ORIGINAL ARTICLE

Mild Hypercapnia or Normocapnia after Out-of-Hospital Cardiac Arrest

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ABSTRACT

BACKGROUND

Guidelines recommend normocapnia for adults with coma who are resuscitated after out-of-hospital cardiac arrest. However, mild hypercapnia increases cerebral blood flow and may improve neurologic outcomes.

METHODS

We randomly assigned adults with coma who had been resuscitated after out-of-hospital cardiac arrest of presumed cardiac or unknown cause and admitted to the intensive care unit (ICU) in a 1:1 ratio to either 24 hours of mild hypercapnia (target partial pressure of arterial carbon dioxide [$PaCO_2$], 50 to 55 mm Hg) or normocapnia (target $PaCO_2$, 35 to 45 mm Hg). The primary outcome was a favorable neurologic outcome, defined as a score of 5 (indicating lower moderate disability) or higher, as assessed with the use of the Glasgow Outcome Scale–Extended (range, 1 [death] to 8, with higher scores indicating better neurologic outcome) at 6 months. Secondary outcomes included death within 6 months.

RESULTS

A total of 1700 patients from 63 ICUs in 17 countries were recruited, with 847 patients assigned to targeted mild hypercapnia and 853 to targeted normocapnia. A favorable neurologic outcome at 6 months occurred in 332 of 764 patients (43.5%) in the mild hypercapnia group and in 350 of 784 (44.6%) in the normocapnia group (relative risk, 0.98; 95% confidence interval [CI], 0.87 to 1.11; P=0.76). Death within 6 months after randomization occurred in 393 of 816 patients (48.2%) in the mild hypercapnia group and in 382 of 832 (45.9%) in the normocapnia group (relative risk, 1.05; 95% CI, 0.94 to 1.16). The incidence of adverse events did not differ significantly between groups.

CONCLUSIONS

In patients with coma who were resuscitated after out-of-hospital cardiac arrest, targeted mild hypercapnia did not lead to better neurologic outcomes at 6 months than targeted normocapnia. (Funded by the National Health and Medical Research Council of Australia and others; TAME ClinicalTrials.gov number, NCT03114033.)

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*A complete list of the TAME Study Investigators, on behalf of the ANZICS Clinical Trials Group, the Irish Critical Care Clinical Trials Group, and the Australasian Resuscitation Outcome Consortium, is provided in the Supplementary Appendix, available at NEJM.org.

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Hypoxic–ischemic encephalopathy is the leading cause of death and disability among adults with coma who have been resuscitated after out-of-hospital cardiac arrest.[1,2] After the return of spontaneous circulation, brain hypoperfusion may contribute to cerebral hypoxia,[1,3] exacerbate brain damage, and lead to poor neurologic outcomes.[1,4-8]

The partial pressure of arterial carbon dioxide ($PaCO_2$) is the major physiological regulator of cerebrovascular tone,[8,9] and hypercapnia increases cerebral blood flow[10] by up to 2 ml per 100 g of brain tissue for each increase of 1 mm Hg in the $PaCO_2$.[11,12] Moreover, such cerebrovascular reactivity to $PaCO_2$ appears to be preserved after cardiac arrest.[13]

International guidelines[14,15] recommend targeting normocapnia in adults with coma who have been resuscitated after out-of-hospital cardiac arrest. However, normocapnia may be insufficient to restore and maintain adequate cerebral perfusion. Two observational studies showed that, after adjustment for illness severity, exposure to hypercapnia was associated with a significantly increased likelihood of discharge home[16] and better neurologic outcomes at 12 months, as compared with hypocapnia or normocapnia.[17] In addition, a physiological study[18] showed that deliberate increases in $PaCO_2$ induced higher cerebral oxygen saturations than normocapnia. Moreover, although it was insufficiently powered to assess patient-centered outcomes, a multicenter, phase 2, randomized trial[19] showed that hypercapnia significantly attenuated the release of neuron-specific enolase, a biomarker of brain injury; 23 patients (59%) in the mild hypercapnia group had a favorable 6-month neurologic recovery, as compared with 18 (46%) in the normocapnia group.[19] Thus, the most effective $PaCO_2$ target in adults with coma who are resuscitated after out-of-hospital cardiac arrest has not been well studied in randomized trials. We conducted the Targeted Therapeutic Mild Hypercapnia after Resuscitated Cardiac Arrest (TAME) trial to test the hypothesis that targeted mild hypercapnia would improve neurologic outcomes at 6 months as compared with targeted normocapnia in adults with coma who had been resuscitated after out-of-hospital cardiac arrest.

Methods

Trial Design

We performed an international, investigator-initiated, open-label, randomized trial. The protocol (which is available with the full text of this article at NEJM.org) was approved by ethics committees in each participating country. Written informed consent was deferred or was obtained from a legal surrogate, depending on the circumstances and local requirements, and consent to continue was obtained from each patient who regained mental capacity.

An independent data and safety monitoring committee reviewed the data and performed one prespecified, blinded interim analysis. The trial was designed and overseen by the steering committee (see the Supplementary Appendix, available at NEJM.org). Data were collected by site personnel and outcome assessors. Two of the authors analyzed the data. The first author wrote the first draft of the manuscript. All the authors contributed to the writing of the manuscript and to the decision to submit the manuscript for publication. The first two authors vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol. Additional information about the trial design and trial sites is provided in the Supplementary Appendix.

Patients

Hospitalized adults (≥18 years of age) with coma who had been resuscitated after out-of-hospital cardiac arrest of a presumed cardiac or unknown cause and who had a sustained return of spontaneous circulation (sustained for ≥20 minutes without chest compressions) were eligible for enrollment. The main exclusion criteria were an interval from the return of spontaneous circulation to screening of more than 180 minutes, unwitnessed cardiac arrest with an initial detected rhythm of asystole, and limitations of care (see the Supplementary Appendix).

Randomization and Blinding

As soon as possible after hospital admission, patients underwent randomization by means of a Web-based system with the use of random permuted block sizes, with stratification according to trial site and, whenever possible, concomitant

enrollment in the Targeted Hypothermia versus Targeted Normothermia after Out-of-Hospital Cardiac Arrest (TTM2) trial.[20] Enrolled patients were randomly assigned in a 1:1 ratio to targeted mild hypercapnia or targeted normocapnia.

Attending clinicians were aware of the intervention assignment, but assessors of prognosis and neurologic outcome were not. During data analysis, the statisticians and authors were unaware of the intervention assignments. A blinded manuscript, in which the intervention assignments were concealed, was written by the first author for each scenario before the randomization code was broken.[21]

TRIAL INTERVENTION

Patients were assigned to targeted mild hypercapnia ($PaCO_2$, 50 to 55 mm Hg) or to targeted normocapnia ($PaCO_2$, 35 to 45 mm Hg) for a 24-hour period beginning at randomization. The protocol recommended deep sedation (a target Richmond Agitation–Sedation Scale score[22] of −4 on a scale from −5 [unarousable] to 4 [combative]); the assessment of arterial blood gases, with no adjustment in blood pH for hypothermia-mediated effects on blood gases, every 4 hours[23]; and the use of end-tidal carbon dioxide levels by clinicians to guide ventilation management during the intervention period. Ventilator settings, sedation, and the use of paralyzing agents were at the discretion of the treating clinician. Details are provided in the Supplementary Appendix.

ASSESSMENT OF NEUROLOGIC PROGNOSIS AND WITHDRAWAL OF LIFE-SUSTAINING THERAPY

To assess for poor neurologic prognosis, at 96 hours after randomization or later, a clinician who was unaware of the intervention assignments performed a protocol-guided neurologic assessment of patients who remained in the intensive care unit (ICU). Full details of the neurologic assessment are provided in the Supplementary Appendix. Decisions regarding withdrawal of life-sustaining therapy were at the discretion of the treating medical team — an approach that is supported by international guidelines.[14]

PRIMARY AND SECONDARY OUTCOMES

The primary outcome was a favorable neurologic outcome, defined as a Glasgow Outcome Scale–Extended (GOS-E) score of 5 to 8 at 6 months[19,24] as determined by assessors who were unaware of the intervention assignments. A GOS-E score of 1 indicates death, 2 indicates a vegetative state, 3 to 4 indicates severe disability, 5 to 6 indicates moderate disability, and 7 to 8 indicates good recovery. If a GOS-E assessment could not be completed at 6 months, a dichotomized neurologic outcome of "favorable" (GOS-E score, 5 to 8) or "unfavorable" (GOS-E score, 1 to 4) was made on the basis of all available data, including a review of medical and interview records, by an assessor who was unaware of the intervention assignment.

Secondary outcomes included death within 6 months and poor functional outcome, which was defined as a modified Rankin scale[25] score of 4 to 6 at 6 months. A modified Rankin scale score of 0 indicates no symptoms, 1 no clinically significant disability, 2 slight disability, 3 moderate disability, 4 moderately severe disability, 5 severe disability, and 6 death. We also assessed patient-perceived health-related quality of life by means of the visual-analogue scale on the EuroQol Group 5-Dimension Self-Report Questionnaire (the EQ Visual Analogue Scale component of the EuroQol-5D-5L),[26] which ranges from 0 to 100 mm, with a score of 0 mm indicating "the worst health you can imagine" and a score of 100 mm as "the best health you can imagine."

Data were managed in a Web-based case-report form. Trained site research coordinators collected prehospital and hospital data. Outcome assessors who were unaware of the intervention assignments assessed 6-month outcomes from the patient (primary candidate) or their proxy (secondary candidate). Verification of trial data and the outcome measures are described in the Supplementary Appendix.

PRESPECIFIED ADVERSE EVENTS

Prespecified adverse events were pneumonia, sepsis, bleeding, arrhythmia resulting in hemodynamic compromise, skin complications related to the device used for targeted temperature management, and suspected or confirmed raised intracranial pressure or seizures necessitating normocapnia. Definitions of the adverse events are provided in the Supplementary Appendix.

STATISTICAL ANALYSIS

We calculated that enrollment of 1624 patients would provide the trial with 90% power to detect or reject a difference of 8 percentage points be-

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Mild Hypercapnia (N=829)	Normocapnia (N=839)
Demographic characteristics		
Age — yr	61.2±14.3	61.6±13.3
Male sex — no. (%)	635 (76.6)	681 (81.2)
Medical history		
Hypertension — no./total no. (%)	270/798 (33.8)	297/795 (37.4)
Diabetes — no. (%)	148 (17.9)	161 (19.2)
Percutaneous coronary intervention — no./total no. (%)	112/798 (14.0)	118/795 (14.8)
Myocardial infarction — no. (%)	96 (11.6)	128 (15.3)
Chronic obstructive pulmonary disease — no. (%)	82 (9.9)	87 (10.4)
Heart failure — no. (%)	59 (7.1)	74 (8.8)
Coronary-artery bypass grafting — no. (%)	48/798 (6.0)	58/795 (7.3)
NYHA class III or IV heart failure — no./total no. (%)	10/804 (1.2)	18/811 (2.2)
Median Charlson comorbidity index (IQR)†	2 (1–4)	2 (1–4)
Characteristics of the cardiac arrest		
Location of the cardiac arrest — no. (%)		
Place of residence	471 (56.8)	461 (54.9)
Public place	266 (32.1)	277 (33.0)
Workplace	59 (7.1)	67 (8.0)
Other	33 (4.0)	34 (4.1)
Bystander-witnessed cardiac arrest — no. (%)	730 (88.1)	744 (88.7)
Bystander-performed CPR — no. (%)	667 (80.5)	681 (81.2)
First monitored rhythm — no. (%)		
Shockable rhythm	581 (70.1)	608 (72.5)
Ventricular fibrillation	554 (66.8)	578 (68.9)
Nonperfusing ventricular tachycardia	27 (3.3)	30 (3.6)
ROSC after bystander-initiated defibrillation	28 (3.4)	27 (3.2)
Unknown rhythm, shock administered	24 (2.9)	19 (2.3)
Nonshockable rhythm	181 (21.8)	176 (21.0)
Pulseless electrical activity	110 (13.3)	98 (11.7)
Asystole	71 (8.6)	78 (9.3)
Unknown rhythm, no shock administered	15 (1.8)	9 (1.1)
Median time from cardiac arrest to sustained ROSC (IQR) — min‡	26 (17–40)	25 (16–39)
Median time from cardiac arrest to randomization (IQR) — min	154 (121–183)	151 (117–180)
Clinical characteristics on hospital admission		
Tympanic temperature — °C	35.4±1.1	35.4±1.1
Median FOUR motor score (IQR)§	0 (0–0)	0 (0–0)
Corneal reflexes present in both eyes — no./total no. (%)	121/277 (43.7)	112/280 (40.0)
Pupillary reflexes present in both eyes — no./total no. (%)	517/664 (77.9)	526/665 (79.1)
Median arterial pH (IQR)	7.20 (7.10–7.28)	7.22 (7.10–7.29)
Arterial lactate level — mmol/liter	6.79±3.58	7.00±3.93
First measured $Paco_2$ — mm Hg	52.8±17.3	52.5±20.3

Table 1. (Continued.)

Characteristic	Mild Hypercapnia (N=829)	Normocapnia (N=839)
Vasopressor therapy — no./total. (%)¶	415/829 (50.1)	366/839 (43.6)
Shock — no. (%)‖	247 (29.8)	215 (25.6)
ST-segment elevation myocardial infarction — no./total. no. (%)	331/814 (40.7)	343/825 (41.6)

* Plus–minus values are means ±SD. Patients were randomly assigned to either 24 hours of mild hypercapnia (target partial pressure of arterial carbon dioxide [$Paco_2$] of 50 to 55 mm Hg) or normocapnia (target $Paco_2$ of 35 to 45 mm Hg). All the analyses were performed in the intention-to-treat population, which included all the patients who had undergone randomization except for those who withdrew consent. Data on tympanic temperature were available for 609 patients in the mild hypercapnia group and for 624 in the normocapnia group; on arterial pH for 817 and 827, respectively; on the arterial lactate level for 349 and 327, respectively; and on the first measured $Paco_2$ for 817 and 829, respectively. For eight patients, the responsible ethics committee granted consent for the use of data regarding the intervention assignment and mortality status but not for other data, which resulted in differing denominators between baseline and outcome data. Percentages may not total 100 because of rounding. CPR denotes cardiopulmonary resuscitation, IQR interquartile range, NYHA New York Heart Association, and ROSC return of spontaneous circulation.

† On the Charlson comorbidity index, each comorbidity category is weighted from 1 to 6 on the basis of adjusted risk of death or resource use, and the sum of the weights produces the score. A score of 0 indicates an absence of known coexisting conditions, and higher scores indicate higher risks of death and greater resource use.

‡ For witnessed cardiac arrests, the time to ROSC was calculated from the time of the emergency call.

§ The scale for the Full Outline of Unresponsiveness (FOUR) motor score ranges from 0 to 4, with higher scores indicating better motor function. Data on the FOUR motor score were available for 775 patients in the mild hypercapnia group and for 781 in the normocapnia group.

¶ Vasopressor therapy was defined as the receipt of any dose of noradrenaline as first recorded on admission to hospital.

‖ Shock at admission was defined as a systolic blood pressure of less than 90 mm Hg for more than 30 minutes or end-organ hypoperfusion (cool arms and legs, urine output <30 ml per hour, and heart rate >60 beats per minute).

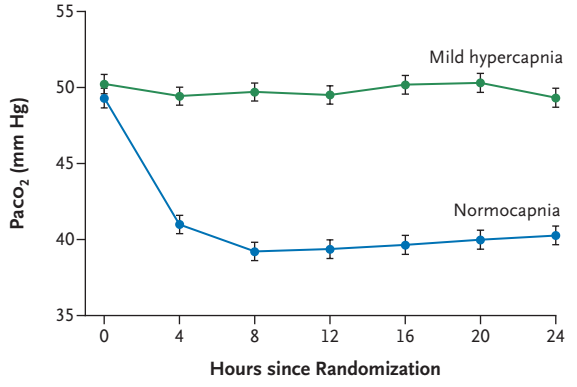
tween the percentages of patients with a favorable neurologic outcome (expected, 58% in the mild hypercapnia group vs. 50% in the normocapnia group) at a two-sided alpha level of 0.05. The sample-size estimation was based on earlier trials of mild hypercapnia for cardiac arrest.[16-19] To allow for the withdrawal of informed consent and loss to follow-up, the sample size was inflated to 1700.

The trial protocol and statistical analysis plan were published before the completion of enrollment.[27] All the analyses were performed in the intention-to-treat population, which included all the patients who had undergone randomization except for those who withdrew consent.

Binary outcomes, including the primary outcome, were analyzed with the use of generalized linear mixed-effects models with a binomial distribution and a log link to facilitate relative risks (with 95% confidence intervals). Quality of life (as assessed with the EQ Visual Analogue Scale) was analyzed with the use of linear mixed-effects models, with results presented as mean differences (with 95% confidence intervals) among survivors only and among all patients (with nonsurviving patients assigned a score of 0). All the analyses included trial center as a random intercept and concomitant enrollment in the TTM2 trial as a fixed covariate, with multiple imputation used for all missing data.

Adverse events were compared by means of chi-square tests for equal proportions, with results reported as numbers with percentages. Survival analysis was performed with the use of Cox proportional-hazards regression. Sensitivity analyses were conducted first in a subpopulation that excluded patients who were also enrolled in the TTM2 trial and second with consideration of the GOS-E as an ordinal outcome. Details relating to imputation, survival, and sensitivity analyses are presented in the Supplementary Appendix.

Complete case analyses were performed in prespecified subgroups defined according to sex, age (≤65 years or >65 years), time from cardiac arrest to the return of spontaneous circulation (<25 minutes or ≥25 minutes), initial cardiac rhythm (shockable or nonshockable), and the presence or absence of circulatory shock on admission to the hospital. To enable the alignment in the effect direction between mortality and the primary (GOS-E–based) outcome, subgroup results for the primary outcome are reported in the forest plot as an unfavorable outcome (GOS-E score, 1 to 4) rather than as a favorable outcome (GOS-E



No. at Risk							
Mild hypercapnia	571	693	693	664	632	606	605
Normocapnia	559	680	666	643	619	617	613

Figure 1. Partial Pressure of Arterial Carbon Dioxide during the 24-Hour Intervention Period.

Shown are curves for the partial pressure of arterial carbon dioxide ($Paco_2$) in patients in the mild hypercapnia group and the normocapnia group for whom $Paco_2$ values were recorded. Patients were assigned to targeted mild hypercapnia ($Paco_2$, 50 to 55 mm Hg) or to targeted normocapnia ($Paco_2$, 35 to 45 mm Hg). Targeting of mild hypercapnia or normocapnia commenced at the time of randomization and continued for 24 hours. The $Paco_2$ curves show the means, and I bars indicate 95% confidence intervals around the mean. A total of 8861 $Paco_2$ measurements were made in accordance with the protocol and were obtained in 1636 patients (818 in each group), with a median of 6 measurements (interquartile range, 4 to 7) per patient in each group during the intervention period. Further details of adherence to the intervention are provided in Figure S4.

score, 5 to 8). Details relating to the subgroup analyses are provided in the Supplementary Appendix.

Statistical significance for the primary outcome was determined with the use of a two-sided hypothesis test with an alpha level of 0.05. Given that we did not correct for multiple comparisons in subgroup analyses, the results should be considered to be exploratory. The widths of the confidence intervals for secondary outcome comparisons have not been adjusted for multiplicity and may not be used in place of hypothesis testing. Analyses were conducted with the use of SAS software, version 9.4 (SAS Institute), and R software, version 4.0.235.[28]

RESULTS

PATIENTS

From March 2018 through September 2021, we enrolled 1700 patients from 63 ICUs in 17 countries. A total of 847 patients (49.8%) were assigned to targeted mild hypercapnia and 853 (50.2%) to targeted normocapnia. Informed consent was withdrawn in 24 patients (Fig. S1). The characteristics of the patients at baseline are shown in Table 1. Details regarding additional baseline variables, procedures and intravenous drugs, assessment of neurologic prognosis, withdrawal of life-sustaining therapy, length of ICU and hospital stays, and status regarding concomitant enrollment in the TTM2 trial are provided in the Supplementary Appendix. The representativeness of the trial population is shown in Table S13.

CARBON DIOXIDE INTERVENTION

The $Paco_2$ values on patients' arrival at the hospital were similar in the two groups. After randomization, a separation in the mean $Paco_2$ values occurred over the first 4 hours and continued throughout the remainder of the 24-hour intervention period (Fig. 1). A total of 8861 $Paco_2$ measurements were made in accordance with the protocol, with 4464 measurements (50.4%) performed in 818 patients in the mild hypercapnia group and 4397 measurements (49.6%) in 818 patients in the normocapnia group. Overall, 835 $Paco_2$ measurements (9.4%) that were made in accordance with the protocol indicated hypocapnia ($Paco_2$ <35 mm Hg), with 139 of 4464 measurements (3.1%) indicating hypocapnia in the mild hypercapnia group, as compared with 696 of 4397 measurements (15.8%) in the normocapnia group. Additional characteristics of the measurement of $Paco_2$ during the intervention period are provided in the Supplementary Appendix. The $Paco_2$ target was abandoned in 68 of 829 patients (8.2%) in the mild hypercapnia group and in 25 of 839 patients (3.0%) in the normocapnia group. The reasons for early discontinuation of $Paco_2$ targeting are shown in Table S3.

The doses of analgesics and sedatives and the duration of neuromuscular blockade are shown in Table S2. The median duration of mechanical ventilation, as assessed from randomization to extubation, was similar in the two groups, and there was no significant between-group difference in the mean arterial blood pressure (Fig. S11).

PRIMARY AND SECONDARY OUTCOMES

Data on the primary outcome were available for 1548 of 1676 patients (92.4%); data were missing for 7.6% of the patients. In addition, a dichotomized neurologic outcome (favorable or unfa-

Table 2. Primary and Secondary Outcomes.*

Outcome	Mild Hypercapnia	Normocapnia	Unadjusted Risk Difference or Mean Difference (95% CI)†	Adjusted Relative Risk or Mean Difference (95% CI)‡	P Value
Primary outcome: favorable neurologic outcome at 6 mo — no./total no. (%)§	332/764 (43.5)	350/784 (44.6)	−1.2 (−6.1 to 3.8)	0.98 (0.87 to 1.11)	0.76
Secondary outcomes					
Dichotomized favorable neurologic outcome at 6 mo — no./total no. (%)¶	348/788 (44.2)	365/806 (45.3)	−1.1 (−6.0 to 3.8)	0.98 (0.87 to 1.11)	
Poor functional outcome at 6 mo — no./total no. (%)‖	407/762 (53.4)	400/779 (51.3)	2.1 (−2.9 to 7.1)	1.05 (0.95 to 1.15)	
Death at ICU discharge — no./total no. (%)	313/823 (38.0)	299/840 (35.6)	2.4 (−2.2 to 7.1)	1.07 (0.97 to 1.18)	
Death at hospital discharge — no./total no. (%)	367/823 (44.6)	349/840 (41.5)	3.0 (−1.7 to 7.8)	1.07 (0.97 to 1.19)	
Death within 6 mo — no./total no. (%)	393/816 (48.2)	382/832 (45.9)	2.2 (−2.6 to 7.1)	1.05 (0.94 to 1.16)	
Mean EQ Visual Analogue Scale score (95% CI)**					
All available patients	35.8 (32.6 to 39.0)	36.8 (33.6 to 40.0)	−1.0 (−5.0 to 3.0)	0.2 (−3.7 to 4.0)	
Surviving patients	76.4 (74.1 to 78.6)	74.5 (72.3 to 76.7)	1.9 (−0.9 to 4.7)	2.9 (−0.3 to 6.1)	

* For eight patients, the responsible ethics committee granted consent for the use of data regarding the intervention assignment and mortality status but not for other data, which resulted in differing denominators between baseline and outcome data. The widths of the confidence intervals (CIs) have not been adjusted for multiplicity and may not be used in place of hypothesis testing. ICU denotes intensive care unit.

† Risk differences are presented in percentage points and are based on unrounded data. Mean differences are provided for the analyses of the EQ Visual Analogue Scale scores.

‡ Analyses were adjusted for trial site and for concomitant enrollment in the TTM2 trial and included multiple imputation in cases where outcome data were missing. Relative risks are shown for analyses involving percentages, and adjusted mean differences for analyses of the EQ Visual Analogue Scale scores.

§ Analyses of favorable neurologic outcome were based on the Glasgow Outcome Scale–Extended (GOS-E). Scores range from 1 to 8, with a score of 1 indicating death, 2 a vegetative state, 3 lower severe disability, 4 upper severe disability, 5 lower moderate disability, 6 upper moderate disability, 7 lower good recovery, and 8 upper good recovery. A favorable neurologic outcome was defined as a score of 5 to 8.

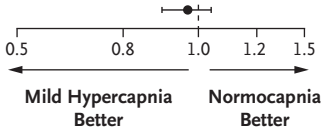
¶ These results were based on all available data, including patients who had a neurologic outcome classified as favorable (GOS-E score, 5 to 8) or unfavorable (score, 1 to 4). The neurologic follow-up was specified in the protocol to be performed at 6 months within a window of 2 weeks, but the time to follow-up was in some cases several weeks longer for logistic reasons. The difference in the number of patients with data for the primary outcome and those for the dichotomized secondary outcome is due to the fact that if a GOS-E assessment could not be completed at 6 months, a dichotomized neurologic outcome of favorable or unfavorable (score of 5 to 8 or 1 to 4, respectively) was made on the basis of all available data, including a review of medical and interview records, by an assessor who was unaware of the intervention assignments. Therefore, more patients were available for such assessment.

‖ The analysis of poor functional outcome was based on the modified Rankin scale. Scores range from 0 to 6, with a score of 0 indicating no symptoms, 1 no clinically significant disability despite some symptoms, 2 slight disability (patient is able to look after own affairs without assistance), 3 moderate disability (patient requires some help but is able to walk unassisted), 4 moderately severe disability (patient is unable to attend to own bodily needs), 5 severe disability (patient is bedridden), and 6 death. A poor functional outcome was defined as a modified Rankin scale score of 4 to 6.

** The visual-analogue component of the EuroQol Group 5-Dimension Self-Report Questionnaire (EQ Visual Analogue Scale) provides a single global rating of patient-perceived health and is scored on a scale from 0 to 100 mm, with a score of 0 mm indicating "the worst health you can imagine" and a score of 100 mm as "the best health you can imagine." Patients who did not survive had their score imputed as 0. EQ Visual Analogue Scale scores were available for 748 patients in the mild hypercapnia group and for 764 in the normocapnia group overall and for 355 surviving patients in the mild hypercapnia group and for 382 in the normocapnia group.

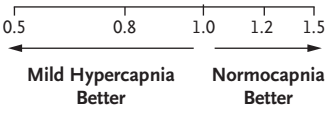
A Unfavorable Neurologic Outcome at 6 Months

Subgroup	Mild Hypercapnia	Normocapnia	Relative Risk (95% CI)
	no. of patients		
All patients	760	780	1.02 (0.93–1.12)
Sex			
Male	578	634	1.00 (0.90–1.12)
Female	182	146	1.03 (0.92–1.15)
Age			
≤65 yr	425	447	1.05 (0.93–1.19)
>65 yr	335	333	0.99 (0.86–1.14)
Time to ROSC from cardiac arrest			
<25 min	370	400	1.04 (0.86–1.26)
≥25 min	390	380	0.99 (0.90–1.09)
Initial rhythm			
Nonshockable	183	177	1.03 (0.93–1.15)
Shockable	577	603	1.00 (0.86–1.16)
Shock on admission			
Not present	527	576	1.03 (0.91–1.16)
Present	233	204	0.96 (0.87–1.05)



B Death from Any Cause within 6 Months

Subgroup	Mild Hypercapnia	Normocapnia	Relative Risk (95% CI)
	no. of patients		
All patients	812	828	1.05 (0.95–1.16)
Sex			
Male	620	672	1.02 (0.91–1.14)
Female	192	156	1.07 (0.93–1.24)
Age			
≤65 yr	463	480	1.10 (0.95–1.27)
>65 yr	349	348	1.00 (0.90–1.11)
Time to ROSC from cardiac arrest			
<25 min	402	428	1.12 (0.91–1.39)
≥25 min	410	400	0.99 (0.89–1.11)
Initial rhythm			
Nonshockable	195	181	1.03 (0.93–1.14)
Shockable	617	647	1.03 (0.87–1.22)
Shock on admission			
Not present	570	617	1.09 (0.96–1.23)
Present	242	211	0.93 (0.84–1.03)



vorable) was available for 1594 of 1676 patients (95.1%). At 6 months, 332 of 764 patients (43.5%) in the mild hypercapnia group had a favorable neurologic outcome, as compared with 350 of 784 patients (44.6%) in the normocapnia group (relative risk with mild hypercapnia, 0.98; 95% confidence interval [CI], 0.87 to 1.11; P=0.76) (Table 2). The effect of the $PaCO_2$ on favorable outcomes was consistent in the analysis that was based on the dichotomized GOS-E categorization and across the prespecified subgroups (Fig. 2).

By 6 months, 393 of 816 patients (48.2%) in the mild hypercapnia group and 382 of 832 patients (45.9%) in the normocapnia group had died (relative risk with mild hypercapnia, 1.05; 95% CI, 0.94 to 1.16). At 6 months, 407 of 762

Figure 2 (facing page). Subgroup Analyses of Unfavorable Neurologic Outcome and Death from Any Cause within 6 Months.

Shown are the results of the analyses of unfavorable neurologic outcome (defined as a Glasgow Outcome Scale–Extended [GOS-E] score of 1 to 4) (Panel A) and death from any cause (Panel B) in prespecified subgroups. GOS-E scores range from 1 to 8, with a score of 1 indicating death, 2 a vegetative state, 3 lower severe disability, 4 upper severe disability, 5 lower moderate disability, 6 upper moderate disability, 7 lower good recovery, and 8 upper good recovery. For the purpose of the subgroup analysis and for the reported direction of subgroup estimates to be aligned between the analyses of GOS-E (Panel A) and 6-month mortality (Panel B), the primary outcome is reported here in terms of an unfavorable outcome rather than a favorable outcome. Relative risks were derived from complete case data with the use of stratified generalized linear modeling adjusting for center as a random effect and concomitant enrollment in the Targeted Hypothermia versus Targeted Normothermia after Out-of-Hospital Cardiac Arrest trial as a fixed covariate. Error bars indicate 95% confidence intervals. For unwitnessed cardiac arrests, the time until a return of spontaneous circulation (ROSC) was calculated in minutes from the time of the emergency call. Shock on admission was defined as a systolic blood pressure of less than 90 mm Hg for more than 30 minutes or end-organ hypoperfusion (cool arms and legs, urine output <30 ml per hour, and heart rate >60 beats per minute). The analyses were performed in the intention-to-treat population, which included all the patients who had undergone randomization except for those who withdrew consent. For eight patients, the responsible ethics committee granted consent for the use of data regarding the intervention assignment and mortality status but not for other data, which resulted in differing denominators between baseline and outcome data. The widths of the confidence intervals have not been adjusted for multiplicity and may not be used in place of hypothesis testing.

patients (53.4%) in the mild hypercapnia group had a poor functional outcome, as compared with 400 of 779 patients (51.3%) in the normocapnia group. Health-related quality of life as assessed by the EQ Visual Analogue Scale component of the EuroQol-5D-5L was similar in the two groups (Table 2). The neurologic scores at 6 months on both scales (GOS-E and modified Rankin scale) are shown in Table 3. Deaths before neurologic prognostication that were due to a cerebral cause (Table S5) and the numbers of patients with confirmed brain death leading to organ donation (Table S8) were similar in the two groups.

Additional sensitivity analyses are reported in Tables S10 and S11. There was no interaction according to treatment assignment and assignment in the TTM2 trial for any outcome for the 370 patients who were enrolled in both trials.

ADVERSE EVENTS

Prespecified adverse events are reported in Table S6. The most frequent adverse events were pneumonia, arrhythmias resulting in hemodynamic compromise, sepsis, and bleeding. The incidence of such events did not differ significantly between the groups. There were no significant between-group differences in the incidence of death before neurologic prognostication, death due to cerebral causes, or the occurrence of myoclonic seizure and tonic–clonic seizures. Four unexpected serious, possibly intervention-related, adverse events occurred: one cerebral edema event in the mild hypercapnia group and three noncerebral events in the normocapnia group.

DISCUSSION

In this randomized trial, we compared targeted mild hypercapnia with targeted normocapnia in adults with coma who had been resuscitated after out-of-hospital cardiac arrest. Targeted mild hypercapnia did not improve neurologic outcomes at 6 months, the risk of death within 6 months, the distribution of scores for functional outcome, or health-related quality of life.

Investigators have hypothesized that disturbances in cerebral perfusion may affect neurologic outcomes after cardiac arrest.[1,3,9] Accordingly, early intervention to improve cerebral perfusion may attenuate hypoxic–ischemic encephalopathy. In studies involving humans and in animal models,[29-34] a higher $Paco_2$ appears to be neuroprotective on the basis of increased cerebral blood flow. Among adults with coma who are resuscitated after out-of-hospital cardiac arrest, observational studies and a phase 2 trial[16,17,19] have shown an association between mild hypercapnia in the first 24 hours in the ICU and an increased likelihood of discharge home.[17] In a phase 2 trial, mild hypercapnia decreased the levels of brain-injury biomarkers; however, the trial lacked the necessary statistical power to detect improved neurologic outcomes at 6 months.[19] Our findings, however, do not support the hypothesis that targeted mild hypercapnia improves neurologic outcomes at 6 months in such patients and suggest that our understanding of the effect of $Paco_2$ on cerebrovascular control is incomplete.

Table 3. Neurologic Outcomes at 6 Months.*

Variable	Mild Hypercapnia	Normocapnia
	no./total no. (%)	
GOS-E score		
1: Death	393/816 (48.2)	382/832 (45.9)
2: Vegetative state	0/764	3/784 (0.4)
3: Lower severe disability	12/764 (1.6)	28/784 (3.6)
4: Upper severe disability	27/764 (3.5)	21/784 (2.7)
5: Lower moderate disability	44/764 (5.8)	43/784 (5.5)
6: Upper moderate disability	72/764 (9.4)	71/784 (9.1)
7: Lower good recovery	109/764 (14.3)	106/784 (13.5)
8: Upper good recovery	107/764 (14.0)	130/784 (16.6)
Modified Rankin scale score		
0: No symptoms	111/758 (14.6)	131/775 (16.9)
1: No clinically significant disability	85/758 (11.2)	81/775 (10.5)
2: Slight disability	118/758 (15.6)	121/775 (15.6)
3: Moderate disability	41/758 (5.4)	46/775 (5.9)
4: Moderately severe disability	10/758 (1.3)	8/775 (1.0)
5: Severe disability	4/758 (0.5)	10/775 (1.3)
6: Death	393/816 (48.2)	382/832 (45.9)

* The 6-month follow-up was specified in the protocol to be performed at 6 months with a window of 2 weeks. However, the time to follow-up was, in some cases, several weeks longer for logistic reasons. For eight patients, the responsible ethics committee granted consent for the use of data regarding intervention assignment and mortality status but not for other data, which resulted in differing denominators between baseline and outcome data. All nonsurviving patients at 6 months were classified as having a GOS-E score of 1 and a modified Rankin scale score of 6, which resulted in differing denominators among the outcome categories.

Mild hypercapnia did not increase the incidence of prespecified adverse events — a finding that was consistent with previous trials involving patients with out-of-hospital cardiac arrest[19,20] and that was similar to findings in the TTM2 trial.[20] Mild hypercapnia may worsen cerebral edema and elevate intracranial pressure[1]; however, elevated intracranial pressure is uncommon in the first 72 hours after the return of spontaneous circulation.[35,36] In our trial, there was a report of possibly intervention-related cerebral edema occurring in one patient in the mild hypercapnia group. Accordingly, our findings suggest that early mild hypercapnia is unlikely to induce clinically relevant elevations in intracranial pressure in this patient population.

Our findings complement those of other trials targeting physiological interventions such as temperature,[20] oxygenation,[37] and blood-pressure[38] manipulation in adults with coma who are resuscitated after out-of-hospital cardiac arrest. Our results were consistent across the individual and dichotomized neurologic outcome categories of the GOS-E. The large sample size, pragmatic eligibility criteria, separation in mean $PaCO_2$ values and in the incidence of hypocapnia, and the numerous hospitals and countries represented in this trial increase the robustness of our findings.

Our trial has several limitations. First, emergency department and ICU staff members were aware of the intervention assignments. Second, except for guidance on sedation targets, mechanical ventilation, and neurologic prognostication, concomitant care was not specified in the protocol. Third, hypercapnia was common at randomization and may have attenuated the difference between groups.[39] An interaction between the mean arterial blood pressure and $PaCO_2$ on cerebral perfusion may have affected our findings. However, no between-group difference in the mean arterial blood pressure was detected in our trial.

Fourth, the trial included only patients with out-of-hospital cardiac arrest of a presumed cardiac or unknown cause, and most patients had a witnessed cardiac arrest with shockable rhythm and bystander resuscitation. Thus, our results are not fully applicable to other causes of cardiac arrest (e.g., trauma or anaphylaxis), to in-hospital or unwitnessed cardiac arrests, or after a nonshockable initial rhythm or no bystander cardiopulmonary resuscitation. Fifth, given that intracerebral pressure is not routinely monitored in current practice, the proportion of patients who had an elevated intracerebral pressure or cerebral edema is unknown. Sixth, follow-up in the trial was challenging because of restrictions due to the coronavirus disease 2019 pandemic. Thus, data on the primary outcome were missing in 7.6% of the patients; however, inferences were not affected by different methods of analysis to account for such missingness. Finally, no between-trial interaction with the TTM2 trial was seen in our analyses; however, such assessment may have been underpowered.

To align with existing international guidelines for the treatment of adults with coma who are resuscitated after out-of-hospital cardiac arrest,[14,15] the duration of the intervention was set

at 24 hours. For pragmatic reasons, such intervention commenced after hospital arrival and typically within 3 hours after the sustained return of spontaneous circulation. However, as in other trials involving patients with cardiac arrest, earlier intervention was not logistically possible.[20,37]

In this trial involving adults with coma who had been resuscitated after out-of-hospital cardiac arrest, targeted mild hypercapnia did not improve neurologic outcomes at 6 months as compared with targeted normocapnia.

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APPENDIX

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REFERENCES

1. Perkins GD, Callaway CW, Haywood K, et al. Brain injury after cardiac arrest. Lancet 2021;398:1269-78.
2. Lemiale V, Dumas F, Mongardon N, et al. Intensive care unit mortality after cardiac arrest: the relative contribution of shock and brain injury in a large cohort. Intensive Care Med 2013;39:1972-80.
3. Sekhon MS, Ainslie PN, Griesdale DE. Clinical pathophysiology of hypoxic ischemic brain injury after cardiac arrest: a "two-hit" model. Crit Care 2017; 21:90.
4. Buunk G, van der Hoeven JG, Meinders AE. Cerebral blood flow after cardiac arrest. Neth J Med 2000;57:106-12.
5. Koch KA, Jackson DL, Schmiedl M, Rosenblatt JI. Total cerebral ischemia: effect of alterations in arterial PCO2 on cerebral microcirculation. J Cereb Blood Flow Metab 1984;4:343-9.
6. Buunk G, van der Hoeven JG, Meinders AE. Prognostic significance of the difference between mixed venous and jugular bulb oxygen saturation in comatose patients resuscitated from a cardiac arrest. Resuscitation 1999;41:257-62.
7. Ahn A, Yang J, Inigo-Santiago L, Parnia S. A feasibility study of cerebral oximetry monitoring during the post-resuscitation period in comatose patients following cardiac arrest. Resuscitation 2014;85: 522-6.
8. Edgren E, Enblad P, Grenvik A, et al. Cerebral blood flow and metabolism after cardiopulmonary resuscitation: a pathophysiologic and prognostic positron emission tomography pilot study. Resuscitation 2003;57:161-70.
9. Sundgreen C, Larsen FS, Herzog TM, Knudsen GM, Boesgaard S, Aldershvile J. Autoregulation of cerebral blood flow in patients resuscitated from cardiac arrest. Stroke 2001;32:128-32.
10. Curley G, Laffey JG, Kavanagh BP. Bench-to-bedside review: carbon dioxide. Crit Care 2010;14:220.
11. Reich T, Rusinek H. Cerebral cortical and white matter reactivity to carbon dioxide. Stroke 1989;20:453-7.
12. Battisti-Charbonney A, Fisher J, Duffin J. The cerebrovascular response to carbon dioxide in humans. J Physiol 2011; 589:3039-48.
13. Bisschops LLA, Hoedemaekers CWE, Simons KS, van der Hoeven JG. Preserved metabolic coupling and cerebrovascular reactivity during mild hypothermia after cardiac arrest. Crit Care Med 2010;38: 1542-7.
14. Nolan JP, Sandroni C, Böttiger BW, et al. European Resuscitation Council and European Society of Intensive Care Medicine guidelines 2021: post-resuscitation care. Intensive Care Med 2021;47:369-421.
15. Panchal AR, Bartos JA, Cabañas JG, et al. Adult basic and advanced life support: 2020 American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. Circulation 2020;142:Suppl 2:S366-S468.
16. Schneider AG, Eastwood GM, Bellomo R, et al. Arterial carbon dioxide tension and outcome in patients admitted to the intensive care unit after cardiac arrest. Resuscitation 2013;84:927-34.
17. Vaahersalo J, Bendel S, Reinikainen M, et al. Arterial blood gas tensions after resuscitation from out-of-hospital cardiac arrest: associations with long-term neurologic outcome. Crit Care Med 2014;42: 1463-70.
18. Eastwood GM, Tanaka A, Bellomo R. Cerebral oxygenation in mechanically ventilated early cardiac arrest survivors: the impact of hypercapnia. Resuscitation 2016;102:11-6.
19. Eastwood GM, Schneider AG, Suzuki S, et al. Targeted therapeutic mild hypercapnia after cardiac arrest: a phase II multi-centre randomised controlled trial (the CCC trial). Resuscitation 2016;104: 83-90.
20. Dankiewicz J, Cronberg T, Lilja G, et al. Hypothermia versus normothermia after out-of-hospital cardiac arrest. N Engl J Med 2021;384:2283-94.
21. Gøtzsche PC. Blinding during data analysis and writing of manuscripts. Control Clin Trials 1996;17:285-93.
22. Sessler CN, Gosnell MS, Grap MJ, et al. The Richmond Agitation-Sedation Scale: validity and reliability in adult intensive care unit patients. Am J Respir Crit Care Med 2002;166:1338-44.
23. Eastwood GM, Nielsen N, Nichol AD, Skrifvars MB, French C, Bellomo R. Reported practice of temperature adjustment (α-stat v pH-stat) for arterial blood gases measurement among investigators from two major cardiac arrest trials. Crit Care Resusc 2019;21:69-71.
24. Cooper DJ, Nichol AD, Bailey M, et al. Effect of early sustained prophylactic hypothermia on neurologic outcomes among patients with severe traumatic brain injury: the POLAR randomized clinical trial. JAMA 2018;320:2211-20.
25. Banks JL, Marotta CA. Outcomes validity and reliability of the modified Rankin scale: implications for stroke clinical trials: a literature review and synthesis. Stroke 2007;38:1091-6.
26. EuroQol Research Foundation. EQ-5D. 2023 (http://euroqol.org).
27. Nichol A, Bellomo R, Ady B, et al. Protocol summary and statistical analysis plan for the Targeted Therapeutic Mild Hypercapnia after Resuscitated Cardiac Arrest (TAME) trial. Crit Care Resusc 2021;23:374-85.
28. R Core Team. The R Project for statistical computing. Vienna: R Foundation for Statistical Computing, 2021 (https://www.R-project.org/).
29. Babini G, Ristagno G, Boccardo A, et al. Effect of mild hypercapnia on outcome and histological injury in a porcine post cardiac arrest model. Resuscitation 2019; 135:110-7.
30. Pollock GH, Stein SN, Gyarfas K. Central inhibitory effects of carbon dioxide: man. Proc Soc Exp Biol Med 1949;70:291.
31. Tolner EA, Hochman DW, Hassinen P, et al. Five percent CO_2 is a potent, fast-acting inhalation anticonvulsant. Epilepsia 2011;52:104-14.
32. Shoja MM, Tubbs RS, Shokouhi G, Loukas M, Ghabili K, Ansarin K. The potential role of carbon dioxide in the neuroimmunoendocrine changes following cerebral ischemia. Life Sci 2008;83:381-7.
33. Vannucci RC, Towfighi J, Heitjan DF, Brucklacher RM. Carbon dioxide protects the perinatal brain from hypoxic-ischemic damage: an experimental study in the immature rat. Pediatrics 1995;95:868-74.
34. Miller CL, Alexander K, Lampard DG, Brown WA, Griffiths R. Local cerebral blood flow following transient cerebral ischemia. II. Effect of arterial PCO2 on reperfusion following global ischemia. Stroke 1980;11:542-8.
35. Nordmark J, Rubertsson S, Mörtberg E, Nilsson P, Enblad P. Intracerebral monitoring in comatose patients treated with hypothermia after a cardiac arrest. Acta Anaesthesiol Scand 2009;53:289-98.
36. Song H, Kang C, Park J, et al. Intracranial pressure patterns and neurological outcomes in out-of-hospital cardiac arrest survivors after targeted temperature management: a retrospective observational study. J Clin Med 2021;10:5697.
37. Schmidt H, Kjaergaard J, Hassager C, et al. Oxygen targets in comatose survivors of cardiac arrest. N Engl J Med 2022; 387:1467-76.
38. Kjaergaard J, Møller JE, Schmidt H, et al. Blood-pressure targets in comatose survivors of cardiac arrest. N Engl J Med 2022;387:1456-66.
39. Beckstead JE, Tweed WA, Lee J, MacKeen WL. Cerebral blood flow and metabolism in man following cardiac arrest. Stroke 1978;9:569-73.