Targeting two different levels of both arterial carbon dioxide and arterial oxygen after cardiac arrest and resuscitation: a randomised pilot trial

Authors

Pekka Jakkula, MD, Department of Anaesthesiology, Intensive Care and Pain Medicine, University of Helsinki and Helsinki University Hospital, Helsinki, Finland, pekka.jakkula@hus.fi, +358 400 552370 (corresponding author)

Matti Reinikainen, MD, PhD, Associate Professor, Department of Intensive Care, North Karelia Central Hospital, Joensuu, Finland

Johanna Hästbacka, MD, PhD, Department of Anaesthesiology, Intensive Care and Pain Medicine, University of Helsinki and Helsinki University Hospital, Helsinki, Finland

Pekka Loisa, MD, PhD, Department of Intensive Care, Päijät-Häme Central Hospital, Lahti, Finland

Marjaana Taïinen, MD, PhD, Department of Neurology, University of Helsinki and Helsinki University Hospital, Helsinki, Finland

Ville Pettilä, MD, PhD, Professor, Department of Anaesthesiology, Intensive Care and Pain Medicine, University of Helsinki and Helsinki University Hospital, Helsinki, Finland

Jussi Toppila, MD, PhD, HUS Medical Imaging Center, Clinical Neurophysiology, University of Helsinki, Helsinki University Hospital and University of Helsinki, Finland

Marika Lähde, MD, Department of Anaesthesia and Intensive Care, Päijät-Häme Central Hospital, Lahti, Finland

Minna Bäcklund, MD, PhD, Department of Anaesthesiology, Intensive Care and Pain Medicine, University of Helsinki and Helsinki University Hospital, Helsinki, Finland

Marjatta Okkonen, MD, PhD, Department of Anaesthesiology, Intensive Care and Pain Medicine, University of Helsinki and Helsinki University Hospital, Helsinki, Finland

Stepani Bendel, MD, PhD, Department of Intensive Care, Kuopio University Hospital, Kuopio, Finland

Thomas Birkelund, MD, Aarhus University Hospital, Aarhus, Denmark

Anni Pulkkinen, MD, Department of Anaesthesia and Intensive Care, Central Finland Central Hospital, Jyväskylä, Finland

Jonna Heinonen, study coordinator, Department of Anaesthesiology, Intensive Care and Pain Medicine, Helsinki University Hospital, Helsinki, Finland

Tuukka Tikka, study nurse, Department of Anaesthesiology, Intensive Care and Pain Medicine, Helsinki University Hospital, Helsinki, Finland

Markus B Skrifvars, MD, PhD, Professor, Department of Anaesthesiology, Intensive Care and Pain Medicine and Department of Emergency Medicine and Services, University of Helsinki and Helsinki University Hospital, Helsinki, Finland

COMACARE study group
Participants

We included adult patients resuscitated from witnessed OHCA with ventricular fibrillation (VF) or ventricular tachycardia (VT) as the initial rhythm. In addition, all of the following inclusion criteria had to be met: (1) return of spontaneous circulation (ROSC) 10-45 minutes from the onset of cardiac arrest; (2) confirmed or suspected cardiac origin of the arrest; (3) mechanical ventilation upon ICU arrival; (4) markedly impaired level of consciousness defined as no response to verbal commands and Glasgow coma scale (GCS) motor score < 5 (withdrawal to painful stimuli at best); (5) deferred consent from next of kin possible or likely; and (6) active intensive care and targeted temperature management (TTM) initiated. We excluded patients with confirmed or suspected acute or pre-existing intracranial pathology and/or suspicion of increased intracranial pressure. We also excluded patients with severe oxygenation failure defined as PaO$_2$/FiO$_2$ (fraction of inspired oxygen) < 100 mmHg upon arrival to ICU and no improvement in oxygenation after adding sufficient PEEP level. Additional exclusion criteria were severe chronic obstructive pulmonary disease, age < 18 or > 80 years and pregnancy.

Six ICUs across Finland and one in Denmark took part in the trial. We screened all patients resuscitated from OHCA and admitted to one of the participating ICUs for eligibility. Because of the nature of the trial, the patients’ unconscious state and the need for timely intervention, it was impossible to obtain informed consent from the participants before randomisation. Accordingly, we randomised the patients and initiated the intervention at the time of ICU admission. We obtained deferred informed consent from the patients’ next of kin as soon as they were present at the hospital. We obtained informed consent later from all patients who regained sufficient neurological function to make independent decisions (cerebral performance category [CPC] 1-2).

The study protocol and the deferred consent procedure were approved by the research ethics committees of Northern Savo Hospital District, Finland (decision No. 295/2015) and Midtjylland region, Denmark (decision No. 1-10-72-163-16). The trial protocol was also approved by the institutional review board at each site.

Data collection

We collected basic information regarding participants’ age, gender, prior health status, functional capacity and details related to the resuscitation in a web-based study database (Absolute Imaginary Software, Helsinki, Finland). For the first 48 h after ICU admission, we recorded all monitored vital parameters in a medical-approved tablet computer (Arbor
M1040, Taiwan) connected to the patient monitor using GE Healthcare S/5 Collect software version 4.0. We obtained blood samples for ABG analysis via arterial cannula and analysed them on site as part of the routine ICU care. We entered the results of the ABG analysis corrected to the patient’s actual temperature manually into the web-based study database. The doses of sedative and vasoactive drug infusions were also entered manually into the database. We exported ventilator parameters directly from the ventilators and saved them into a USB drive after the intervention. If this was not possible, we entered the ventilator data manually into the electronic database.

We obtained blood samples for the analysis of NSE, S100B and TnT concentrations at ICU admission and 24 h, 48 h and 72 h after cardiac arrest. In the Finnish centres, the samples were centrifuged (2000 G, 10 min) and frozen at -70 °C at the hospital laboratory. Later, the samples were sent to ISLAB laboratories (Kuopio, Finland) and analysed with electrochemiluminescence immunoassay (reagents: Roche Diagnostics GmbH, Mannheim, Germany; instrumentation: cobas e 601 analyzer, Hitachi High Technology Co, Tokyo, Japan) for NSE (cat number 12133113 122), S100B (cat number 03175243 190) and TnT (cat number 05092744 190) in January 2018. Because of possible interference with the NSE results, all serum samples were tested for haemolysis using the Roche haemolysis index and all samples with a haemolysis index > 500 mg of free haemoglobin per litre (n = 7) were excluded from the NSE analyses. In Aarhus University Hospital, Denmark, the samples were analysed immediately by the local laboratory using kits from the same manufacturer as ISLAB laboratories.

We measured frontal rSO₂ with a Covidien INVOS 5100C device (Covidien Company, USA). Two non-invasive skin sensors were attached to the patient’s forehead on both sides by a study nurse after randomisation. We saved the rSO₂ values (approximately 10 measurements per minute) from both sensors into a USB memory stick attached to the device. Later, we calculated hourly medians of the rSO₂ values of the left channel to be used in the analysis.

We applied continuous four-channel EEG monitoring to all patients upon ICU admission. We recorded the EEG with a GE Carescape module connected to the monitor (Datex-Ohmeda S/5 or GE B650/B850 depending on the centre) for 48 h after admission and saved the EEG data in the tablet computer recording the vital parameters using GE Healthcare Collect software. Later, all EEG recordings were analysed by one senior neurophysiologist blinded to the study group allocations. The EEG recordings were categorized into three groups according to the degree of abnormality (mild, moderate or
severe) as proposed by Crepeau et al. [1] at the beginning and at the end of the intervention.

Randomisation

We used a web-based randomisation system where a cryptographically strong random number generator with modulo bias eliminated was used to generate random numbers, and an unbiased Fisher-Yates (Durstenfeld) algorithm was used to shuffle blocks. We stratified the randomisation according to the target temperature of TTM (33°C or 36°C). The participants were enrolled and assigned to study interventions by a study nurse or the treating clinician at the ICU. The treating personnel was not blinded from the treatment targets because of the nature of the interventions. As NIRS monitoring is not part of the routine post-resuscitation care at the study centres, the NIRS monitor screens were not visible for the ICU staff. The neurophysiologist analysing the EEG results and the neurologist evaluating the neurologic recovery of the participants were blinded to the study group allocations.

Sample size calculation

Based on a previous cohort of OHCA patients, we expected the mean NSE concentration at 48 h to be close to 17 µg/l, and the standard deviation near 20 µg/l [2]. A study with 39 patients in each arm would have a power of 80 %, with the significance set at 0.05, to detect a 50 % difference in NSE. Given the possibility of death prior to 48 h and loss of follow-up, we decided to recruit 50 % more patients. Therefore, the sample size was set at 120 patients.

Statistical methods

We compared categorical data with the Chi-square test. We checked the continuous data for normality and compared the data with a normal distribution with the Student’s t-test and the data with a non-normal distribution with the Mann–Whitney U test. The intervention time was divided into 3 h periods starting from the time of ICU admission and the mean PaCO$_2$ and PaO$_2$ was calculated for each period for each patient. The median of these 3 h means was then compared between the low-normal and high-normal PaO$_2$ groups and normoxia and moderate hyperoxia groups over time using a generalized mixed model with a compound-symmetry covariance matrix. We compared the NSE serum concentrations at 48 h using the Mann–Whitney U test. The NSE, S100B, TnT and rSO$_2$
values over time were compared using a generalized mixed model with a compound-symmetry covariance matrix. The distributions of EEG abnormalities (mild, moderate, or severe), 30-day mortality and the six-month CPC results were compared with the Chi-square test. We analysed the interaction effect of the PaCO$_2$ and PaO$_2$ targets and the TTM, PaCO$_2$, PaO$_2$ and MAP targets on the CPC results at 6 months with a binary logistic regression model. We analysed the interaction effect of the PaCO$_2$ and PaO$_2$ targets and the TTM, PaCO$_2$, PaO$_2$ and MAP targets on the NSE results at 48 h with univariate analysis of variance. We performed all statistical analyses with the SPSS version 24.0.

References

1. Crepeau AZ, Rabinstein AA, Fugate JE, et al (2013) Continuous EEG in therapeutic hypothermia after cardiac arrest. Neurology 80:339–344.

2. Vaahersalo J, Hiltunen P, Tiainen M, et al (2013) Therapeutic hypothermia after out-of-hospital cardiac arrest in Finnish intensive care units: the FINNRESUSCI study. Intensive Care Med 39:826–837. doi: 10.1007/s00134-013-2868-1
352 Patients admitted to ICU after OHCA and assessed for eligibility

229 Excluded
  185 Did not meet inclusion criteria \( ^a \)
  71 Met exclusion criteria \( ^b \)
  17 Excluded because there was no study personnel available
  7 Excluded because study equipment was not functional or available
  9 Excluded for other reasons \( ^c \)

123 Randomised

61 Assigned to low-normal PaCO\(_2\) for 36 h

62 Assigned to high-normal PaCO\(_2\) for 36 h

3 Excluded after randomisation \( ^d \)

61 Completed the trial and were included in the analysis

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\( ^a \) Reasons for not meeting inclusion criteria were as follows: cardiac arrest not witnessed \( (n=82) \), initial rhythm other than ventricular fibrillation or ventricular tachycardia \( (n=104) \), time to return of spontaneous circulation \( < 10 \) or \( > 45 \) min \( (n=62) \), cardiac arrest with presumed non cardiac cause \( \text{e.g. asphyxia, trauma, massive bleeding, aortic dissection, intracranial bleeding} \) \( (n=68) \), patient not mechanically ventilated upon ICU admission \( (n=7) \), Glasgow Coma Scale motor score 5-6 \( (n=45) \), deferred consent from next of kin not possible or likely \( (n=17) \) and active intensive care or targeted temperature management not initiated \( (n=46) \).

\( ^b \) Exclusion criteria met were as follows: withdrawal from active intensive care due to terminal illness or severely reduced functional status \( (n=19) \), confirmed or suspected intracranial pathology and/or suspicion of increased intracranial pressure \( (n=15) \), age \( < 18 \) or \( > 80 \) years \( (n=26) \), pregnancy \( (n=1) \), severe oxygenation disorder at ICU admission \( (n=26) \) and severe chronic obstructive pulmonary disease \( (n=4) \).

\( ^c \) Other reasons for exclusion were as follows: long delay \( (> 6 \) h) from OHCA to ICU admission \( (n=3) \), study personnel was not informed about the patient \( (n=3) \), patient died during coronary angiography before ICU admission \( (n=1) \), problems with pregnancy test \( (n=1) \) and extracorporeal membrane oxygenation initiated at ICU admission \( (n=1) \).

\( ^d \) Reasons for exclusion after randomisation were as follows: deferred consent from next of kin denied \( (n=2) \), randomisation error \( (n=1) \).

Abbreviations: OHCA, out-of-hospital cardiac arrest; ICU, intensive care unit; PaCO\(_2\), arterial carbon dioxide tension.

**Figure 1a** Screened, excluded and included patients in the study and allocations to low-normal and high-normal PaCO\(_2\) groups
**Figure 1b** Screened, excluded and included patients in the study and allocations to normoxia and moderate hyperoxia groups

* Reasons for not meeting inclusion criteria were as follows: cardiac arrest not witnessed (n=82), initial rhythm other than ventricular fibrillation or ventricular tachycardia (n=104), time to return of spontaneous circulation < 10 or > 45 min (n=82), cardiac arrest with presumed non cardiac cause (e.g. asphyxia, trauma, massive bleeding, aortic dissection, intracranial bleeding) (n=68), patient not mechanically ventilated upon ICU admission (n=7), Glasgow Coma Scale motor score 5-6 (n=45), deferred consent from next of kin not possible or likely (n=17) and active intensive care or targeted temperature management not initiated (n=46).

* Exclusion criteria met were as follows: withdrawal from active intensive care due to terminal illness or severely reduced functional status (n=19), confirmed or suspected intracranial pathology and/or suspicion of increased intracranial pressure (n=15), age < 18 or > 80 years (n=26), pregnancy (n=1), severe oxygenation disorder at ICU admission (n=26) and severe chronic obstructive pulmonary disease (n=4).

* Other reasons for exclusion were as follows: long delay (> 6 h) from OHCA to ICU admission (n=3), study personnel was not informed about the patient (n=3), patient died during coronary angiography before ICU admission (n=1), problems with pregnancy test (n=1) and extracorporeal membrane oxygenation intiated at ICU admission (n=1).

* Reasons for exclusion after randomisation were as follows: deferred consent from next of kin denied (n=2), randomisation error (n=1).

Abbreviations: OHCA, out-of-hospital cardiac arrest; ICU, intensive care unit; PaCO₂, arterial carbon dioxide tension.
### Table 4. Results (p values) of the interaction analyses

|                     | PaCO₂ | PaO₂  | MAP  | TTM target |
|---------------------|-------|-------|------|------------|
| **NSE at 48 h**     |       |       |      |            |
| PaCO₂               | –     | 0.378 | 0.300| 0.959      |
| PaO₂                | 0.378 | –     | 0.098| 0.139      |
| MAP                 | 0.300 | 0.098 | –    | 0.244      |
| TTM target          | 0.959 | 0.139 | 0.244| –          |
| **Good neurological outcome (CPC 1-2) at 6 months** | | | | |
| PaCO₂               | –     | 0.421 | 0.858| 0.737      |
| PaO₂                | 0.421 | –     | 0.467| 0.126      |
| MAP                 | 0.858 | 0.467 | –    | 0.213      |
| TTM target          | 0.737 | 0.126 | 0.213| –          |

1 The interaction effects of PaCO₂, PaO₂, MAP and TTM targets on the NSE results at 48 h was assessed with the univariate analysis of variance. The interaction effects of PaCO₂, PaO₂, MAP and TTM targets on the CPC results at 6 months was analysed with a binary logistic regression model.

Abbreviations: PaCO₂, arterial carbon dioxide tension; PaO₂, arterial oxygen tension; MAP, mean arterial pressure; TTM, targeted temperature management; NSE, neuron-specific enolase and CPC, Cerebral Performance Category.

### Table 5. Causes of death during the 6 month follow-up

|                     | Low-normal PaCO₂ group | High-normal PaCO₂ group | Normoxia group | Moderate hyperoxia group |
|---------------------|------------------------|-------------------------|----------------|------------------------|
| **HIE**             | 14                     | 20                      | 16             | 18                     |
| **Other**           | 2                      | 2                       | 2              | 2                      |
| **Total**           | 16                     | 22                      | 18             | 20                     |

Abbreviations: HIE, hypoxic ischaemic encephalopathy and PaCO₂, arterial carbon dioxide tension.