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Protocol paper

CardioPulmonary resuscitation with *Ar*gon (CP*Ar*): A protocol for a randomised controlled multicentre clinical trial

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Abstract

Aims: The CardioPulmonary resuscitation with Argon (CP*Ar*) trial evaluates the clinical neuroprotective efficacy and safety of post-resuscitation ventilation with a 70/30 argon/oxygen (Ar/O_2) gas mixture compared to standard care ventilation with 30% O_2 in unconscious adults resuscitated from out-of-hospital cardiac arrest (OHCA).

Methods: CP*Ar* 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/O_2 via an experimental ventilator, or standard ICU ventilation with 30% O_2. 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 O_2 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: CP*Ar* 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 identifier: NCT05482945.

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

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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 (O_2). 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 O_2 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/O_2 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/O_2 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 (CP*Ar*) 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

CP*Ar* 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 Helsinki[29] 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 clinicaltrial.gov (NCT05482945).

CP*Ar* 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 O_2 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/O_2 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 *Ar*gon (CP*Ar*): 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
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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/O_2 using an experimental ventilator (Bellavista 1000 IMT, Switzerland) (*interventional arm*); or ventilation with an inspiratory oxygen fraction (FiO_2) 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 FiO_2 used in both study arms, only patients who demonstrate adequate arterial oxygenation (SaO_2 ≥94 %) on 30 % FiO_2 prior to randomisation are eligible for enrolment. If, during Ar ventilation, a desaturation event occurs, defined as peripheral oxygen saturation (SpO_2) < 90 % (and recruitment manoeuvres fail to restore adequate oxygenation), the Ar mixture is discontinued and FiO_2 is increased. Once SpO_2 stability is regained on 30 % FiO_2, Ar ventilation may resume to conclude the 4-hr treatment, with the total time exposure not exceeding 8-hr post-resuscitation. SpO_2 evolution 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/O_2 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/O_2 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 O_2, which showed a clear dose-dependent neuroprotective effect.[13] Additionally, the safety of the 4-hr 70/30-Ar/O_2 ventilation using the experimental Bellavista ventilator was confirmed in healthy anesthetised 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 % FiO_2 in air, was selected to isolate the effect of Ar while keeping O_2 concentrations consistent across groups.

Other than the fixed FiO_2 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 CP*Ar* 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).

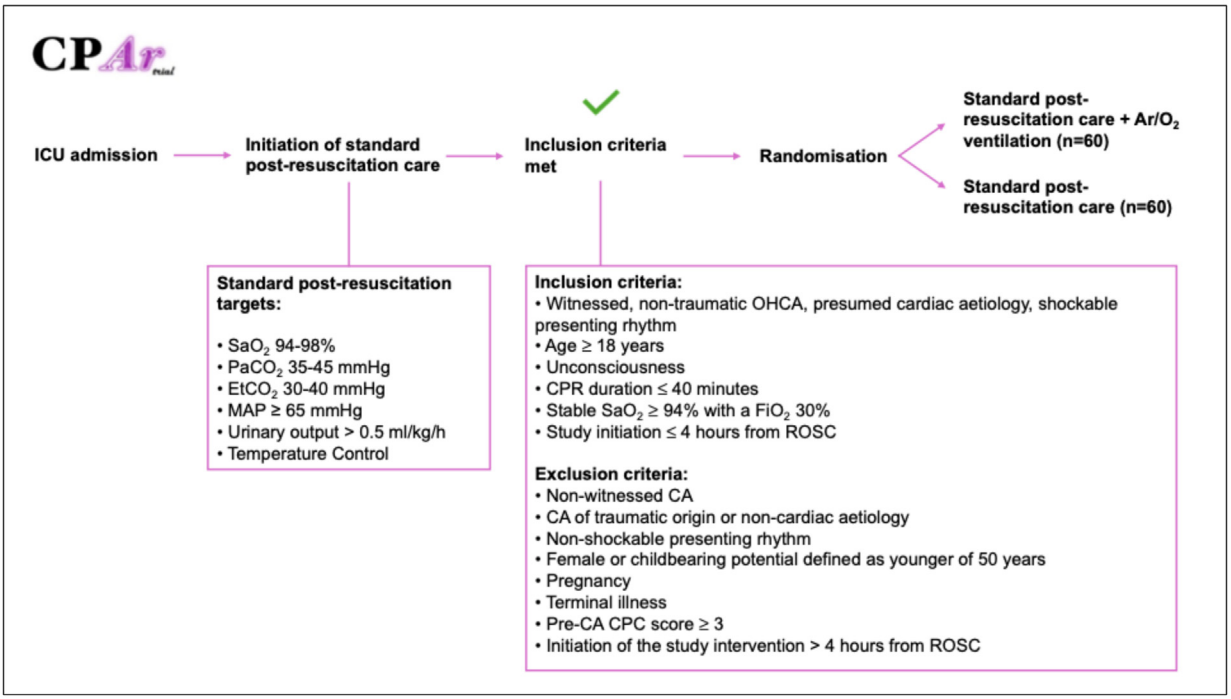

Fig. 1 – Inclusion and randomization flow diagram. CA, cardiac arrest; CPC, cerebral performance category score; CPR, cardiopulmonary resuscitation; $EtCO_2$, end-tidal carbon dioxide; FiO_2, inspiratory oxygen fraction; MAP, mean arterial pressure; $PaCO_2$, arterial partial pressure of carbon dioxide; OHCA, out-of-hospital cardiac arrest; ROSC, return of spontaneous circulation; SaO_2, arterial oxygen saturation.

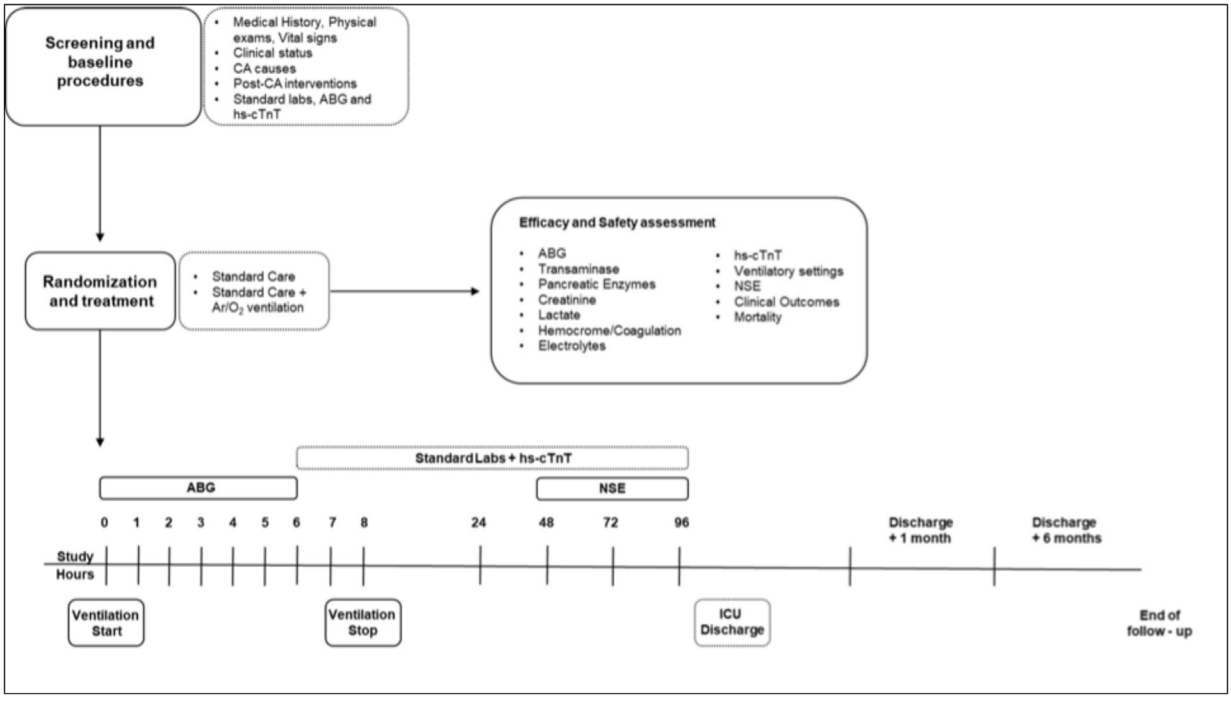

Fig. 2 – Study flow diagram. ABG, arterial blood gas; CA, cardiac arrest; hs-cTnT, high sensitivity cardiac troponin T; ICU, intensive care unit; NSE, neuron-specific enolase.

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, haemachrome, 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 O_2 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 kynurenine 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/O_2 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 CP*Ar* 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 ± 20 μg/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 O_2 desaturation will be summarised using descriptive statistics and compared to the SpO_2 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/O_2 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 O_2 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 DMSB 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 CP*Ar* 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/O_2 or 30 % O_2, 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.

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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.

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Appendix A. Supplementary material

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

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