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Clinical paper

Cardiovascular changes induced by targeted mild hypercapnia after out of hospital cardiac arrest. A sub-study of the TAME cardiac arrest trial

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Abstract

Aim: Hypercapnia may elicit detrimental haemodynamic effects in critically ill patients. We aimed to investigate the consequences of targeted mild hypercapnia versus targeted normocapnia on pulmonary vascular resistance and right ventricular function in patients resuscitated from out-of-hospital cardiac arrest (OHCA).

Methods: Pre-planned, single-centre, prospective, sub-study of the Targeted Therapeutic Mild Hypercapnia After Resuscitated Cardiac Arrest (TAME) trial. Patients were randomised to mild hypercapnia ($PaCO_2$ = 6.7–7.3 kPa) or normocapnia ($PaCO_2$ = 4.7–6.0 kPa) for 24 hours. Haemodynamic assessment was performed with right heart catheterisation and serial blood-gas analyses every 4th hour for 48 hours.

Results: We studied 84 patients. Mean pH was 7.24 (95% CI 7.22–7.30) and 7.32 (95% CI 7.31–7.34) with hypercapnia and normocapnia, respectively (*P*-group < 0.001). Pulmonary vascular resistance index (PVRI), pulmonary artery pulsatility index, and right atrial pressure did not differ between groups (*P*-group > 0.05). Mean cardiac index was higher with mild hypercapnia (*P*-group < 0.001): 2.0 (95% CI 1.85–2.1) vs 1.6 (95% CI 1.52–1.76) L/min/m^2. Systemic vascular resistance index was 2579 dyne-sec/cm-5/ m^2 (95% CI 2356–2830) with hypercapnia, and 3249 dyne-sec/cm-5/ m^2 (95% CI 2930–3368) with normocapnia (*P*-group < 0.001). Stroke volumes (*P*-group = 0.013) and mixed venous oxygen saturation (*P*-group < 0.001) were higher in the hypercapnic group.

Conclusion: In resuscitated OHCA patients, targeting mild hypercapnia did not increase PVRI or worsen right ventricular function compared to normocapnia. Mild hypercapnia comparatively improved cardiac performance and mixed venous oxygen saturation.

Keywords: Out-of-hospital cardiac arrest, Targeted mild hypercapnia, Right heart catheterisation, Post-cardiac arrest care, TAME cardiac arrest trial

Introduction

Myocardial dysfunction is prevalent in adults admitted to hospital following resuscitation after out-of-hospital cardiac arrest (OHCA), and cardiovascular failure is a major contributor to early mortality in these patients.[1–3] The haemodynamic profile of resuscitated cardiac arrest patients is typically characterised by reduced cardiac output, hypotension, and disturbed vasomotor regulation.[1,4,5] European guidelines for post-resuscitation care highlight the importance of optimising haemodynamics after cardiac arrest.[6]

The Targeted Therapeutic Mild Hypercapnia After Resuscitated Cardiac Arrest (TAME) trial[7] investigated whether targeting mild hypercapnia ($PaCO_2$ = 6.7–7.3 kPa) compared to targeting normocapnia ($PaCO_2$ = 4.7–6.0 kPa) for 24 hours in comatose adults resuscitated after OHCA could improve neurological outcomes at 6 months. In this regard, hypercapnia increases cerebral blood flow,[8] but hypercapnic acidosis is also believed to exert significant systemic haemodynamic effects.[8–10] Such putative effects include impaired myocardial contractility, systemic vasodilation, improved systemic oxygenation and increased pulmonary vascular resistance (PVR). Our current understanding of the cardiovascular effects of hypercap-

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nic acidosis, however, is primarily based on pre-clinical and animal studies.[9,11] Thus, the haemodynamic consequences for comatose adults resuscitated after OHCA are unclear.

Prior to the TAME trial, there was concern that hypercapnic acidosis would increase pulmonary vascular resistance, right ventricular afterload and exacerbate right ventricular failure.[12–14] This, in turn, could increase systemic venous congestion and worsen renal function.[15] If induced, these adverse haemodynamic effects could have significant consequences as right ventricular dysfunction after cardiac arrest is both common and associated with worse outcomes.[16,17]

We hypothesised that mild hypercapnia compared with normocapnia for the first 24 hours after OHCA would increase PVR, exacerbate right ventricular dysfunction, and adversely alter the systemic circulation. To test this hypothesis, we compared pulmonary vascular resistance index (PVRI); pulmonary artery pulsatility index (PAPI) and right atrial pressure (RAP); Cardiac index (CI) and cardiac power output (CPO) and systemic vascular resistance index (SVRI) and fluid balance in patients randomised to either mild hypercapnia or normocapnia within the TAME trial.

Methods

Trial design and patients

The study was a pre-planned, prospective sub-study of patients enrolled in the TAME trial at Oslo University Hospital. Patients were randomised in a 1:1 ratio to mild hypercapnia ($PaCO_2$ = 6.7–7.3 kPa) or normocapnia ($PaCO_2$ = 4.7–6.0 kPa) for a 24-hour period beginning at randomisation. Hospitalised comatose adults (18 years or older) resuscitated from OHCA of a presumed cardiac cause with sustained return of spontaneous circulation (ROSC) for 20 minutes, were eligible for enrolment. Full eligibility criteria are detailed in the main trial manuscript.[7] Haemodynamically unstable patients and those deemed to be in cardiogenic shock were not excluded. Shock on admission was defined as a systolic blood pressure of <90 mmHg for at least 30 minutes or the need for supportive measures to maintain a systolic blood pressure of ≥90 mmHg and end-organ hypoperfusion (cool extremities, or urine output of <30 mL/hour and heart rate >60 beats/minute).

Prehospital data were systematically collected according to the Utstein Guidelines.[18] The TAME trial and the sub-study were approved by the regional ethics committee (NCT03114033, REK 2018/386). Patients were initially included and randomised without consent. Written informed consent was obtained from patients' next of kin in all cases and from patients regaining consciousness after cardiac arrest.

Emergency coronary angiography and coronary intervention, defined as prior to or immediately after ICU admission, was performed in all patients presenting with ST-segment elevation or at the discretion of the treating physician. A pulmonary artery catheter was inserted in all eligible patients if qualified personnel was available for the procedure. Haemodynamic information from right heart catheterisation were available for treatment decisions that were made at the discretion of the treating physician.

Post-cardiac arrest care

All patients were sedated, intubated, and mechanically ventilated during the intervention period. A target Richmond Agitation-Sedation Scale score[19] of −4 (scale range –5 (unarousable) to +4 (combative)) was achieved by titrating propofol in combination with fentanyl. Propofol was replaced with midazolam, if needed, in haemodynamically unstable patients. Neuromuscular blockade was administered if needed. Active cooling with a surface cooling device (*Arctic Sun™, BD, Franklin, NJ*) was initiated immediately after ICU admission with targeted temperature management (TTM) set to 33 °C (TTM 33) for the initial 24 hours after cardiac arrest. This was followed by gradual re-warming by 0.5 °C/hour, and fever control for an additional 48 hours.

Arterial blood gas (See supplementary material for technical details) measurements were used to guide the respiratory rate adjustments of minute ventilation to optimise time in the target $PaCO_2$ range. For patients allocated to mild hypercapnia, in the event of severe metabolic acidosis (pH < 7.1 and base excess < −6 mmol/L), the initiation of the study protocol was to commence after correction of the acidosis. Respiratory acidosis was not corrected with buffer solutions. Return to normocapnia after hypercapnia was conducted over a minimum of 4 hours.

Crystalloid fluids were administered initially in all patients to optimise right ventricular filling pressures. Urine output was targeted at >1.0 mL/kg per hour. Vasopressors and inotropes (primarily norepinephrine and dobutamine) were used, if needed, to achieve adequate organ perfusion and a target mean arterial pressure (MAP) of >65 mmHg.

Haemodynamic measurements

Advanced haemodynamic monitoring was obtained by ultrasound-guided insertion of a 7.5F triple lumen balloon-tipped catheter into the pulmonary artery (*Swan Ganz, Edwards Lifesciences, Irvine, CA*). The first haemodynamic measurements were obtained 4 hours *after* randomisation and the start of mild hypercapnia or normocapnia. All measurements were performed with the patient in a supine position. The validity of the thermodilution technique during surface-induced hypothermia has been previously reported, and has been used in numerous clinical trials.[20,21] Systolic, diastolic, and mean pulmonary artery pressures (sPAP, dPAP and mPAP) were obtained from the distal port. Right atrial pressure (RAP) was obtained from the proximal port. Systemic mean arterial pressure (MAP) was acquired from a radial arterial line. Cardiac output (CO) and index (CI) were obtained through a thermodilution technique with bolus infusions of 10 ml of cold 5% glucose. The average of 3 measurements with less than 10% variance was sampled. Pulmonary capillary wedge pressure (PCWP) was measured with the catheter balloon inflated in wedge position and registered at end-expiration. Central mixed venous blood samples were drawn from the distal port of the pulmonary artery catheter and time-matched with arterial blood samples drawn from the radial arterial line. Indexed systemic (SVRI) and pulmonary (PVRI) vascular resistance were calculated by the following equations: SVRI = (MAP-RAP) *80/CI and PVRI = (mPAP-PCWP) *80/CI. Cardiac power output (CPO) was calculated using the formula; CO*MAP*0.0022. Pulmonary artery pulsative index (PAPi) was estimated as (sPAP-dPAP/RAP).[22]

Haemodynamic measurements, ventilator settings and arterial and mixed venous blood samples were taken every 4th hour after insertion of the pulmonary artery catheter in a time matched manner throughout the 48 hours study period. The doses of relevant administered drugs and intravenous fluids were time-matched with PAC measurements, and included propofol, fentanyl, midazolam, dobutamine and norepinephrine. Intravenous fluids and urine output were recorded every 4 hours.

Statistical analysis

All data in this study were analysed by the intention-to-treat principle. Differences between baseline variables and rates of coronary pathologies were compared using Student *t* test, χ^2 test, Fisher's exact test and Wilcoxon rank-sum test, as appropriate. Baseline variables are presented as mean ± SD or proportions (%), and for variables with a non-normal distribution, data are presented as median and lower to upper quartile (Q1–Q3).

Between-group differences for the continuous haemodynamic and metabolic variables in the intervention period (24 hours) were evaluated with repeated-measures mixed models with a heterogenous first-order autoregressive covariance structure with treatment-group, time, and the interaction term of treatment group with time (if significant) as fixed effects. Ventilator settings and doses of administered drugs and fluids were evaluated in the same fashion. Models were fitted using the restricted maximum likelihood (REML) method. Overall differences between treatment groups are reported as β-coefficients (estimate of treatment effect) and *P* - values, denoted as *P-group*. Model estimated marginal means (EM) for the entire intervention period are reported with 95% confidence intervals. Dependent variables with a non-normal distribution of the residuals were log-transformed to improve the model fit. Tests were 2-sided, and statistical significance was defined as $P < 0.05$. Statistical analysis was performed using *IBM SPSS* (Version 28.0. Armonk, NY: IBM Corp) and *R* (Version 2022.12.0+353. R Foundation for Statistical Computing, Vienna, Austria.). Graphs were made using *R*.

Results

Patient population

Between January 2019 and August 2021, 84 out of 137 patients enrolled in the TAME trial received a PAC and were eligible for the present sub-study. Of these, 41 and 43 patients were randomised to mild hypercapnia and normocapnia, respectively. In accordance with the inclusion criteria of the TAME trial, the patients enrolled

Table 1 – Baseline and admission characteristics.

Baseline and admission characteristics	*All patients* (*n* = 84)	*Targeted mild hypercapnia* (*n* = 41)	*Targeted Normocapnia* (*n* = 43)	*P-value*
Age, *mean years ± SD*	62 ± 12	60 ± 11	63 ± 13	0.28
Male sex, *n (%)*	69 (82)	33 (81)	36 (84)	0.91
Comorbidities:				
- Hypertension, *n (%)*	39 (46)	18 (44)	21 (49)	0.82
- Diabetes mellitus, *n (%)*	14 (17)	6 (15)	8 (19)	0.84
- Known IHD, *n (%)*	25 (30)	14 (34)	11 (25)	0.53
- Previous myocardial infarction, *n (%)*	22 (26)	12 (29)	10 (23)	0.71
- Heart failure, *n (%)*	21 (25)	10 (24)	11 (26)	1
- COPD, *n (%)*	9 (11)	4 (10)	5 (12)	1
- Renal failure, *n (%)*	0 (0)	0 (0)	0 (0)	-
- Cerebrovascular disease, *n (%)*	6 (7)	4 (10)	2 (5)	0.43
- Peripheral vascular disease, *n (%)*	9 (11)	6 (15)	3 (7)	0.31
Initial rhythm				
- Shockable, *n (%)*	79 (94)	36 (88)	43 (100)	
- Asystole, *n (%)*	2 (2)	2 (5)	0 (0)	
- Pulseless electric activity, *n (%)*	3 (4)	3 (7)	0 (0)	0.26
- Bystander AED-defibrillation, *n (%)*	4 (5)	2 (5)	2 (2)	
Witnessed cardiac arrest, *n (%)*	77 (92)	38 (93)	39 (91)	1
Bystander CPR, *n (%)*	74 (88)	35 (85)	39 (91)	0.5
Time to advanced life support, *median minutes (Q1–Q3)*	8 (4–11)	8 (5–11)	7 (4–11)	0.69
Cardiac arrest at home, *n (%)*	41 (49)	21 (51)	20 (47)	0.831
Number of defibrillations, *n (Q1–Q3)*	2 (1–3)	2 (1–3)	2 (1–4)	0.55
Time to ROSC, *median minutes (Q1–Q3)*	22 (15–35)	20 (15–35)	24 (15–34)	0.72
Time from cardiac arrest to randomisation, *median minutes (Q1–Q3)*	134 (106–156)	150 (123–162)	117 (98–148)	0.022
Acute ST–segment elevation in ECG, *n (%)*	40 (48)	18 (44)	22 (51)	0.495
Shock on admission *, *n (%)*	29 (35)	17 (41)	12 (28)	0.252
Assumed cause of cardiac arrest				
- Acute myocardial infarction, *n (%)*	37 (44)	19 (48)	18 (42)	
- Chronic ischemic heart disease, *n (%)*	29 (35)	11 (28)	18 (42)	
- Heart failure, *n (%)*	2 (2)	2 (5)	0 (0)	0.453
- Idiopathic arrythmia, *n (%)*	15 (18)	8 (19)	7 (16)	
- Complete heart block, *n (%)*	1 (1)	1 (2)	0 (0)	

Data are presented as mean ± SD or proportions (%), and for variables with a non-normal distribution, data are presented as median and lower to upper quartile (Q1–Q3). Differences were compared using Student t test, $\chi 2$ test, Fisher's exact test and Wilcoxon rank-sum test, as appropriate. Significance level is set to p-value < 0.05. IHD denotes ischemic heart disease; COPD, chronic obstructive pulmonary disease; AED, automatic external defibrillator; CPR, cardiopulmonary resuscitation; ROSC, return of spontaneous circulation. * Shock on admission was defined as a systolic blood pressure of < 90 mmHg for at least 30 minutes or the need for supportive measures to maintain a systolic blood pressure of ≥ 90 mmHg and end-organ hypoperfusion (cool extremities, or urine output of < 30 mL/h and heart rate > 60 beats/min).

had a presumed cardiac cause of OHCA. See consort diagram (Electronic supplementary material, Fig. S1).

Acute myocardial infarction (including ST-elevation and non-ST-elevation myocardial infarction) was assumed to be the cause of cardiac arrest in 44% of patients. Chronic ischemic heart disease was the suspected cause in 35% of cases (Table 1). There were no instances of pulmonary embolism or cardiac tamponade. Prior to randomisation, 17 (41%) patients assigned to targeted mild hypercapnia were deemed to be in shock on admission to the emergency department, compared to 12 (28%) in the targeted normocapnia group (Table 1). Emergency coronary angiography was performed in all patients prior to ICU admission. Distribution of coronary pathologies and success-rates of PCI did not differ between the two groups (Table 3). The proportions of 6-month survival and favourable functional outcome (defined as a Glasgow Outcome Scale Extended score [23] of 5–8) was 78% and 66% respectively in the hypercapnia-group, versus 65% and 53% in the normocapnia-group ($P > 0.05$, Table S1).

Intervention

Both groups achieved the desired levels of $PaCO_2$ (Fig. 1A, Table 2) within 4 hours and during the intervention period. Respiratory rate and tidal volumes were significantly lower in the hypercapnia-group, whereas positive end expiratory pressures (PEEP) and plateau pressures were similar (Table 2, Electronic supplementary Fig. S2). Mild hypercapnic acidosis (Fig. 1B, Table 2) was present in the hypercapnia-group (*P*-group < 0.001). PaO_2/FiO_2-ratio (Fig. 1C, Table 2) did not differ significantly between groups, and the estimated mean temperatures (Table 2) were similar during the intervention.

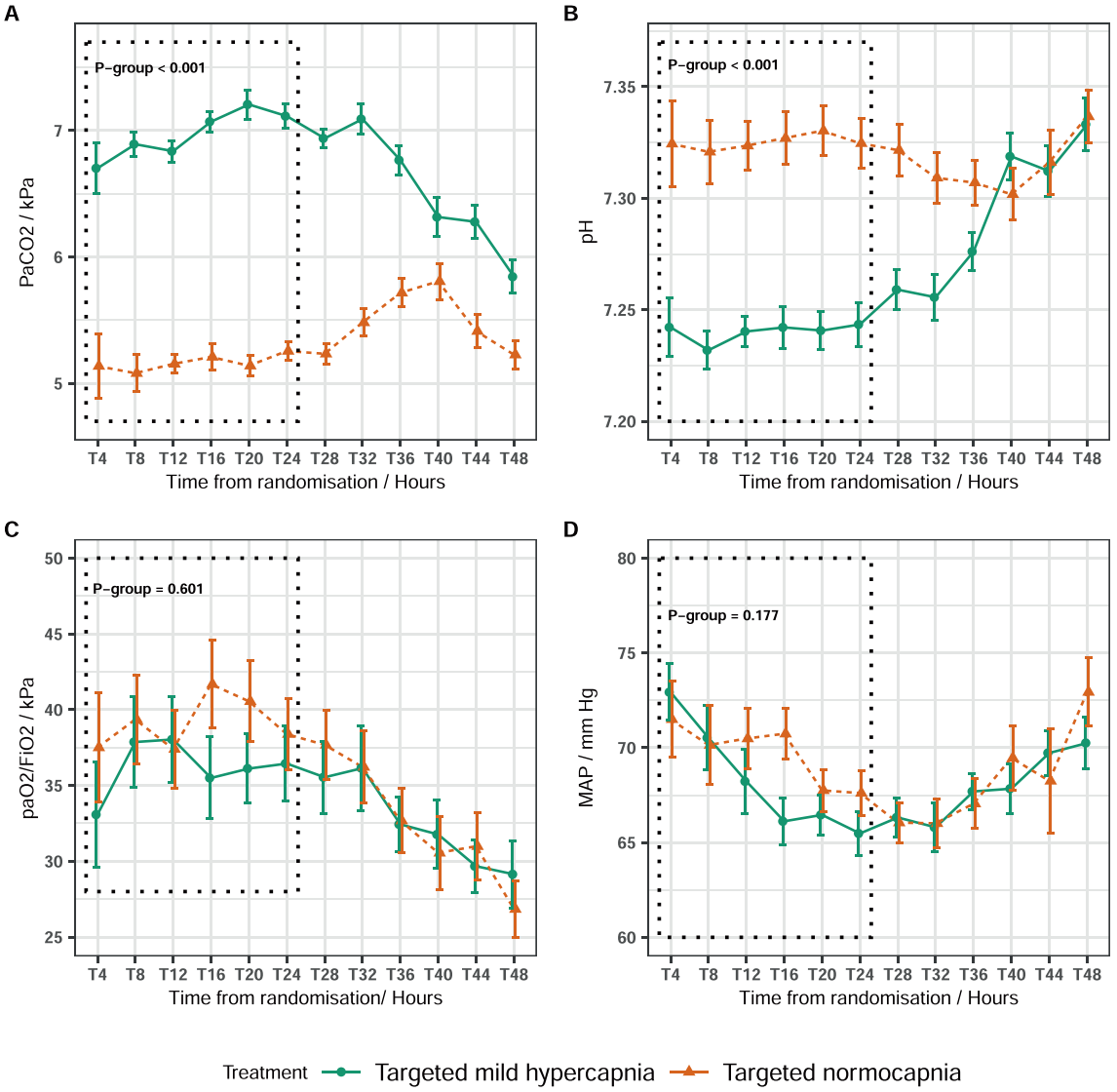

Fig. 1 – Respiratory, metabolic, and haemodynamic changes during targeted mild hypercapnia and targeted normocapnia. A, arterial partial pressure of carbon dioxide. B, pH. C, the ratio of arterial oxygen partial pressure to fractional inspired oxygen. D, Mean arterial blood pressure. Points represent the mean, and error bars represent the 95% confidence interval. P-group denotes the significance of the overall difference between treatment groups, which were analysed with repeated measures mixed models. The 24-hour intervention period is highlighted with the dotted line.

Table 2 – Respiratory, ventilator, haemodynamic and metabolic parameters during targeted mild hypercapnia and targeted normocapnia.

Parameters	Treatment group	Estimated marginal means with 95 % CI during the intervention	Treatment effect (β)	P-group
$PaCO_2$, kPa	Mild hypercapnia	7.0 (6.83 – 7.12)	β = 1.9 kPa (95 % CI 1.60 – 2.10).	< 0.001
	Normocapnia	5.2 (5.1 – 5.3)		
pH	Mild hypercapnia	7.24 (7.22 – 7.30)	β = −0.08 (95 % CI −0.11 to −0.05).	< 0.001
	Normocapnia	7.32 (7.31 – 7.34)		
PaO_2/FiO_2-ratio, kPa	Mild hypercapnia	36.5 (32.0 – 40.7)	β = 0.23 kPa (95 % CI −0.64 to 1.10)	0.601
	Normocapnia	39.2 (35.0 – 43.5)		
Respiratory rate, breaths/min	Mild hypercapnia	11 (10 – 13)	β = −2 breaths/min (95% CI −4 to −1)	< 0.001
	Normocapnia	13 (12 – 14)		
Tidal volumes, mL	Mild hypercapnia	475 (457 – 494)	β = −29 mL (95% CI −52 to −6)	0.013
	Normocapnia	504 (487 – 522)		
Plateau pressure, cm H2O	Mild hypercapnia	19 (18 – 20)	β = −1 cm H2O (95% CI −3 to 0)	0.151
	Normocapnia	20 (19 – 21)		
PEEP, cm H2O	Mild hypercapnia	6 (5–7)	β = −0.2 cm H2O (95% CI – 0.3 to 0.8)	0.387
	Normocapnia	6 (5–6)		
Temperatures,°C	Mild hypercapnia	33.6 (33.3 – 33.9)	β = 0.3 °C (95 % CI −0.20 to 0.80)	0.258
	Normocapnia	33.5 (33.1 – 33.8)		
PVRI, dynes m2/cm5	Mild hypercapnia	586 (532 – 639)	β = −49 dynes m^2/cm^5 (95 % CI −126 to 28)	0.211
	Normocapnia	629 (577 – 682)		
RAP, mm Hg	Mild hypercapnia	10 (10 – 12)	β = 0.80 mm Hg (95 % CI −2.5 to 0.8)	0.315
	Normocapnia	10 (9 – 11)		
mPAP, mm Hg	Mild hypercapnia	26 (25 – 27)	β = 2.0 mm Hg (95 % CI −0.5 to 3.5)	0.006
	Normocapnia	24 (23 – 25)		
PAPi, mm Hg	Mild hypercapnia	2.5 (2.1 – 2.8)	β = 0.39 mm Hg (95 % CI −0.5 to 1.3)	0.379
	Normocapnia	2.6 (2.2 – 2.9)		
CI, L/min/m^2	Mild hypercapnia	2.0 (1.9 – 2.1)	β = 0.45 L/min/m^2 (95 % CI 0.18 −0.7)	< 0.001
	Normocapnia	1.6 (1.5 – 1.8)		
SV, mL	Mild hypercapnia	67 (60 – 74)	β = 9 mL (95 % CI 2 – 17)	0.013
	Normocapnia	55 (52 – 62)		
CPO, Watt	Mild hypercapnia	0.60 (0.56 – 0.65)	β = 0.11 W (95 % CI 0.04 – 0.2)	0.003
	Normocapnia	0.49 (0.45 – 0.54)		
Heart rate per minute	Mild hypercapnia	60 (54 – 65)	β = 5.1 bpm (95 % CI −2.4 to 12.5)	0.179
	Normocapnia	56 (51 – 61)		
SVRI, dynes m2/cm5	Mild hypercapnia	2580 (2356 – 2803)	β = −579 dynes m^2/cm^5 (95 % CI – 878 to – 279)	< 0.001
	Normocapnia	3149 (2930 – 3368)		
MAP, mm Hg	Mild hypercapnia	68 (67 – 70)	β = −2.3 mm Hg (95 % CI −5.6 to 1.1)	0.177
	Normocapnia	70 (69 – 72)		
PCWP, mm Hg	Mild hypercapnia	13 (12 – 14)	β = −0.35 mm Hg (95 % CI −2.3 to 1.6)	0.727
	Normocapnia	12 (11 – 13)		
MVO2, %	Mild hypercapnia	74 (73 – 76)	β = 6.0 % (95 % CI 3.5 – 8.3)	< 0.001
	Normocapnia	69 (67 – 70)		
Lactate, mmol/L	Mild hypercapnia	1.9 (1.6 – 2.3)	β = −0.32 mmol/L (95 % CI −0.83 to 0.18)	0.202
	Normocapnia	2.2 (1.9 – 2.5)		
Fluid balance, mL	Mild hypercapnia	3369 (2779 – 3396)	β = −1174 mL (95 % CI −2216 – 132). *Treatment interaction with time (p-value = 0.037).*	0.028
	Normocapnia	4083 (3507 – 4658)		
Urine output, mL	Mild hypercapnia	2082 (1868 – 2296)	β = −89 mL (95 % CI −83 – 260)	0.290
	Normocapnia	1994 (1779 – 2209)		

Overall differences during the interventions period (24 hours) were evaluated with repeated measures mixed models (P-group) and are reported as estimated marginal means and the treatment effect (β) with 95 % confidence intervals (95 % CI). Statistical significance level is set to p-value < 0.05. PaCO2, denotes arterial partial pressure of carbon dioxide; PaO2/ FiO2-ratio, ratio of arterial oxygen partial pressure to fractional inspired oxygen; PVRI, pulmonary vascular resistance index; RAP, right atrial pressure; mPAP, mean pulmonary artery pressure; PAPi, pulmonary artery pulsatility index; CI, cardiac index; SV, stroke volumes; CPO, cardiac power output; SVRI, systemic vascular resistance index; MAP, mean arterial blood pressure; PCWP, pulmonary capillary wedge pressure; MVO2, mixed venous oxygen saturation.

Haemodynamic measurements

Compared to the normal range, PVRI was considerably elevated in both treatment groups after ICU-admission, and gradually declined during the observation period (Fig. 2A). PVRI was not significantly different in the hypercapnia-group compared to the normocapnia-group (Fig. 2A, Table 2). Mean pulmonary artery pressure (Fig. 2B, Table 2) was mildly, but significantly, elevated in the hypercapnia-group. RAP (Fig. 2C, Table 2) and the haemodynamic

Table 3 – Distribution of coronary pathologies and coronary interventions in 84 patients examined with emergency coronary angiography (prior to ICU admission) after out-of-hospital cardiac arrest.

Coronary pathologies and interventions	All patients ($n = 84$)	Targeted mild hypercapnia ($n = 41$)	Targeted Normocapnia ($n = 43$)	P-value
1-Vessel disease, *n (%)*	29 (35)	13 (32)	16 (37)	
2-Vessel disease, *n (%)*	12 (14)	5 (12)	7 (16)	
3-Vessel disease, *n (%)*	23 (27)	12 (29)	11 (26)	
Unprotected left main disease, *n (%)*	8 (10)	3 (7)	5 (12)	0.946
Atheromatosis without significant stenosis, *n (%)*	13 (15)	7 (17)	6 (14)	
No coronary pathology, *n (%)*	7 (8)	4 (10)	3 (7)	
Significant coronary artery disease, *n (%)*	68 (81)	32 (78)	36 (84)	0.701
Identified culprit lesion, n (%)	43 (51)	21 (51)	22 (51)	
- *RCA lesion*	15 (35)	6 (29)	9 (41)	
- *LAD lesion*	15 (35)	9 (43)	9 (41)	0.738
- *LCX lesion*	7 (16)	3 (14)	4 (18)	
- *LM lesion*	3 (7)	1 (5)	2 (9)	
- *Vein grafts*	2 (5)	2 (9)	0 (0)	
PCI attempted in significant lesions, *n (%)*	45 (54)	24 (71)	21 (54)	0.220
TIMI grade 0–2 before PCI attempt, *n (%)*	44 (98)	23 (96)	21 (100)	0.492
PCI successful, *n (%)*	40 (89)	21 (88)	19 (90)	0.673
Time to needle from OHCA, *median minutes (Q1–Q3)*	90 (70–128)	100 (70–121)	90 (60–130)	0.617

Distribution of coronary pathologies and coronary interventions in 84 patients examined with emergency coronary angiography (prior to ICU admission) after out-of-hospital cardiac arrest. Data are presented as proportions (%) and for variables with a non-normal distribution, as median and lower to upper quartile (Q1–Q3). Differences were evaluated with the $\chi 2$ test, Fisher's exact test and Wilcoxon rank-sum test, as appropriate. Significance level is set to P-value < 0.05. RCA denotes right coronary artery; LAD, left anterior descending coronary artery; LCX, left circumflex coronary artery; LM, left main coronary artery.

parameter of right ventricular function, PAPi (Fig. 2D, Table 2), was similar in the treatment groups.

Overall, the parameters of cardiac function represented by cardiac index, stroke volume, and cardiac power output (CPO) were impaired in the initial post-resuscitation phase and improved gradually over time (Fig. 3A, B and C). The hypercapnia-group had a significantly higher cardiac index (Fig. 3A, Table 2) compared to the normocapnia-group (*P*-group < 0.001). This was mainly due to higher stroke volumes (Fig. 3B, Table 2) in the hypercapnia-group (*P*-group = 0.013). The heart rate (Table 2) did not differ significantly. CPO (Fig. 3C, Table 2) was significantly higher in the hypercapnia-group compared to the normocapnia-group (*P*-group = 0.003).

SVRI (Fig. 3D, Table 2) was significantly lower in the hypercapnia-group (*P*-group < 0.001). MAP (Fig. 1D, Table 2); however, was not different between groups. PCWP (Table 2) was similar. Mixed venous oxygen saturation (MVO2, Fig. 3E, Table 2) was significantly higher in the hypercapnia-group (*P*-group < 0.001), whereas lactate (Table 2) did not differ significantly.

Positive fluid balance (Fig. 3F, Table 2) was significantly lower in the hypercapnia-group (*P*-group = 0.028, with a significant overall interaction term between treatment-group and time: *p*-value = 0.037), with an estimated mean positive fluid balance over 24 hours at 3369 mL (95% CI 2779–3396) versus 4083 mL (95% CI 3507–4658) in the normocapnia-group. Total urine output (Table 2) was not significantly different during the observation period.

Sedation and vasoactive medication

The groups received similar amounts of sedatives during the intervention: Propofol (*P*-group = 0.984 [β = 0.01 mg/kg/hour, 95% CI – 0.61 to 0.62].), fentanyl (*P*-group = 0.349 [β = 0.18 mcg/kg/hour, 95% CI – 0.20 to 0.57].) and midazolam (*P*-group = 0.655 [β = 0.0 1 mg/kg/hour, 95% CI – 0.80 to 0.05].). All patients received norepinephrine, and the hypercapnia-group were on average treated with slightly higher doses of norepinephrine than the normocapnia-group (*P*-group = 0.026 [β = 0.06 mcg/kg/minute, 95% CI 0.008–0.11].). 22 patients in each treatment arm received dobutamine at some point during the intervention, and dobutamine was the only inotrope administered. Dobutamine dosage did not differ significantly between the groups (*P*-group = 0.835 [β = −0.08 mcg/kg/min, 95% CI – 0.87 to 0.70].).

Discussion

We hypothesised that targeting mild hypercapnia for the first 24 hours after OHCA would increase pulmonary vascular resistance, worsen right ventricular function and adversely affect systemic circulation. Compared to targeted normocapnia, hypercapnia after OHCA was associated with hypercapnic acidosis and no increase in pulmonary vascular resistance. We found no signs of worsened right ventricular function, as expressed by right atrial pressure and pulmonary artery pulsatility index. Mild hypercapnia increased cardiac index and power output, lowered systemic vascular resistance and curbed positive fluid balance. Accordingly, our main concern prior to study initiation was refuted.

To the best of our knowledge, this is the first study to prospectively explore the haemodynamic effects of mild hypercapnia in a cohort of patients from a large randomised cardiac arrest trial population. Our results indicate that targeting mild hypercapnia after OHCA was associated with improved haemodynamic parameters, and that potential adverse haemodynamic effects on right sided cardiac function and haemodynamics in general were not observed. This may have important clinical implications because a significant increase in right ventricular afterload can precipitate right ventricular

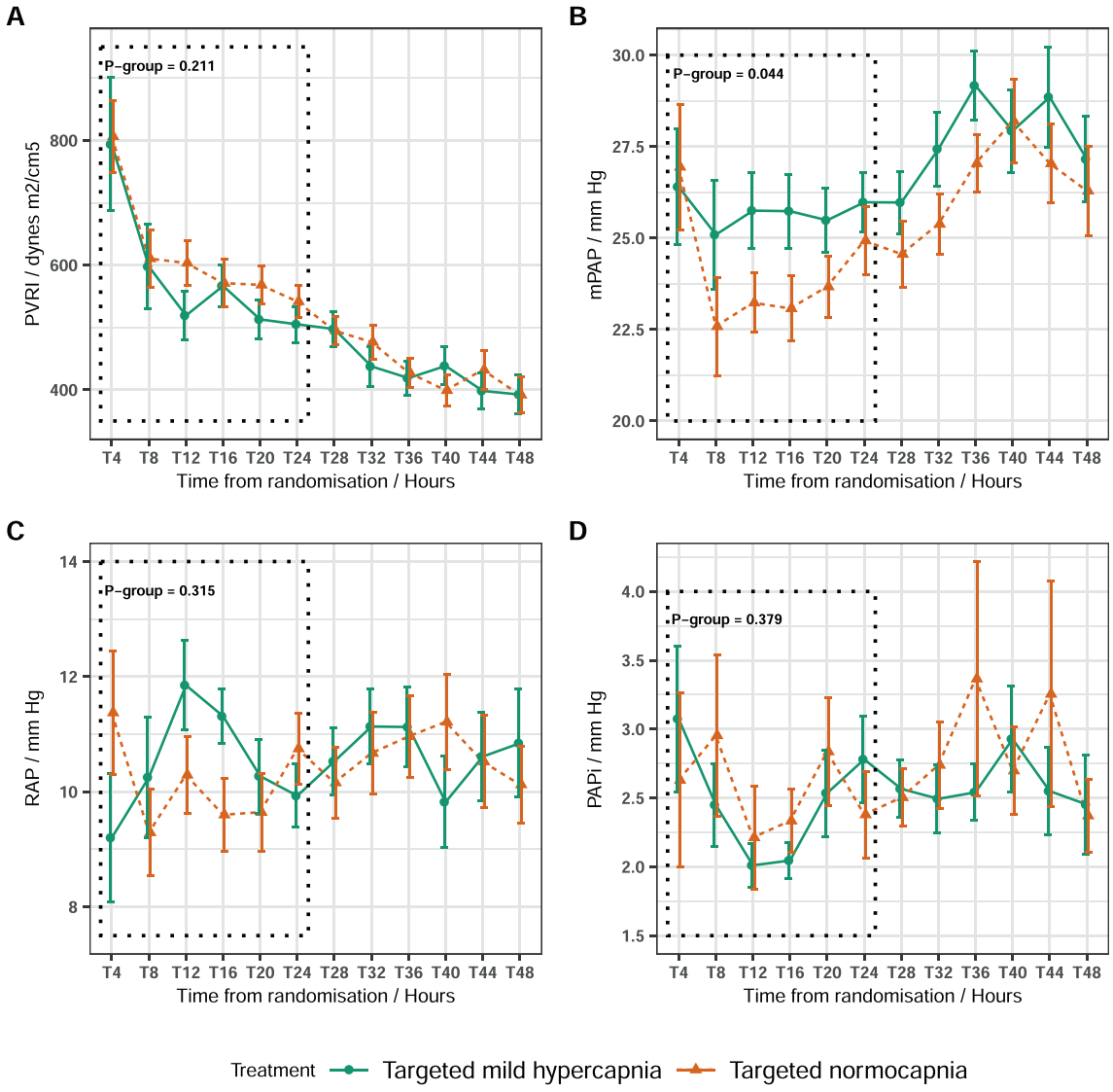

Fig. 2 – Haemodynamic changes during targeted mild hypercapnia and targeted normocapnia. A, Pulmonary vascular resistance index. B, Mean pulmonary artery pressure. C, Right atrial pressure. D, Pulmonary artery pulsatility index. Points represent the mean, and error bars represent a 95% confidence interval. P-group denotes the significance of the overall difference between treatment groups, which were analysed with repeated measures mixed models. The 24-hour intervention period is highlighted with the dotted line.

failure, especially in patients with compromised right ventricular function.[10,12,14,17]

The cardiac index was likely elevated by mild hypercapnia due to increased stroke volumes and lowering of the systemic vascular resistance. The hypercapnic patients were treated with modestly lower tidal volumes and respiratory rates, but similar PEEP and plateau pressures. Lower ventilator settings may increase venous return, thus contributing to the increase in cardiac output and lower positive fluid balance. However, differences in intrathoracic pressure will likely be more important for patients groups treated with high PEEP values, such as ARDS-patients.[24] Cardiac power output, a measure of cardiac pumping ability,[25] was also significantly higher in the hypercapnia-group and suggests improved cardiac function. CPO is strongly correlated to outcomes across a broad spectrum of acute cardiac diseases, including cardiac arrest.[25–27] In addition, hypercapnic acidosis has a direct vasodilatory effect on both the coronary and systemic vessels, is associated with higher mean arterial pressure, and several studies have shown that venous return may be increased.[10,14,28–30]

The increased mixed venous oxygen saturation in the hypercapnia-group likely reflects both improved oxygen delivery with higher cardiac output and improved peripheral tissue oxygenation.[31,32] Hypercapnia improves oxygen unloading into tissues by decreasing haemoglobin oxygen affinity,[8,33] and has been shown to cause microvascular vasodilation, which promotes tissue perfusion.[34] Lactate was numerically lower for the hypercapnia-group,

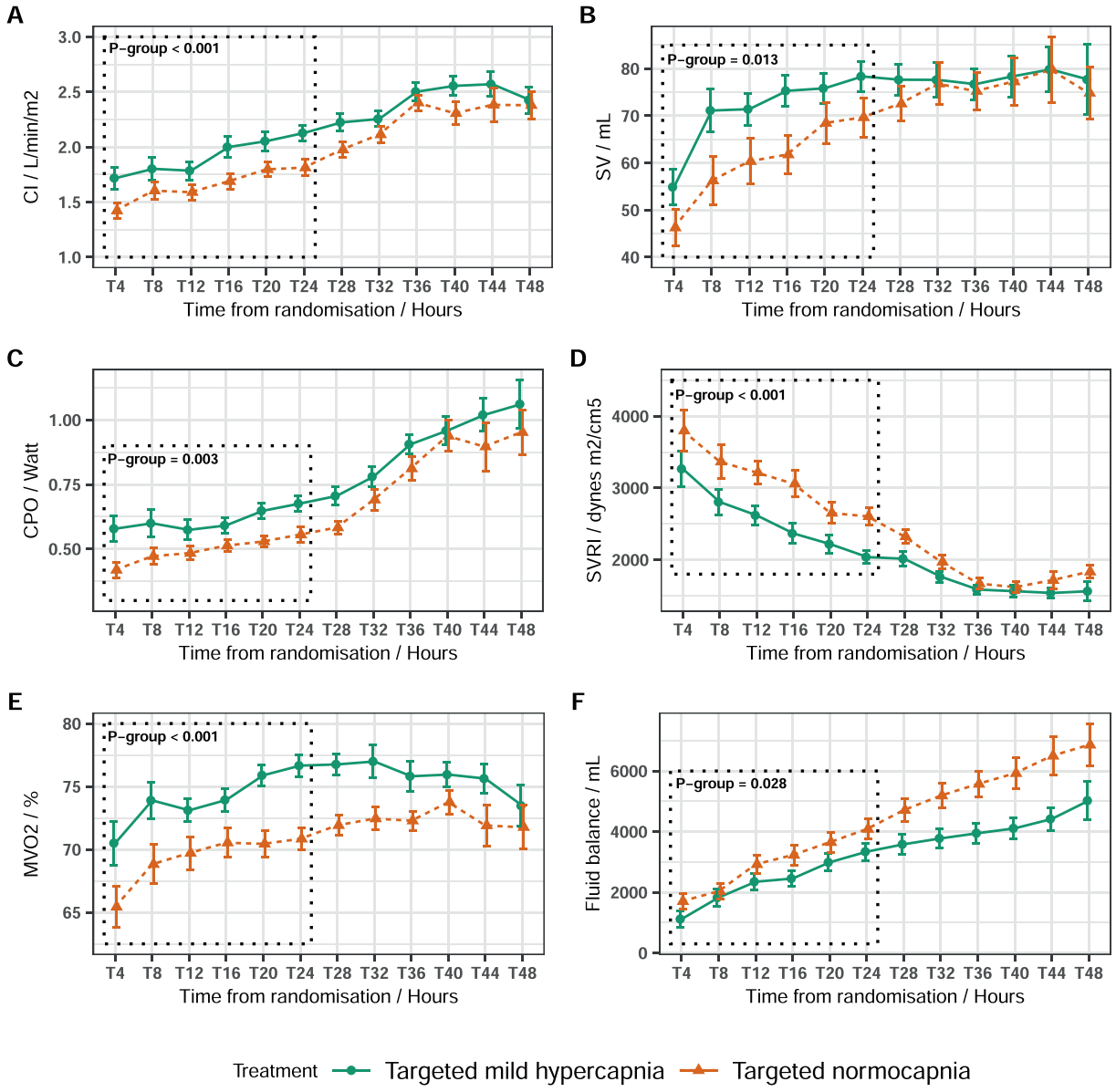

Fig. 3 – Haemodynamic and metabolic changes during targeted mild hypercapnia and targeted normocapnia. A, Cardiac index. B, Stroke volume C, Cardiac power output. D, Systemic vascular resistance index. E, Mixed venous oxygen saturation. F, Fluid balance. Points represent the mean, and error bars represent a 95% confidence interval. P-group denotes the significance of the overall difference between treatment groups, which were analysed with repeated measures mixed models. The 24-hour intervention period is highlighted with the dotted line.

but the difference was not statistically significant. Hypercapnia may reduce cellular respiration and oxygen consumption,[35] which could theoretically also increase the MVO2.

Hypercapnia causes respiratory acidosis, and the cardiovascular consequences observed in this trial is likely caused by hypercapnic acidosis.[8] The haemodynamic effects of mild hypercapnia were apparent at the first right heart catheterisation and dissipated soon after reversal. This confers a fast acting and quickly reversible effect. Importantly, the effect was sustained during treatment. The slightly higher doses of norepinephrine administered in the hypercapnia-group may be due to systemic vasodilation and/or impaired catecholamine sensitivity caused by acidosis.[8,42]

Beyond the situation of post-cardiac arrest management, hypercapnia and hypercapnic acidosis are common in critically ill patients.[37,38] Our investigation may add clinical knowledge relevant to other conditions where hypercapnia is relatively frequent (e.g., acute respiratory distress syndrome), and where there is no randomised controlled evidence of its physiological effects.[14,37] In this regard, cardiac arrest is frequently followed by pulmonary complications and a significant number of resuscitated OHCA patients eventually fulfil the criteria for acute respiratory distress syndrome.[41] Myocardial dysfunction and congestion likely play a significant role in impaired gas exchange and lung damage after cardiac arrest, but their significance remains unclear.[36,42] Lung protective ventilation has become standard post-ROSC care,[36] but there is insufficient evidence to advise for or against mild hypercapnia.[6] Balancing ventilation targets against the potentially detrimental haemodynamic effects have been a concern.[36,42] Our study is currently the largest randomised

study to demonstrate that mild hypercapnia is not associated with adverse cardiovascular effects. In contrast, we observed that mild hypercapnia was associated with improved cardiac performance, increased oxygen delivery, and a curbed positive fluid balance. The clinical significance, however, of improving haemodynamics in OHCA-patients is uncertain and the TAME trial demonstrated no difference in neurological outcome and survival at 6 months.[7,21,39]

This single centre study has important strengths and limitations. The post-arrest management in this study was homogeneous, the hemodynamic monitoring granular, and data collection rigorous, strengthening the confidence in our observations. On the other hand, the limited number of patients may represent a select population, and 53 out of 137 patients included at our site did not receive a PAC. Compared to the TAME and general OHCA population there were higher proportions of shockable rhythms and bystander CPR. Furthermore, the haemodynamic effects demonstrated in comatose, primarily male adults resuscitated after OHCA may not be extrapolated to a more general intensive care population. TTM at 33 degrees centigrade is associated with a significant increase in systemic and pulmonary vascular resistance, and cardiac output is frequently decreased.[40] This may influence the effect of mild hypercapnia. Lactate levels are typically mildly elevated as compared with 36 °C.[40]

Conclusions

In comatose adults resuscitated after out-of-hospital cardiac arrest, targeted mild hypercapnia, compared to targeted normocapnia, was not associated with increased pulmonary vascular resistance, indices of right ventricular failure or adverse haemodynamic effects. Mild hypercapnia improved cardiac performance and increased MVO2.

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CRediT authorship contribution statement

Mathias Baumann Melberg: Validation, Methodology, Visualization, Data curation, Conceptualization, Writing - original, Writing review, Investigation. **Arnljot Flaa:** Methodology, Investigation, Formal analysis, Data curation, Conceptualization, Supervision, Validation, Writing - original draft, Writing - review & editing. **Geir Øystein Andersen:** Validation, Supervision, Methodology, Investigation, Formal analysis, Data curation, Conceptualization, Project administration, Writing - original draft, Writing - review & editing. **Kjetil Sunde:** Investigation, Formal analysis, Data curation, Conceptualization, Methodology, Validation, Writing - original draft, Writing - review & editing. **Rinaldo Bellomo:** Methodology, Investigation, Funding acquisition, Formal analysis, Conceptualization, Validation, Writing - original draft, Writing - review & editing. **Glenn Eastwood:** Methodology, Formal analysis, Conceptualization, Investigation, Validation, Writing - original draft, Writing - review & editing. **Theresa Mariero Olasveengen:** Validation, Supervision, Methodology, Investigation, Formal analysis, Data curation, Conceptualization, Project administration, Writing - original draft, Writing - review & editing. **Eirik Qvigstad:** Validation, Supervision, Methodology, Investigation, Formal analysis, Data curation, Conceptualization, Project administration, Writing - original draft, Writing - review & editing.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Theresa Olasveengen reports a relationship with Laerdal Foundation For Acute Medicine that includes: board membership. Kjetil Sunde and Theresa Olasveengen are part of the Resuscitation Editorial Board.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.resuscitation.2023.109970.

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