Early restricted oxygen therapy after resuscitation from cardiac arrest (ER-OXYTRAC): protocol for a stepped-wedge cluster randomised controlled trial


ABSTRACT

Introduction Cardiac arrest is a critical condition, and patients often experience postcardiac arrest syndrome (PCAS) even after the return of spontaneous circulation (ROSC). Administering a restricted amount of oxygen in the early phase after ROSC has been suggested as a potential therapy for PCAS; however, the optimal target for arterial partial pressure of oxygen or peripheral oxygen saturation (SpO₂) to safely and effectively reduce oxygen remains unclear. Therefore, we aimed to validate the efficacy of restricted oxygen treatment with 94%–95% of the target SpO₂ during the initial 12 hours after ROSC for patients with PCAS.

Methods and analysis ER-OXYTRAC (early restricted oxygen therapy after resuscitation from cardiac arrest) is a nationwide, multicentre, pragmatic, single-blind, stepped-wedge cluster randomised controlled trial targeting cases of non-traumatic cardiac arrest. This study includes adult patients with out-of-hospital or in-hospital cardiac arrest who achieved ROSC in 39 tertiary centres across Japan, with a target sample size of 1000. Patients whose circulation has returned before hospital arrival and those with cardiac arrest due to intracranial disease or intoxication are excluded. Study participants are assigned to either the restricted oxygen (titration of a fraction of inspired oxygen with 94%–95% of the target SpO₂) or the control (98%–100% of the target SpO₂) group based on cluster randomisation per institution. The trial intervention continues until 12 hours after ROSC. Other treatments for PCAS, including oxygen administration later than 12 hours, can be determined by the treating physicians. The primary outcome is favourable neurological function, defined as cerebral performance category 1–2 at 90 days after ROSC, to be compared using an intention-to-treat analysis.

Ethics and dissemination This study has been approved by the Institutional Review Board at Keio University School of Medicine (approval number: 20211106). Written informed consent will be obtained from all participants or their legal representatives. Results will be disseminated via publications and presentations.
INTRODUCTION
Cardiac arrest, an emergency and critical condition, should be appropriately managed to prevent unfavourable clinical outcomes. Administering strenuous resuscitative efforts while transporting a patient from the site of cardiac arrest to a hospital leads to the return of spontaneous circulation (ROSC) from cardiac arrest, whereas haemodynamic instability and neurological dysfunction are known to emerge even after ROSC, a condition known as postcardiac arrest syndrome (PCAS). While targeted temperature management (TTM) after ROSC improves the neurological outcomes of patients with PCAS, various studies have failed to elucidate an effective treatment that would help patients with PCAS regain optimal neurological functions.

Avoiding supraphysiological oxygen in patients with ROSC following cardiac arrest has been suggested as a potential therapy for PCAS by several observational studies. Meta-analyses and prospective observational studies have reported that a lower partial pressure of arterial oxygen (PaO₂) within 6–24 hours after ROSC, particularly <300 mm Hg, is associated with favourable neurological outcomes and decreased mortality in patients with PCAS. Accordingly, the American Heart Association, the European Resuscitation Council and the European Society of Intensive Care Medicine guidelines for cardiopulmonary resuscitation have recommended 92%–94% of peripheral oxygen saturation (SpO₂) as a lower threshold of target oxygenation in patients achieving ROSC. However, studies validating the safety and effectiveness of restricted oxygen administration with a lower SpO₂ target in patients with PCAS are limited.

A recent randomised controlled trial (RCT) demonstrated the ineffectiveness of a low PaO₂ target (68–75 mm Hg) in patients with ROSC from out-of-hospital cardiac arrest (OHCA), although the control target (98–105 mm Hg) was lower than the usual practice reported in observational studies and continuous measurements of PaO₂ to avoid hyperoxia would not be a standard practice. Another RCT reported higher in-hospital mortality following restricted oxygen administration from the scene to the intensive care unit (ICU) admission using a target SpO₂ of 90%–94%, in which suboptimal power was considered because of early trial termination due to the coronavirus disease 2019 (COVID-19) pandemic. An individual-level patient data meta-analysis of RCTs on restricted oxygen for OHCA revealed that conservative oxygen therapy was associated with reduced mortality at the last follow-up; however, low or very low certainty of evidence could not conclude its clinical utility. Furthermore, these studies only included patients with OHCA; thus, the therapeutic effects of restricted oxygen administration with a low SpO₂ target remain unclear among patients with in-hospital cardiac arrest.

In the present study, we aimed to elucidate the effectiveness of early restricted oxygen therapy within 12 hours after ROSC using 94% of target SpO₂ in patients with cardiac arrest. Considering that the tight adjustment of oxygen levels with continuous PaO₂ measurement is impractical, oxygen titration is conducted based on SpO₂ monitoring in this trial. We hypothesised that early restricted oxygen therapy with 94%–95% of target SpO₂ is associated with a higher rate of favourable neurological functions, defined as cerebral performance category (CPC) 1 or 2, at 90 days after ROSC than liberal oxygen therapy with 98%–100% of target SpO₂.

METHODS AND ANALYSIS
Trial design and setting
The early restricted oxygen therapy after resuscitation from cardiac arrest (ER-OXYTRAC) trial is a multicentre, pragmatic, single-blind, stepped-wedge cluster RCT that will include adult patients diagnosed with PCAS following ROSC after cardiac arrest. The ER-OXYTRAC trial is being conducted in 39 tertiary care centres, including academic and community hospitals, in both urban and rural areas across Japan. The geographical location is shown in figure 1.

Participants and interventions
A flowchart of the patient enrolment process is shown in figure 2. The inclusion criteria for patients are as follows: (1) those aged ≥20 years; (2) those with non-traumatic out-of-hospital or in-hospital cardiac arrest; and (3) those who achieve ROSC at a hospital. The patients are included regardless of the place of cardiac arrest, rhythm type during cardiac arrest (shockable vs non-shockable) and witness status. Cardiac arrest needs to be confirmed by healthcare providers, including emergency medical service personnel, nurses and physicians.

The exclusion criteria are as follows: (1) patients in whom ROSC is confirmed before hospital arrival (for patients with OHCA); (2) patients not receiving ventilator support after ROSC; (3) patients whose Glasgow Coma Scale is >8 when ROSC is confirmed; (4) patients receiving extracorporeal membrane oxygenation when ROSC is confirmed; (5) patients who are not expected to survive >24 hours when ROSC is confirmed; (6) patients in whom an aetiology for cardiac arrest is considered an intracranial disease; (7) patients in whom intoxication is considered the aetiology of cardiac arrest; (8) patients with cerebral dysfunction before cardiac arrest, defined as a CPC of 3 or 4; (9) patients diagnosed with COVID-19 and required medications for COVID-19; (10) patients in whom withholding or withdrawal of treatment is based on advanced directives or relatives when ROSC was confirmed; (11) patients with other diseases, such as chronic lung and congenital diseases, which require stricter control of oxygen administration or adjustment.
of target SpO₂; (12) patients in whom SpO₂ is considered not to have been correctly measured by a clinical physician (eg, SpO₂ is 5% lower or higher than arterial oxygen saturation); (13) patients who participate in other clinical trials that require a therapeutic intervention; (14) patients who need to be arrested, detained or put in custody by law enforcement or legal agencies; (15) patients who refuse to participate in the trial; and (16) patients deemed ineligible to participate by a clinical physician. ROSC is confirmed in patients with continuous spontaneous circulation for >10 min.

The investigators will explain the study verbally and in writing and provide the consent form approved by the institutional review board to potential trial participants or their legally authorised representatives to obtain voluntary written consent. If written consent cannot be immediately obtained from a legally authorised representative, explanations and consent will be provided over the phone and written consent will be obtained later.

Participants will be assigned to either of the two groups: (1) restricted oxygen group (target SpO₂ is 94%–95%) or (2) control group (target SpO₂ is 98%–100%). The
adjustment of the amount of oxygen administered (fraction of inspiratory oxygen ($\text{FiO}_2$)) is summarised in Figure 3. In both the restricted oxygen and control groups, $\text{FiO}_2$ is decreased by 5% when $\text{SpO}_2$ is higher than the upper limit of target $\text{SpO}_2$ and increased by 5% when $\text{SpO}_2$ is lower than the lower limit of target $\text{SpO}_2$. Other treatments, including adjustment of tidal volume, positive endoexpiratory pressure and driving pressure, will be provided according to the clinical physician's discretion. $\text{SpO}_2$ will be measured with any device and at any location (eg, fingertip, forehead and earlobe). $\text{SpO}_2$ is evaluated at least every 10 min and when any treatment that can cause a change in $\text{SpO}_2$ is conducted. An arterial blood gas assay is conducted every 3 hours after ROSC, and when $\text{PaO}_2$ is $\geq 300 \text{ mm Hg}$, $\text{FiO}_2$ is decreased regardless of $\text{SpO}_2$. This adjustment of $\text{FiO}_2$ as a study intervention is conducted until 12 hours after ROSC; thereafter, $\text{FiO}_2$ is adjusted by a clinical physician.

In both the restricted oxygen and control groups, allocated interventions are not discontinued nor modified when $\text{SpO}_2$ within the target ranges cannot be obtained by adjusting $\text{FiO}_2$ ($\text{SpO}_2$ is lower than the lower limit of the target with 100% of $\text{FiO}_2$ or higher than the upper limit of the target with 21% of $\text{FiO}_2$). When any disease or condition requiring stricter control of oxygen administration emerges, the allocated interventions are discontinued and $\text{FiO}_2$ is adjusted appropriately by a clinical physician. After the treatment for such diseases or conditions is completed, the allocated interventions are reinitiated and continued until 12 hours after ROSC. In the
restricted oxygen group, when hypoxia (PaO₂ < 60 mm Hg) or adverse events, such as haemodynamic instability, due to hypoxia emerges when SpO₂ is 94%–95%, the target SpO₂ is changed to 98%–100%. Trial monitoring experts, who are independent of the conduct of the trial, will ensure that the trial is conducted in accordance with the protocol.

Other than the adjustment of FiO₂, any treatments after ROSC, including the adjustment of the ventilator setting, are provided based on the decision of a clinical physician. When treatments that can change SpO₂ are conducted, SpO₂ is measured immediately and FiO₂ is adjusted following the allocated interventions. TTM is conducted on all participants. The temperature target, TTM methods, TTM duration and medications, including sedatives and muscle relaxants, during TTM are decided by a clinical physician.

Outcome measures
The primary endpoint is CPC at 90 days after the intervention. The secondary endpoints are as follows: (1) survival at 30 days after intervention initiation; (2) survival at 90 days after intervention initiation; (3) hospital-free days until 90 days after intervention initiation; (4) ICU-free days until 90 days after intervention initiation; (5) ventilator-free days until 90 days after intervention initiation; (6) renal replacement therapy (RRT)-free days until 90 days after intervention initiation; (7) oxygen-free days until 90 days after intervention initiation; (8) Clinical Frailty Scale at 90 days after intervention initiation; (9) presence of hyperoxia, defined as PaO₂ ≥ 300 mm Hg, within 12 hours after intervention initiation; and (10) presence of hypoxia, defined as PaO₂ < 60 mm Hg, within 12 hours after intervention initiation.

The hospital-free, ICU-free, ventilator-free, RRT-free and oxygen-free days were defined as the number of days from day 1 to day 90 after intervention initiation when the patient was alive and free from support for at least 24 consecutive hours. If patients die within 90 days or are still supported after 90 days, zero will be assigned.
Randomised assignment of interventions and participant timeline

This study adopts a stepped-wedge cluster randomisation design, and the intervention is allocated per cluster that includes at least five institutions. Before the initiation of the study, the participating institutions will submit an estimated annual number of patients with OHCA and in-hospital cardiac arrest, an estimated frequency of cardiogenic cardiac arrest, the average transportation time for patients with OHCA and TTM methods. Stratified randomisation of the institution by the submitted information is conducted by a statistician who is not involved in the trial, and five clusters are generated. The study period is divided into six periods (the first to sixth period), and the timing of crossover of the intervention (control to restricted oxygen) will be randomly assigned to each cluster from the first day of either of the second to sixth periods.

The schedule of enrolment, interventions and assessments is summarised in figure 5. Assessment data will be recorded using an electronic trial data capture system (HOPE eACReSS, https://alliance-cresc-h-u-tokyo.net/acress/login). Trial monitoring experts, who are independent of the conduct of the trial, will ensure that the data reported by the investigators are being collected accurately. Participants will be followed-up for 90 days after intervention initiation. If a participant is discharged from the hospital before 90 days, the investigators will contact the participant via telephone to obtain information regarding their status.

Owing to the nature of the trial, participants, care providers and outcome assessors cannot be blinded to the assigned intervention. However, the statisticians who will analyse the data will be blinded to group allocation.

Statistical methods

We hypothesised that restricted oxygen therapy with 94%–95% of target SpO₂ until 12 hours after ROSC is associated with a higher rate of favourable neurological functions, defined as CPC of 1 or 2, at 90 days after ROSC than liberal oxygen therapy with 98%–100% of target SpO₂. Based on previous studies, we estimated that the incidence of a CPC 1 or 2 at 90 days after ROSC was 12% in the control group and the absolute difference from the restricted oxygen therapy was 10%. To evaluate the difference in the incidence between the groups, a two-sided significance level of 0.05 and a power of 0.80 are set. We adopt a stepped-wedge cluster randomisation design, in which each study institution is randomly allocated into five different clusters. The study period is divided into

six periods (first to sixth period), and the study intervention is initiated as a control (target SpO₂ is 98%–100%) and then changed to restricted oxygen (target SpO₂ is 95%–95%) at the beginning of one of the second to sixth periods that is predetermined prior to study initiation (crossover design). When at least five study institutions are allocated into each cluster and intercluster and intracluster correlations are estimated at 0.008 and 0.1, respectively, 6 cases in each institution (30 cases in each cluster) in each divided period would be needed, leading to a total of 900 cases. Assuming that approximately 10% of the patients will drop out because of withdrawal or other reasons, 1000 patients will be required.

We will report patient flow according to the Consolidated Standards of Reporting Trials flowchart for stepped-wedge cluster RCTs as per the allocated sequence and period. The final analysis will be performed after collecting the 90-day outcomes of the participants. Eligibility for the analysis is decided by the primary investigator and statisticians, who are not involved in the conduct of the trial. The intention-to-treat cohort includes all eligible patients admitted to the eligible wards. The proportion of patients with CPC 1 or 2 will be compared between the groups at the individual level using a generalised linear mixed model with binary distribution. The jackknife method will be used to estimate SEs to account for grouping within clusters. A log-link function will be incorporated to estimate the relative risk as a measure of effect. The best model with a unique covariance structure that produces the lowest Bayesian information criterion value will be selected. The covariance structures considered in the model are the unstructured covariance structure, Toeplitz covariance structure and variance component structure. The Kenward-Roger method will be applied to adjust for the denominator degree of freedom for tests of the fixed effects. Results will be expressed as a relative risk with a 95% CI and p value.

Secondary analysis will be conducted to interpret the primary analysis rather than test a hypothesis. Secondary endpoints will be compared between the groups in a model similar to the one used in the primary analysis. Moreover, subgroup analyses will be conducted by...
dividing the participants based on adjusted mortality and institutional characteristics, including geographical location, transportation time and temperature for TTM, which were used for cluster generation.

Interim analysis will be conducted after 500 cases are registered when their survival/death is confirmed at 90 days. Participant enrolment will continue during the interim analysis. In the interim analysis, the proportion of CPC 1 or 2 will be compared between the groups and statistical significance will be evaluated. To maintain a two-sided significance level of <0.05, the multiplicity of testing will be adjusted using the Pocock boundary. The Data and Safety Monitoring Committee (DSMC) will assess the results of the interim analyses and make recommendations on the continuation, modification or termination of the trial. Based on the recommendations by the DSMC, the primary investigator will make the final decision to continue or terminate the trial. When trial continuation is decided, the results of the interim analysis will remain concealed.

There are no plans to conduct additional analyses. Although researchers at the participating centres may conduct ancillary studies using data obtained from this trial, specific analysis methods have not been determined. If many missing values cannot be ignored, sensitivity analysis will be performed using multiple imputations of the missing values.

Oversight and monitoring
This trial is led by the Japanese Association for Acute Medicine. The steering committee consists of four clinical researchers who supervise the implementation of the trial and check its progress. The steering committee and a clinical research centre within the principal institution designed the study. Another clinical research centre at an institution, to which a member of the steering committee belongs, developed the clinical trial data management system and will monitor the registered data. The endpoint adjudication committee consists of three clinical researchers at different institutions.

DSMC comprises three clinical researchers at different institutions who are independent from the sponsor and have competing interests. DSMC receives any reports of severe adverse events; assesses the relationship between the study intervention and severe adverse events; and recommends the continuation, modification or termination of the trial. The DSMC will assess the results of the interim analyses and make recommendations on the continuation, modification or termination of the trial. The DSMC will hold a meeting at least every year, assess the clinical trial data management system and evaluate the safety of continuing the trial.

All investigators at participating institutions are mandated to collect, assess, record and manage solicited and spontaneously reported adverse events. The DSMC, which is independent of the conduct of the trial, monitors the study to ensure the reliability of the trial in terms of the protection of human rights, safety and welfare of the participants. If the principal investigator is notified of a severe adverse event related to the trial intervention, a prompt report will be presented to the DSMC and ethics review board of the principal institution. In addition, the principal investigator will take appropriate action and promptly share information on the severe adverse event with other investigators involved in the trial. The DSMC and ethics review board of the principal institution will review and examine the report and send written recommendations made in response to it to the principal investigator.

Patient and public involvement
Patients were involved in the design of this research. During the feasibility stage, the choice of outcome measures and methods of recruitment were informed by discussions with patients who were participating as members of the institutional review board.

ETHICS AND DISSEMINATION
The clinical trial is conducted according to the principles of the Declaration of Helsinki and the Ethical Guidelines for Medical and Health Research Involving Human Subjects published by the Ministry of Health, Labour and Welfare of Japan and the Japanese Ministry of Education, Culture, Sports, Science and Technology. The study was approved by the Institutional Review Board at Keio University School of Medicine, the principal hospital (approval number: 20211106); the approval process was initiated in 2021. Written informed consent to participate will be obtained from all participants or their legally acceptable representatives (online supplemental files 1,2).

The insurance company will provide compensation to trial participants who suffer from health issues related to flaws in the trial protocol during the first year after trial participation.

The need for protocol changes will be initially discussed by the steering committee, followed by a meeting including representatives from all participating institutions. When a decision is reached to change the protocol, the revised protocol will be discussed by the institutional review board of the principal institution. After obtaining approval from the institutional review board, the revised protocol will be promptly disseminated to relevant parties via email or other means. Any modifications will also be reflected in the trial registry.

Data registered in the clinical trial data management system do not contain personal information. After the completion of all planned analyses, the findings of the trial will be presented at relevant scientific meetings and disseminated through publications in peer-reviewed journals. Following the completion of all ancillary analyses by the trial group, the data sets analysed during the current study and statistical
codes will be available from the corresponding author on reasonable request.

**DISCUSSION**

This multicentre, pragmatic, single-blind, stepped-wedge cluster RCT will investigate the efficacy of restricted oxygen administration until 12 hours after ROSC and examine whether the neurological functions would recover more in patients treated with 94%–95% of target SpO2 than in those treated with 98%–100% of target SpO2.

One rationale for restricted oxygen therapy is based on the observation that supraphysiological arterial oxygen in the early phase after ROSC is associated with unfavourable clinical outcomes among patients with PCAS. Therefore, titrating the amount of oxygen delivered to patients with PCAS should ideally follow serial PaO2 measurements to avoid hyperoxia. However, continuous SpO2 monitoring is a more pragmatic and common practice in the ICU than frequent collection of arterial blood samples; therefore, the present study uses SpO2 instead of PaO2 as a target for oxygen titration. In addition, the target SpO2 range is recommended and has been revised without high-quality evidence in the American Heart Association guidelines; in this trial, the target SpO2 range for restricted oxygen treatment is set at 94%–95% considering patient safety.

In this study, the duration of oxygen restriction is 12 hours because a considerable number of studies have shown adverse effects of hyperoxia during the first 4–24 hours after ROSC, whereas other studies have reported that hyperoxia within 1–2 hours after ROSC was not associated with decreased neurological functions. Although the study protocol mandates treating physicians to restrict (or liberally adjust) the amount of oxygen administered only 12 hours after ROSC, restricted oxygen therapy can linger thereafter based on the decision of the treating physicians. Therefore, it should be noted that the restriction duration would be prolonged for >12 hours.

There are several limitations of this study in the context of its design. First, the treating physicians are not blinded to the study intervention. To adjust the amount of oxygen to a predefined target SpO2, healthcare providers need to know the intervention assigned. Second, the difference in target SpO2 between the two interventions is only 4%–5% (94%–95% vs 98%–100%). Similar cohorts may have eventually been generated. Third, a stepped-wedge cluster randomised design cannot adapt to a significant change in non-study-related treatments during the study period. When a novel treatment for PCAS is reported, the DSMC will discuss the continuation of the trial based on the absolute effect of such treatments on patients with PCAS. Fourth, as this study targets patients with both out-of-hospital and in-hospital cardiac arrest, confounding effects between them will exist. Finally, although the sample size has been calculated with a 10% absolute difference in outcome based on previous studies, smaller effects of restricted oxygen treatment cannot be validated.

**TRIAL STATUS**

The trial protocol V.1 was approved on 10 February 2022 (approval number: 20211106), with the approval process initiated in 2021. The latest protocol is V.6.0, which was approved on 28 February 2023, after minor revisions regarding the addition of participating hospitals, clarification on the statements of exclusion criteria and modification of the study period due to the lower-than-expected enrolment of patients. The first participant was recruited on 5 June 2022, in 1 of the 38 participating hospitals; subsequently, 1 more hospital joined the trial. The trial is ongoing, and approximately 150 patients had been enrolled as of the end of February 2023. The estimated primary completion date is 31 August 2025.

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REFERENCES


We have decided to conduct the following research on patients visiting Keio University Hospital. We would appreciate your cooperation. We will do our best to protect the patients’ privacy. This research has been approved by the Institutional Review Board and the Dean of Keio University School of Medicine. Those who meet the selection criteria for this study are considered research participants.

1. Purpose and Significance of this Study

(1) Purpose of this study
The treatment of cardiopulmonary arrest is an important issue worldwide, and resuscitation has been developed in various studies. However, even after successful resuscitation, severe clinical consequences such as post-cardiac arrest syndrome (PCAS) occur.

Oxygen therapy has long been used to prevent PCAS. However, recent reports have suggested that excessive oxygen administration can cause cerebral damage. Therefore, global guidelines for cardiopulmonary resuscitation recommend that oxygen administration can be adjusted to achieve a peripheral blood oxygen saturation ($SpO_2$) of "94% or higher" or should be adjusted with $SpO_2$ of "92% to 98%" during post-resuscitation oxygen therapy; however, the effectiveness of this strategy has not been clarified. In addition, many facilities are still treating patients with $SpO_2$ of 98% or higher.

Therefore, this study aimed to determine whether a therapeutic strategy of adjusting the oxygen dosage with a target $SpO_2$ of 94–95% after cardiac arrest resuscitation improves neurological outcomes.

(2) Significance of conducting this study
If this study finds that adjusting oxygen administration to a target $SpO_2$ of 94–95% after cardiac arrest resuscitation improves the prognosis of brain function, or if no effect is seen, the results are expected to be disseminated as international guidelines. These results may lead to improvements
in cardiac arrest resuscitation worldwide.

2. Voluntary nature of participation in research and freedom to withdraw
   (1) Participation in this study is voluntary. It is up to the patient to "participate" or "not participate" in this trial.
   (2) You may withdraw your consent to participate in this study at any time. You may refuse at any time, even after participating in the study. At that time, the patient will not be disadvantaged in any way.
   (3) Existence or nonexistence of medical treatment beyond the scope of normal medical care (if yes, matters related to other treatment methods). No medical treatment beyond normal medical practice is involved in this study.

3. Methods of Conducting Research and Items of Research Cooperation
   (1) Study duration
   From the date of approval to conduct the study to March 31, 2026
   (2) Methods of conducting this study
   The study, as specified by the participating sites and the timing of the study, will provide one of the following two oxygen therapies for 12 h following cardiac arrest resuscitation.

   Restricted oxygen therapy: After return of spontaneous circulation (ROSC), the fraction of inhaled oxygen (FiO$_2$) will be adjusted with a target SpO$_2$ level of 94–95%.
   Conventional oxygen therapy After ROSC, the fraction of inhaled oxygen (FiO$_2$) will be adjusted with a target SpO$_2$ level of 98% or higher.

   All treatments other than the adjustment of FiO$_2$ will be performed as usual according to the treating physician’s judgment. If a more precise FiO$_2$ adjustment is required, FiO$_2$ will be adjusted regardless of the target SpO$_2$ values mentioned above.

   Please note that this study will be conducted as a cluster randomized controlled trial. In a cluster-randomized controlled trial, the treatment to be administered is determined by each facility; therefore, patients could not choose the above treatments at their own will. However, both restricted and conventional oxygen therapies do not deviate from the treatment recommended in the global cardiopulmonary resuscitation guidelines.

   (3) Items for which cooperation is requested
   For the first 12 h after resuscitation from cardiac arrest, patients will be treated with either restricted or conventional oxygen therapy (determined by the facility and timing of the study inclusion; patients do not have a choice). None of the treatments deviated from the recommendations of the global cardiopulmonary resuscitation guidelines. If the treating physician determines that a condition requires more rigorous FiO$_2$ adjustment, FiO$_2$ will be adjusted independently of the abovementioned oxygen therapies.
You will also be asked to provide the following information:

1) Sample and information to be obtained
   1. Basic patient information, including age, sex, height, weight, clinical frailty scale score before cardiac arrest, comorbidities (myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic respiratory disease, collagen disease, peptic ulcers, liver disease, diabetes, chronic kidney disease, malignant tumor, and AIDS), and Cerebral Performance Category

2. Information related to cardiac arrest: details of cardiac arrest (date and time of occurrence of cardiac arrest determined by an emergency medical service (EMS) or in-hospital medical staff, place of cardiac arrest, witness status, and date and time of witness), resuscitation process (date and time of diagnosis of cardiac arrest, bystander cardiopulmonary resuscitation [CPR], bystander CPR immediately after cardiac arrest, personal conducting bystander CPR, CRP start date/time, presence/absence/start time of EMS CPR, initial rhythm, pupil diameter and light reflex at confirmation of cardiac arrest), prehospital life-saving procedures (presence/absence of prehospital physician, presence/absence of life-saving procedures, presence/absence/number of electrical defibrillation, presence/absence/time/method and equipment used for airway clearance, whether or not a foreign body in the upper airway was removed, presence/absence of intravenous line placement, whether or not a drug [adrenaline] was administered and how much was used), in-hospital life-saving procedures (date and time of in-hospital ACL initiation, ECG waveform at ACL initiation, whether or not and how many times electrical cardioversion was performed, whether or not a drug [adrenaline] was administered and how much was used, date and time of ROSC, ECG waveform changes until ROSC, presence/absence of intratracheal intubation before ROSC, FiO₂ before ROSC, presence/absence of CAG/PCI), use of mechanical CPR and complications, etiology of cardiac arrest (definite cardiogenic, presumed cardiogenic, or non-cardiogenic)

3. Pathophysiology and severity at the start of intervention: SOFA score, vital signs (systolic blood pressure, diastolic blood pressure, mean blood pressure, heart rate, Glasgow Coma Scale [GCS], pupil diameter, and light reflex) immediately after ROSC, blood tests (pH, PCO₂, PO₂, and HCO₃⁻ in arterial blood samples, lactate level, P/F ratio, hemoglobin, platelets, total bilirubin, BUN, creatinine, D-dimer, FDP, fibrinogen, and PT-INR), ventilator settings (PEEP, maximum airway pressure [measured], mean airway pressure [measured], respiratory rate [measured], minute ventilation volume [measured]), FiO₂ (maximum value) from ROSC to start of intervention.

4. Clinical information within 12 h of intervention: hourly SpO₂ and 3-hourly arterial PO₂ and FiO₂ from the start of intervention to 12 h; maximum and minimum SpO₂ from the start of intervention to 12 h; number of times SpO₂ fell below 90% from the start of intervention to 12 h; presence of hypoxemia from the start of intervention to 12 h; Scvo₂ or PvO₂ measured within 12 h of intervention and time of measurement; ECMO and analgesics administered during RASS from the start of intervention to 12 h; and antimicrobials administered during RASS from the start of intervention to 12 h. hypoxemia, SCVO₂ or PvO₂, and time of
measurement within 12 h of intervention; ECMO and analgesic sedatives started within 12 h of intervention; RASS/antimicrobials administered/muscle relaxants administered at 12 h of intervention, resuscitation leader medical emotion scale and self-efficacy scale information, vital signs (systolic blood pressure, diastolic blood pressure, mean blood pressure, pulse, GCS, pupil diameter, and presence/absence of light reflex) at 12 h after the start of the intervention, blood tests (pH, PCO₂, PO₂, and HCO₃ in arterial blood sample, lactate level, P/F ratio, hemoglobin, platelets, total bilirubin, BUN, creatinine, D-dimer, FDP, fibrinogen, and PT-INR)

5. Clinical information at 30 days post-intervention: CPC at 30 days post-intervention; targeted temperature; duration, methods, and time to target temperature of Targeted Temperature Management, DVT prophylaxis with medications up to 7 days post-intervention; nutritional therapy administered up to 7 days post-intervention; and pneumonia and PE/DVT diagnosed up to 30 days post-intervention.

6. Clinical information 90 days post-intervention: CPC 90 days post-intervention, hospital-free days 90 days after intervention, ICU-free days 90 days post-intervention, ventilator-free days 90 days post-intervention, RRT-free days 90 days post-intervention, oxygen-free days 90 days post-intervention, Clinical Frailty Scale score 90 days post-intervention

7. Adverse events that occurred during the study period

2) Purpose of use and handling method of samples and information
Information and other data obtained in this study will be stored in a secured cabinet in the Office of the Department of Emergency and Critical Care Medicine, Keio University School of Medicine (Building No. 3, North Wing, 2nd floor). Electronic data will be stored on a hard disk in the Research Office of the Department of Emergency and Critical Care Medicine, Keio University School of Medicine, and the stored hard disk will be stored in the Office of the Department of Emergency and Critical Care Medicine, Keio University School of Medicine.

(4) Groups for conducting this research
1) Research institutions (including own institution) conducting this research and representatives

<table>
<thead>
<tr>
<th>Study institution</th>
<th>Information of representative</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Keio University Hospital</td>
<td>Name Ryo Yamamoto</td>
</tr>
<tr>
<td></td>
<td>Affiliation Department of Emergency and Critical Care Medicine, Keio University School of Medicine</td>
</tr>
<tr>
<td></td>
<td>Position Research associate</td>
</tr>
<tr>
<td></td>
<td>Role Principal investigator</td>
</tr>
<tr>
<td>2 Osaka Medical and Pharmaceutical University</td>
<td>Name Kazuma Yamakawa</td>
</tr>
<tr>
<td></td>
<td>Affiliation Department of Emergency and Critical Care Medicine, Osaka Medical and Pharmaceutical University</td>
</tr>
<tr>
<td></td>
<td>Position Associate professor</td>
</tr>
<tr>
<td></td>
<td>Role Co-investigator</td>
</tr>
<tr>
<td>3 Tokyo Medical and Dental</td>
<td>Name Wataru Takayama</td>
</tr>
<tr>
<td>Name</td>
<td>Affiliation</td>
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</tr>
<tr>
<td>Tomohiro Kurihara</td>
<td>Department of Emergency and Critical Care Medicine, National Hospital Organization Tokyo Medical Center</td>
</tr>
<tr>
<td>Takeshi Wada</td>
<td>Division of Acute and Critical Care Medicine, Hokkaido University Faculty of Medicine</td>
</tr>
<tr>
<td>Manabu Sugita</td>
<td>Department of Emergency and Critical Care Medicine, Juntendo University Nerima Hospital</td>
</tr>
<tr>
<td>Naoya Miura</td>
<td>Department of Emergency and Critical Care Medicine, Tokai University School of Medicine</td>
</tr>
<tr>
<td>Takahiro Shoji</td>
<td>Department of Emergency Medicine, Saiseikai Central Hospital</td>
</tr>
<tr>
<td>Masayuki Shimizu</td>
<td>Department of Emergency and Critical Care Medicine, Saiseikai Yokohamashi Tobu Hospital</td>
</tr>
<tr>
<td>Tomoaki Natsukawa</td>
<td>Department of Emergency and Critical Care Medicine, Yodogawa Christian Hospital</td>
</tr>
</tbody>
</table>

**Position:**
- Research associate
- Director
- Cheif
- Professor
- Lecturer
- Medical staff (doctor)
- Director

**Role:**
- Co-investigator
- Research associate
- Co-investigator
- Research associate
- Co-investigator
- Co-investigator
- Co-investigator
- Co-investigator
- Co-investigator
- Co-investigator
- Co-investigator
- Co-investigator

**University Hospital of Medicine**

**Position:**
- Research associate

**Role:**
- Co-investigator

**Hokkaido University Hospital**

**Name:**
- Takeshi Wada

**Affiliation:**
- Division of Acute and Critical Care Medicine, Department of Anesthesiology and Critical Care Medicine, Hokkaido University Faculty of Medicine

**Role:**
- Co-investigator

**National Hospital Organization Tokyo Medical Center**

**Name:**
- Tomohiro Kurihara

**Affiliation:**
- Department of Emergency and Critical Care Medicine, National Hospital Organization Tokyo Medical Center

**Role:**
- Co-investigator

**Hyogo Prefectural Nishinomiya Hospital,**

**Name:**
- Kyosuke Takahashi

**Affiliation:**
- Emergency and Critical Care Center, Hyogo Prefectural Nishinomiya Hospital

**Role:**
- Co-investigator

**Juntendo University Nerima Hospital**

**Name:**
- Manabu Sugita

**Affiliation:**
- Department of Emergency and Critical Care Medicine, Juntendo University Nerima Hospital

**Role:**
- Co-investigator

**Tokai University School of Medicine**

**Name:**
- Naoya Miura

**Affiliation:**
- Department of Emergency and Critical Care Medicine, Tokai University School of Medicine

**Role:**
- Co-investigator

**Saiseikai Central Hospital**

**Name:**
- Takahiro Shoji

**Affiliation:**
- Department of Emergency Medicine, Saiseikai Central Hospital

**Role:**
- Co-investigator

**Saiseikai Yokohamashi Tobu Hospital**

**Name:**
- Masayuki Shimizu

**Affiliation:**
- Department of Emergency and Critical Care Medicine, Saiseikai Yokohamashi Tobu Hospital

**Role:**
- Co-investigator

**Yodogawa Christian Hospital**

**Name:**
- Tomoaki Natsukawa

**Affiliation:**
- Department of Emergency and Critical Care Medicine, Yodogawa Christian Hospital

**Role:**
- Co-investigator
<table>
<thead>
<tr>
<th>12</th>
<th>Asahikawa City Hospital</th>
<th>Name</th>
<th>Akihito Tampo</th>
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<tr>
<td></td>
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<td>Name</td>
<td>Kota Shinada</td>
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<tr>
<td>14</td>
<td>Fujita Medical School Bantane Hospital</td>
<td>Name</td>
<td>Hideki Tokuyama</td>
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<tr>
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<tr>
<td>15</td>
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<td>Name</td>
<td>Kyoko Yokokawa</td>
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<td></td>
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<td>Emergency Medical Center of Tokyo Metropolitan Tama Medical Center</td>
<td>Name</td>
<td>Keiki Shimizu</td>
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<tr>
<td>17</td>
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<td>Name</td>
<td>Kazuki Akieda</td>
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<td>Shinichi Iizuka</td>
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<td>19</td>
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<td>Name</td>
<td>Masaki Nakane</td>
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<td>Takayuki Taira</td>
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<td>Mie University Hospital</td>
<td>Imai Hiroshi</td>
<td>Department of Emergency and Disaster Medicine, Mie University Graduate School of Medicine</td>
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<td>Ebina General Hospital</td>
<td>Takeshi Yamagiwa</td>
<td>Department of Emergency and Critical Care Medicine, Ebina General Hospital</td>
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<tr>
<td>23</td>
<td>Hitachi General Hospital</td>
<td>Kensuke Nakamura</td>
<td>Department of Emergency and Critical Care Medicine, Hitachi General Hospital</td>
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<tr>
<td>24</td>
<td>Sapporo City General Hospital</td>
<td>Hisako Sageshima</td>
<td>Department of Emergency Medicine, Sapporo City General Hospital</td>
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<tr>
<td>25</td>
<td>Sunagawa City Medical Center</td>
<td>Shota Kawahara</td>
<td>Department of Emergency Medicine, Sunagawa City Medical Center</td>
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<td>26</td>
<td>Tsuchiura Kyodo General Hospital</td>
<td>Akira Endo</td>
<td>Department of Acute Critical Care Medicine, Tsuchiura Kyodo General Hospital</td>
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<tr>
<td>27</td>
<td>Nippon Medical School</td>
<td>Shoji Yokobori</td>
<td>Department of Emergency and Critical Care Medicine, Nippon Medical School</td>
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<td>28</td>
<td>Nippon Medical School Musashikosugi Hospital</td>
<td>Takashi Tagami</td>
<td>Department of Emergency and Critical Care Medicine, Nippon Medical School Musashikosugi Hospital</td>
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<tr>
<td>29</td>
<td>Japan Red Cross Maebashi Hospital</td>
<td>Jun Nagayama</td>
<td>Department of Emergency and Critical Care Medicine, Japan Red Cross Maebashi Hospital</td>
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<tr>
<td>30</td>
<td>Hirosaki University Hospital</td>
<td>Hiroyuki Hanada</td>
<td>Department of Emergency and Disaster Medicine</td>
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<td>31</td>
<td>Shizuoka General Hospital</td>
<td>Chihiro Narita</td>
<td>Department of Emergency Medicine, Shizuoka General Hospital</td>
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<td>Jiro Takahashi</td>
<td>Department of Acute Medicine, Kawasaki Medical School</td>
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<td>Hitoshi Kikuchi</td>
<td>Department of Emergency Medicine, Sagamihara Kyodo Hospital</td>
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<td>Akita Redcross Hospital</td>
<td>Yasuo Fujita</td>
<td>Department of Emergency and Critical Care Center, Akita Redcross Hospital</td>
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<tr>
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<td>Yoshihisa Fujinami</td>
<td>Department of Emergency Medicine, Kakogawa Central City Hospital</td>
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<tr>
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<td>Toho University Omori Medical Center</td>
<td>Mitsuru Honda</td>
<td>Critical Care Center, Toho University Omori Medical Center</td>
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<td>Matsudo City General Hospital</td>
<td>Kiyoshi Murata</td>
<td>Emergency Medicine and Acute Care Surgery, Matsudo City General Hospital</td>
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<tr>
<td>38</td>
<td>Dokkyo medical University</td>
<td>Eisei Hoshiyama</td>
<td>Department of Neurology/Emergency and Critical Care Medicine, Dokkyo medical University</td>
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<tr>
<td>39</td>
<td>National Center for Global Health and Medicine</td>
<td>Yumi Funato</td>
<td>Department of Emergency Medicine and Critical Care, National Center for Global Health and Medicine</td>
</tr>
</tbody>
</table>

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**BMJ Open**

4. Benefits and disadvantages for research participants
   (1) Benefits of participation in this study
   Since it is not clear whether restricted or conventional oxygen therapy is more effective, there is no uniform benefit from participating in this study.

   (2) Disadvantages of participation in this study
   1) Burdens associated with participation in this study
      1. Physical and mental strain
      Hypoxemia may occur more frequently in patients receiving restricted oxygen therapy with a target SpO\textsubscript{2} of 94–95% than in those receiving conventional oxygen therapy with a target SpO\textsubscript{2} of 98% or higher. If hypoxemia persists, multiple organ damage may occur. However, a pilot study of prehospital oxygen therapy in post-cardiac arrest patients with a lower target SpO\textsubscript{2} limit of 90% showed no significant increase in adverse events. As mentioned above, limited oxygen therapy can be expected to improve neurological function; therefore, the balance of anticipated benefits and disadvantages is acceptable based on current medical knowledge.

      2. Economic burden
      The administration of the pharmaceuticals used in this study and the tests performed will be covered by the National Health Insurance. There will be no additional cost burden to the research participants as a result of their participation in the study.

   2) Risks associated with participation in this study
   Participation in research creates risks, such as the disclosure of personal patient information.

   3) Reduction of burdens and risks
   Patient information obtained will be registered through the clinical research data management system (HOPE eACReSS) and anonymized in advance with a number unrelated to the personal information of the research participant. Sufficient care will be taken to protect the confidentiality of research participants. The person in charge of the treatment facility will supervise the strict management of correspondence anonymization and ensure that information is kept strictly confidential. This number will be used when information is sent to the research secretariat or other related organizations, and sufficient care will be taken to ensure that the research participant's personal information is not leaked.
      1. Burden reduction expenses
      There are no burden reduction costs in this study.

      2. Compensation for damage to health
      If a health hazard occurs to a research participant as a result of the implementation of this research, the person in charge of the research will take appropriate measures. In such cases, if treatment or examinations are necessary, they will be performed under the research participant’s normal insurance coverage. This study will not provide financial compensation.
for any health damage to research participants.

3. Disadvantages associated with not participating in this study
There will be no disadvantages resulting from the failure to participate in the study. If you do not participate in the study, you will receive oxygen therapy according to the policies of the treatment facility where you are receiving the treatment.

5. Handling of personal information.
Patient information obtained will be registered through the clinical research data management system (HOPE eACReSS) and anonymized in advance with a number unrelated to the personal information of the research participant. Sufficient care will be taken to protect the confidentiality of research participants. The person in charge of the treatment facility will supervise the strict management of correspondence anonymization and ensure that information is kept strictly confidential. This number will be used when information is sent to the research secretariat or other related organizations, and sufficient care will be taken to ensure that the research participant’s personal information is not leaked.

(1) Protection of privacy
When handling information related to the implementation of the research, we will anonymize the information by attaching a number unrelated to the personal information of the research participant in advance. Due consideration will be given to protect the research participant’s confidentiality.

(2) Anonymization of samples and information
Anonymization will be performed by assigning a number unrelated to the personal information of the research participant in advance. Due consideration will be given to protect the research participant’s confidentiality. The person in charge of the treatment facility will supervise the strict anonymization of charts and ensure that information is kept strictly confidential.

(3) Provision of personal and other information to joint research institutions
Personal information and any other information will not be provided to joint research institutions.

(4) Ethical review committees, regulatory authorities, monitoring and auditing personnel, and others may have access to samples and information.
The Ethics Review Committee, regulatory authorities, monitoring personnel, and Data and Safety Monitoring Committee may have access to samples and information in accordance with established procedures.

6. Methods of disclosure of research protocols and other documents and information on research
(1) Disclosure of research protocols
The Principal Investigator will register a summary of such research in the public database (UMIN-CTR) prior to its implementation and update it as appropriate according to changes in the research protocol and the progress of the research.
(2) Disclosure of research information
In addition to the disclosure of the abovementioned research protocol, when the research is completed, the results will be registered without delay. When publishing the results, we will take necessary measures to protect the human rights of research participants and related parties, as well as the rights and interests of the persons in charge of the research and their related parties. When the final results are published, we will report them to the head of the research institution without delay.

We also have a system in place to contact the principal investigator for direct consultation.

7. Handling of research results related to the research participants
If the research collaborators wish to know about the research plan or related materials regarding this research, they may do so except for personal information about other patients or matters that may interfere with the overall research. The overall research results will also be provided at the patient's request. No information will be provided if a request is made by a person other than the patient himself/herself.

8. Publication of research results
The results of this research will be published in medical societies and scientific papers after ensuring that the individuals cannot be identified.

9. Attribution of intellectual property rights arising from research
If any intellectual property rights arise from this study, they will belong to the researcher, not the patient.

10. Storage of Samples and Information and Handling Policy after Completion of Research
(1) Methods for storage and destruction of samples and information
Information and other data obtained in this study will be stored in a secured cabinet in the Office of the Department of Emergency and Critical Care Medicine, Keio University School of Medicine (Building No. 3, North Wing, 2nd floor). Electronic data will be stored on a hard disk in the Research Office of the Department of Emergency and Critical Care Medicine, Keio University School of Medicine, and the stored hard disk will be kept in the Office of the Department of Emergency and Critical Care Medicine, Keio University School of Medicine. When destroying information, it is cut into illegible pieces and destroyed. In the case of non-rewritable electronic media, the data will be physically destroyed to make them unreadable and then properly disposed of in accordance with waste management regulations. In the case of rewritable electronic media data, the data will be physically destroyed to make them unreadable or overwritten with dummy data multiple times to make the original data unrecoverable and disposed of in the same manner.

(2) Handling samples and information after completion of the research.
Within a certain period determined by the Ethics Committee, the information will be kept
according to the method specified in (1).

(3) Possibility of being used for future research or provided to other research institutions.
The information obtained in this study may be used for future research that was not identified at the time consent was obtained. However, in such cases, we will prepare or modify the research protocol and obtain approval from the review committee and permission from the head of the research institution. If the information is to be provided to other research institutions, it will be reported to the head of the research institution and anonymized before being provided.

11. Matters related to Research funding and conflicts of interest
(1) Research funding for this research
Funding for this study will be obtained by applying for research led by the Japanese Association of Emergency Medicine and Grants-in-Aid for Scientific Research.

(2) Conflicts of interest of researchers and research institutions
A conflict of interest review will be handled in accordance with the regulations of each institution. The person in charge of the research at Keio University School of Medicine shall report the necessary information to the Conflict of Interest Review Committee for review and approval in accordance with university regulations.

12. Inquiries
Research Secretariat
Principal Investigator: Ryo Yamamoto
Name of Institution: Department of Emergency and Critical Care Medicine, Keio University School of Medicine
Position: Research Associate
Address: 35 Shinanomachi, Shinjuku, Tokyo
Phone: 03-3225-1323, weekdays 8:40-17:00
E-mail: ryoyamamoto@keio.jp
Early Restricted Oxygen Therapy after Resuscitation from Cardiac Arrest: A Multicenter Stepped-Wedge Cluster Randomized Controlled Trial

I have received an explanation of the abovementioned research using the explanatory document with the same version number as this consent document, understood each of the following items, and agreed to participate in the research on my own volition.

[Items explained and understood]
1. Purpose and Significance of this Study
2. Voluntary nature of participation in research and freedom to withdraw
3. Methods of Conducting Research and Items of Research Cooperation
4. Benefits and Disadvantages for Research Subjects
5. Handling of Personal Information
6. Methods of Disclosure of Research Protocols and Other Documents and Information on Research
7. Handling of research results concerning the research subjects themselves
8. Publication of research results
9. Attribution of intellectual property rights arising from research
10. Storage of Samples and Information and Handling Policy after Completion of Research
11. Matters related to Research funding and conflicts of interest
12. Inquiries

Consent to Handling of Samples/Information
1. I agree that after completing this research, the sample/information I have provided will be stored as described in the explanatory document.
   Yes (→ Go to 2 below) / No
2. I consent to the use of the samples and information stored in accordance with consent in 1 above for future medical research with the same purpose as this research, which is newly planned and carried out.
   Yes / No

Research Participant Entry (to be completed by you)
Date of consent (Year, Month, Date) Research Participant Name: ____________________________
(Required: In case of consent by the applicant) <Signature>
Alternate Name: ____________________________
(By proxy) <Signature>

(To be completed only by the personal information manager)
Research Participant ID (Anonymized ID)
説明文書

研究課題名
心停止後患者に対する初期制限酸素療法：
多施設共同 stepped wedge クラスターランダム化比較試験
（略称 ER-OXYTRAC）

研究グループ名 JAAAM ER-OXYTRAC trial Group

研究責任者 佐々木淳一
研究機関名 慶應義塾大学医学部（所属） 救急医学教室

この度、慶應義塾大学病院に受診される患者さんに下記の研究を実施することとなりました。つきましては、ご協力をお願いいたします。患者さんのプライバシー保護については最善を尽きます。本研究は倫理委員会での承認、慶應義塾大学医学部長の許可を受けており、本研究における選択基準を満たした方を研究対象者候補としております。

1 この研究の目的と意義
(1) この研究の目的
心停止に対する治療は世界的な重要課題で、様々な研究によって蘇生治療が発展してきております。しかし、蘇生に成功したとしても心停止蘇生後症候群（Post cardiac arrest syndrome; PCAS）と呼ばれる重度の後遺症が発症することが知られています。

古くより PCAS 予防として酸素投与療法が行われてきましたが、近年の報告によると、過剰な酸素投与によって脳神経障害を引き起こすことが示唆されております。そのため、世界的な心肺蘇生ガイドラインでは、蘇生後の酸素療法において、末梢血酸素飽和度（SpO2）が「94%以上」になる様に酸素投与量を調整しても「良い」という記載、あるいは「92%～98%」に調整するという記載に至っていますが、その有効性は明らかになっていません。また、多くの施設で98%以上にするという治療が現在も行われています。

そこで、本研究では、心停止蘇生後にSpO2の目標値を94～95%として酸素投与量を調整する治療戦略が、神経学的予後を改善させるかを明らかにすることを目的としています。

(2) この研究を実施する意義
本研究によって、心停止蘇生後のSpO2の目標値を94～95%として酸素投与量を調節することが、脳機能予後を改善させることが判明した場合、あるいはその効果がないと判明した場合、いずれの場合であっても、その結果は国際的なガイドラインとして広まっていくことが予想されます。つまり、全世界での心停止蘇生治療の改善へつなげることが出来ると考えられます。
2 研究参加の任意性と撤回の自由
(1) この研究への参加は任意です。
　この試験に「参加する」、「参加しない」は患者さんの自由です。

(2) この研究への参加に同意された後でも、いつでも撤回することができます。
　研究に参加された後でも、いつでも断ることができます。その時、患者さんが不利益を受けることは一切ありません。

(3) 通常の診療を超える医療行為の有無（有りの場合、他の治療方法等に関する事項）
　本研究において、通常の診療を超える医療行為はありません。

3 研究の実施方法・研究協力事項
(1) この研究の実施期間
　実施許可日から 2026 年 3 月 31 日まで

(2) この研究の実施方法
　この研究では、研究の参加施設および時期によって指定された下記の 2 つの酸素療法のいずれかを、心停止蘇生後から 12 時間行います。
　制限酸素療法：自己心拍再開後、目標 SpO2 値を 94～95%として吸入酸素濃度 (FiO2) を調整する。
　通常酸素療法：自己心拍再開後、目標 SpO2 値を 98%以上として吸入酸素濃度 (FiO2) を調整する。
　吸入酸素濃度 (FiO2) の調整以外のすべての治療に関しては、治療担当医の判断に従って通常通り行います。また、より厳密な FiO2 の調整が必要な病態であると判断された場合も、上記の目標 SpO2 値とは無関係に FiO2 の調整を行います。

なお、この研究はクラスターランダム化比較試験という方法で行います。クラスターランダム化比較試験では、施設毎に行う治療が決定するため、患者さんの意思で上記の治療法を選択することは出来ません。ただ、制限酸素療法も通常酸素療法も、世界的な心肺蘇生ガイドラインで推奨されている治療内容を逸脱しないものとなっております。

(3) 協力をお願いする事項
　心停止蘇生後 12 時間は、制限酸素療法あるいは通常酸素療法（施設および研究の時期によって決定されるので、患者さんを選択できません）による治療を受けていただきます。どちらの治療も、世界的な心肺蘇生ガイドラインで推奨されている治療内容を逸脱しないものとなっております。また、より厳密な FiO2 の調整が必要な病態であると治療医が判断した場合は、上記酸素療法とは無関係に FiO2 の調整を行います。
　また、下記の情報を提供していただきます。
1) 取得する試料・情報
①患者基本情報：年齢、性別、身長、体重、心停止前のclinical frailty scale、併存疾患（心筋梗塞、うっ血性心不全、末梢血管疾患、脳血管障害、認知症、慢性呼吸器疾患、胃腸障害、脳血管障害、認知症、慢性呼吸器疾患、膠原病、消化性潰瘍、肝疾患、糖尿病、慢性腎臓病、悪性腫瘍、AIDS）、心停止前のCerebral Performance Category
②心停止関連情報：発生状況（消防あるいは病院内医療従事者の救急発生年月日時刻、発生場所、目撃の有無、目撃の年月日時刻）、蘇生経過（心停止診断年月日時刻、バイスタンダーセルビングの有無、緊急から生じたバイスタンダーセルビングの有無、バイスタンダー実施者の概要、CRP開始年月日時刻、救急隊セールビングの有無、開始時刻、初期波形、心停止確認時の瞳孔径、対光反射）
③介入開始時の病態・重症度：SOFAスコア、自己心拍再開直後のバイタルサイン（収縮期血圧、拡張期血圧、平均血圧、脈拍、GCS、瞳孔径、対光反射）、自己心拍再開直後の血液検査等（動脈血pH、動脈血PO2、酸素分圧、乳酸値、D-dimer、塩基異常、P/F ratio、ヘモグロビン、血小板、総ビリルビン、BUN、クレアチニン、Dダイマー、FDP、フィブリノーゲン、Pt-INR）
④介入後12時間以内の臨床情報：介入開始から12時間までの、1時間毎のSpO2、3時間毎の動脈血PO2とFiO2、介入開始から12時間までのSpO2最大値、最小値、介在開始から12時間までにSpO2が90%未満となった回数、介入開始から12時間までの、低酸素血症の有無、介入開始から12時間以内に測定したSCVO2あるいはPaO2と測定時間、介入開始から12時間以内に開始したECMO・鎮静鎮痛薬、介入開始から12時間時点でのRASS・投与中の抗菌薬・投与中的筋弛緩薬、蘇生リーダーの医療感情尺度、介在開始から12時間後のバイタルサイン（収縮期血圧、拡張期血圧、平均血圧、脈拍、GCS、瞳孔径、対光反射）、介入開始から12時間後の血液検査等（動脈血pH、動脈血PO2、動脈血PCO2、乳酸値、P/F ratio、ヘモグロビン、血小板、総ビリルビン、BUN、クレアチニン、Dダイマー、FDP、フィブリノーゲン、Pt-INR）
⑤介在開始から30日時点の臨床情報：介在から30日後のCPC、体温管理療法の維持体温、施行時間、方法、目標体温までの到達時間、介在から7日目までのDVT予防、介在から7日目までに行った栄養療法、介在から30日までに診断された肺炎、PE/DVT
⑥介在から90日時点の臨床情報：介在から90日後のCPC、介在から90日目までのHospital-free days、介在から90日目までのICU-free days、介在から90日目までのVentilator-free days、介在から90日目までのRRT-free days、介在から90日目までのOxygen-free days、介在から90日後のclinical frailty scale
⑦研究実施期間中に発生した有害事象

2) 調査・情報の利用目的と取り扱い方法
(4) この研究の実施体制

1) 本研究を実施する共同研究機関（自機関も含む）と責任者

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<td>東邦大学医療センター大森病院</td>
<td>氏名</td>
<td>本多満</td>
<td>教授</td>
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</tbody>
</table>
4 研究対象者の利益と不利益

（1）この研究への参加による利益
制限酸素療法と通常酸素療法のどちらがより有効であるかは明らかになっておりませんので、本研究に参加することで、一様にうける利益はありません。

（2）この研究への参加による不利益
1）この研究への参加に伴う負担について
①身体・精神の負担
SpO2 の目標値を 94～95% として制限酸素療法を行う患者において、SpO2 の目標値を 98% 以上として酸素投与量を調節する患者に比較して、低酸素血症が出現する頻度があがる可能性があります。低酸素血症が持続した場合は複数臓器の障害が発生する可能性があります。しかしながら、SpO2 の目標下限を 90% とした心停止後患者に対する病院前の酸素療法の研究において、有害事象の有意な上昇は認められず、また、上記の通り制限酸素療法にて神経学的機能予後が改善することが期待できるため、予想される利益と不利益のバランスは、現時点での医学的知見から許容できる範囲内のものであると考えられます。

②経済的な負担
本研究で用いる医薬品の投与及び実施する検査は保険診療内で行われます。研究に参加することによる研究対象者の追加の費用負担は発生しません。

2）この研究への参加に伴うリスクについて
研究参加によって患者個人情報の漏洩などのリスクが生じます。
3) 負担・リスクの軽減について

取得した患者情報は臨床研究データ管理システム（HOPE eACReSS）を通じて登録を行い、研究実施に係る情報を取り扱う際は、予め研究対象者の個人情報とは無関係の番号を付して匿名化し、研究対象者の秘密保護に十分配慮します。匿名化対応表は、治療施設の責任者が厳重に保管するよう監督します。情報を研究事務局等の関連機関に送付する場合はこの番号を使用し、研究対象者の個人情報が院外に漏れないよう十分配慮します。

①負担軽減費について
本研究における負担軽減費はありません。

②健康被害に対する補償について
本研究の実施に伴い、研究対象者に健康被害が発生した場合は、研究担当者は適切な処置を講じます。その際、治療又は検査等が必要となった場合は、研究対象者の通常の保険診療内で実施します。以上のことから、本研究では研究対象者の健康被害に対する金銭的な補償は準備しません。

③この研究へ参加しなかったことに伴う不利益について
研究に参加しなかったことによって生じる不利益はありません。研究に参加しなかった場合は、治療を受けている施設の方針にしたがって、酸素療法が行われます。

5) 個人情報等の取り扱い

取得した患者情報は臨床研究データ管理システム（HOPE eACReSS）を通じて登録を行い、研究実施に係る情報を取り扱う際は、予め研究対象者の個人情報とは無関係の番号を付して匿名化し、研究対象者の秘密保護に十分配慮します。匿名化対応表は、治療施設の責任者が厳重に保管するよう監督します。情報を研究事務局等の関連機関に送付する場合はこの番号を使用し、研究対象者の個人情報が院外に漏れないよう十分配慮します。

(1) プライバシーの保護について
研究実施に係る情報を取り扱う際は、予め研究対象者の個人情報とは無関係の番号を付して匿名化し、研究対象者の秘密保護に十分配慮します。

(2) 試料・情報の匿名化
予め研究対象者の個人情報とは無関係の番号を付して匿名化し、研究対象者の秘密保護に十分配慮します。匿名化対応表は、治療施設の責任者が厳重に保管するよう監督します。

(3) 共同研究機関への個人情報等の提供
共同研究機関への個人情報等の提供は行いません。

(4) 倫理審査委員会、規制当局、モニタリング・監査担当者などが、試料・情報を閲覧する場合があること。
倫理審査委員会、規制当局、モニタリング担当者、効果・安全性評価委員会が、決められた手順に則って、試料・情報を閲覧する場合があります。

6 研究計画書等の開示・研究に関する情報公開の方法

(1) 研究計画書等の開示

研究代表者は、公開データベース（UMIN-CTR）に当該研究の概要をその実施に先立って登録し、研究計画書の変更及び研究の進捗に応じて適宜更新します。

(2) 研究に関する情報公開

上記研究計画書等の開示に加え、研究を終了したときは、遅滞なく、当該研究の結果を登録します。また、結果を公表する際は、研究対象者及びその関係者の人権又は研究担当者及びその関係者の権利利益の保護のために必要な措置を講じた上で行います。結果の最終の公表を行ったときは、遅滞なく研究機関の長へ報告します。

また、研究責任者に連絡のうえ、直接相談していただく体制を整えています。

7 研究対象者本人に関する研究結果等の取り扱い

この研究に関して、研究協力者本人が研究計画や関係する資料を知りたい場合は、他の患者さんの個人情報や研究全体に支障となる事項以外はお知らせすることができます。また研究全体の成果につきましては、患者さん本人のご希望があればお知らせいたします。なお本人以外からの請求の場合にはいかなる情報も提供しません。

8 研究成果の公表

研究成果は、本人の特定ができないようにしたうえで、医学会や学術論文で発表される予定です。

9 研究から生じる知的財産権等の帰属

本研究で知的所有権が発生した場合、その権利は研究者に帰属し、患者さんには帰属しません。

10 試料・情報の保管および研究終了後の取り扱い方針

(1) 試料・情報の保管および破棄の方法

本研究で得られた情報等は、慶應義塾大学医学部救急医学医局（三号館北棟2階）内の施錠ができるキャビネットに保存します。電子データは慶應義塾大学医学部救急医学研究室のハードディスクに保存し、保存されたハードディスクは慶應義塾大学医学部救急医学研究室に保管されます。また、情報等を破棄する際は、全ての情報を判読不能な状態に裁断し、破棄します。書き換え不可な電子媒体の場合、物理的破壊してデータ読み取りを不可能にした上で、廃棄物管理規程に従って適切に廃棄いたします。書き換え可能な電子媒体のデータの場合、物理的に破壊してデータ読み取りを不可能にするか、又はダミーデータを複数回お書きして元のデータを復元不可能な状態にして、同様に廃棄いたします。
研究終了後の試料・情報の取り扱い

倫理委員会で定めた一定期間内は、上記(1)で定めた方法によって保管します。

将来の研究のために用いられる可能性又は他の研究機関に提供する可能性

本研究で得られた情報は、同意を受ける時点では特定されない将来の研究のために用いる可能性があります。ただし、その場合には、改めて研究計画書を作成又は変更し、審査委員会の承認及び、研究機関の長の許可を得ます。また、他の研究機関に情報を提供する場合には、研究機関の長に報告し匿名化した上で提供します。

研究資金等および利益相反に関する事項

(1) 本研究を実施するための研究資金等について

本研究の資金は日本救急医学会主導研究や科研費などに応募することで今後取得する予定です。

(2) 研究者等および研究機関の利益相反について

利益相反審査の取り扱いは、各施設の規定に従って実施します。慶應義塾大学医学部の研究担当者は、大学規定にしたがって、利益相反審査委員会に必要事項を申告し、その審査と承認を得るもののとします。

問い合わせ先

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同意文書

心停止後患者に対する初期制限酸素療法:
多施設共同 stepped wedge クラスターランダム化比較試験

私は、上記の研究について、本同意文書と同じ版番号の説明文書を用いて説明を受け、以下の各項目について理解し、自らの意思により研究への参加に同意します。

【説明を受け理解した項目】
1 この研究の目的と意義 8 研究成果の公表
2 研究参加の任意性と撤回の自由 9 研究から生じる知的財産権等の帰属
3 研究の実施方法・研究協力事項 10 試料・情報の保管および研究終了後の取り扱い方針
4 研究対象者の利益と不利益 11 研究資金等および利益相反に関する事項
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6 研究計画書等の開示・研究に関する情報公開の方法
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・試料・情報の取り扱いに関する同意
1. 本研究の終了後、提供した試料・情報が、説明文書に記載の通り保管されることに同意します。
   □はい (⇒下記2へ) □いいえ
2. 上記1の同意に基づいて保管された試料・情報が、将来新たに計画および実施される、本研究と同趣旨の医学研究に利用されることに同意します。
   □はい □いいえ

研究対象者記入欄 (ご自身で記入して下さい)

同意日 西暦 20 年 月 日 研究対象者 氏名：

(代読：本人同意の場合) <署名>

代読者 氏名：

(代読による場合) <署名>

統柄：

(研究者等記入欄)

説明日 西暦 20 年 月 日 説明者：

(必須：研究責任者、実務責任者、または分担当者)<署名>

説明補助者：

(任意：上記以外)<署名>

(個人情報管理者のみ記入)

研究対象者 ID（匿名化 ID）