa-THREE) – EMS response time influence on outcome in Europe. *Resuscitation* 2025;7:110704.