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Clinical paper

Cardiac output, heart rate and stroke volume during targeted temperature management after out-of-hospital cardiac arrest: Association with mortality and cause of death

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Abstract

Aim: Myocardial dysfunction and low cardiac index are common after out-of-hospital cardiac arrest (OHCA) as part of the post-cardiac arrest syndrome. This study investigates the association of cardiac index during targeted temperature management (TTM) with mortality.

Methods: In the TTM-trial, which randomly allocated patients to TTM of 33 °C or 36 °C for 24 h, we prospectively and consecutively monitored 151 patients with protocolized measurements from pulmonary artery catheters (PAC) as a single site substudy. Cardiac index, heart rate and stroke volume were measured at 3 time-points during the 24 h TTM period and averaged. Uni- and multivariate Cox regression was used to assess association with mortality.

Results: Of 151 patients, 50 (33%) were deceased after 180 days. Cardiac index during TTM was not significantly associated with mortality in univariate (HR: 0.84 [0.54–1.31], $p = 0.59$) or multivariate analyses ($HR_{adjusted}$: 1.03 [0.57–1.83], $p = 0.93$). Cardiac index during TTM was also not significantly associated with non-neurological death ($HR_{adjusted}$: 1.25 [0.43–3.59], $p = 0.68$). Higher heart rate ($p = 0.03$) and lower stroke volume ($p = 0.04$) were associated with increased mortality in univariate, but not multivariate analyses. No hemodynamic variables were associated with cerebral death, however, increasing lactate during TTM ($HR_{adjusted}$: 2.15 [1.19–3.85], $p = 0.01$) and lower mean arterial pressure during TTM ($HR_{adjusted}$: 0.89 [0.81–0.97], $p = 0.008$) were independently associated with non-neurological death.

Conclusion: Cardiac index during TTM after resuscitation from OHCA is not associated with mortality. Future studies should investigate whether certain subgroups of patients could benefit from targeting higher goals for cardiac index.

Keywords: Cardiac arrest, Cardiac index, Hemodynamic parameters, Targeted temperature management, Mortality, Post-cardiac arrest syndrome

Introduction

The immediate post-cardiac arrest period is characterized by profound hemodynamic instability including reversible myocardial dysfunction and systemic inflammation leading to vasoregulatory dysfunction.[1–7] International guidelines recommend hemodynamic optimization after out-of-hospital cardiac arrest (OHCA) and treatment with fluids and vasopressors may be initiated to avoid hypotension, secure organ blood flow and oxygen delivery.[8,9] Studies have

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reported associations between low blood pressure after OHCA and poor outcome[3,10–12] and two recent randomized clinical trials have investigated blood pressure targets after resuscitated OHCA without any impact on endpoints.[13,14] Blood pressure is dependent of cardiac index and systemic vascular resistance (SVR) and blood pressure can be normal despite inadequate cardiac index if SVR is high.[15] Various methods can be utilized to estimate cardiac index in critical illness,[16,17] however the consequences of low cardiac index after OHCA is unknown. In patients with cardiogenic shock, low cardiac index is associated with adverse outcome[18,19] and after OHCA, low cardiac index is actively treated with inotropes or mechanical support in some published protocols.[20–22] Furthermore 2015 guidelines from the European Resuscitation Council state that post-resuscitation myocardial dysfunction often requires inotropic support, unreferenced.[8] No randomized studies and only few observational studies have investigated low cardiac index after OHCA in relation to clinical outcomes. A significant limitation to these few studies is the monitoring of cardiac index in selected patients from large cohorts in addition to retrospective study designs.[12,20,22–25] In a single center substudy from the Targeted Temperature Management (TTM)-trial we prospectively and consecutively monitored included patients with protocolized measurements from pulmonary artery catheters (PAC). In this cohort, we aimed to test the hypothesis, that cardiac index during TTM is associated with mortality. Furthermore, we assessed the association of other central hemodynamic variables during TTM with mortality.

Methods

This is a post hoc analysis of 171 comatose OHCA-patients included at Copenhagen University Hospital, Rigshospitalet in the TTM-trial from 2010 to 2013.[7] The TTM-trial was a randomized clinical trial comparing TTM of 33 °C with 36 °C for 28 h before rewarming. The trial found no differences in clinical outcomes of the intervention and the results and protocol have been published[7,26] (ClinicalTrials.gov Identifier: NCT01020916). The Ethics Committee of the Capital Region of Denmark (H-1-2010-059) approved the protocol including the use of PACs in all patients for research purposes. Informed consent was immediately obtained from relatives and subsequently from the patient's general practitioner. If the patients regained consciousness, an informed consent was obtained as soon as possibly in all cases. The study was performed according to Good Clinical Practice guidelines. Patients were unconscious (Glasgow Coma Score <8) and adult (aged ≥18 years) patients resuscitated after OHCA of presumed cardiac cause. Main exclusion criteria included unwitnessed asystole as primary rhythm, time from return of spontaneous circulation (ROSC) to randomization of more than 4 h and refractory shock (systolic blood pressure <80 mmHg despite treatment).[26] Prehospital data are reported according to the Utstein style protocol.[27] An analysis of hemodynamics between the two intervention groups has been published previously.[1]

Hemodynamic monitoring and post-cardiac arrest care

A complete hemodynamic assessment was made at the following five prespecified time points: Upon insertion of the PAC (T0), at target temperature (T4), after 16 h (T16), after 28 h (T28), after 36 h (at 37 °C) (T36) and after 48 h (T48). Hemodynamics were monitored with an arterial pressure catheter in the radial artery, and a balloon-tipped, 7.5F triple lumen PAC (Swan-Ganz, Edwards Lifesciences, Irvine, CA) in the internal vena jugularis. Central venous pressure (CVP) values were attained from the proximal port. Cardiac output was measured using the thermodilution technique: A bolus of cold isotonic glucose was rapidly injected and a temperature gradient >10 °C was

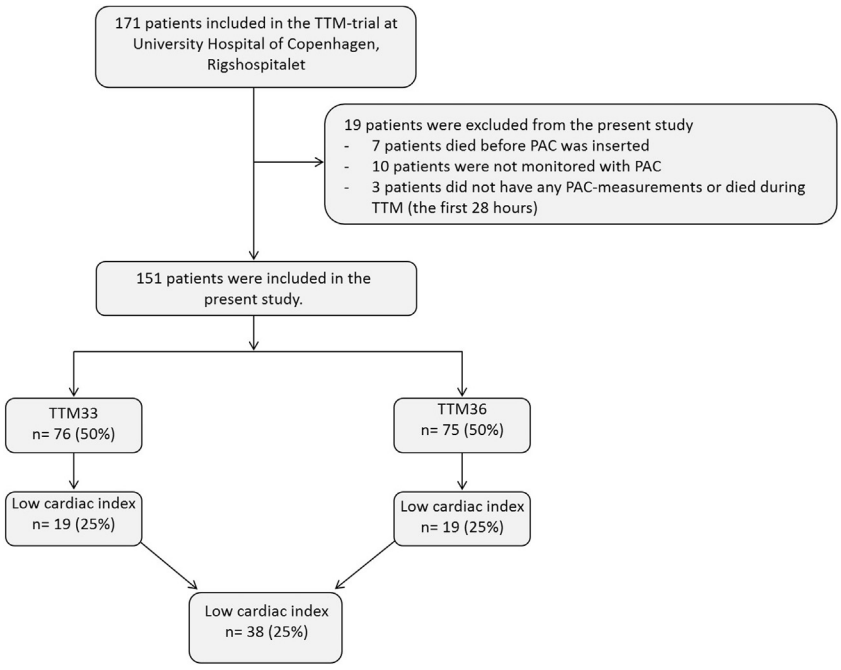

Fig. 1 – Flowchart of study population. The quartile of patients in each TTM-group with the lowest cardiac index were pooled into one group termed "Low cardiac index". This group therefore consists of 19 patients from each TTM-group. TTM = targeted temperature management, PAC = pulmonary artery catheter.

Table 1 – Demographic and prehospital data of 151 comatose out-of-hospital cardiac arrest patients included in the targeted temperature management (TTM)-study stratified according to cardiac index value during TTM. Low cardiac index is defined as the lowest quartile within each TTM-group.

	Normal cardiac index *n* = 113 (75%)	Low cardiac index *n* = 38 (25%)	*p*-value
Demography			
Age – year (±SD)	60 (±12)	64 (±10)	0.09
Male gender – *n* (%)	94 (83%)	37 (97%)	**0.03**
Randomization			
TTM at 36 °C – *n* (%)	56 (50%)	19 (50%)	0.96
Cardiac arrest characteristics			
Witnessed arrest – *n* (%)	102 (90%)	36 (95%)	0.52
Bystander CPR – *n* (%)	93 (82%)	28 (74%)	0.25
Bystander defibrillation – *n* (%)	8 (7%)	1 (3%)	0.45
Shockable primary rhythm – *n* (%)	105 (93%)	32 (84%)	0.12
Time to ROSC – min. (Q1–Q3)	23 (14–30)	19 (12–25)	0.15
Lactate at admission – mmol/L. (Q1–Q3)	6.9 (3.9–10.6)	5.4 (2.4–9.9)	0.22
ST-elevations at admission – *n* (%)	63 (56%)	22 (58%)	0.82
Prehospital epinephrine – mg (Q1–Q3)	2 (1–4)	1 (0–3)	0.45
Acute CAG – *n* (%)	90 (80%)	29 (76%)	0.65
PCI – *n* (%)	60 (53%)	21 (55%)	0.82
Primary diseased vessel			
LAD – *n* (%)	35 (31%)	13 (34%)	0.71
LCX – *n* (%)	18 (16%)	8 (21%)	0.46
LM – *n* (%)	1 (1)	1 (3%)	0.44
RCA – *n* (%)	30 (27%)	6 (16%)	0.18
No coronary artery disease – *n* (%)	29 (26%)	10 (26%)	0.82
Number of coronary artery stenosis			
0 or no CAG – *n* (%)	29 (26%)	11 (29%)	0.95
1 – *n* (%)	41 (36%)	8 (32%)	
2 – *n* (%)	21 (19%)	7 (18%)	
3 or more – *n* (%)	22 (19%)	8 (21%)	
LVEF			
Normal or preserved (>50%) – *n* (%)	11 (10%)	4 (11%)	0.08
Moderately impaired (30–50%) – *n* (%)	58 (52%)	4 (29%)	
Severely impaired (<30%) – *n* (%)	31 (28%)	16 (42%)	
Not performed – *n* (%)	11 (10%)	7 (18%)	
Pre-arrest comorbidities			
Coronary disease – *n* (%)	24 (21%)	7 (18%)	0.71
Previous AMI – *n* (%)	19 (17%)	4 (11%)	0.36
Congestive heart failure – *n* (%)	2 (2%)	3 (8%)	0.41
Hypertension – *n* (%)	38 (34%)	9 (24%)	0.31
Previous TCI/stroke – *n* (%)	5 (4%)	5 (13%)	0.12
Diabetes – *n* (%)	17 (15%)	3 (8%)	0.26
Asthma/COPD – *n* (%)	2 (2%)	0 (0%)	0.99
Markers of oxygen delivery during TTM			
Lactate at target temperature – mmol/L	3.5 (2.2–6.3)	2.6 (1.5–5.8)	0.28
Lactate after 12 h TTM – mmol/L	1.2 (0.8–1.9)	1.3 (0.9–2.0)	0.74
Lactate after 24 h TTM – mmol/L	1.2 (0.8–1.7)	1.2 (0.9–1.8)	0.62
SVO_2 at target temperature – %	74 (68–78)	68 (64–73)	**0.002**
SVO_2 after 12 h TTM – %	74 (71–78)	68 (65–71)	**<0.0001**
SVO_2 after 24 h TTM – %	75 (72–78)	69 (67–73)	**<0.0001**

Abbreviations. AMI: acute myocardial infarction; CAG: coronary angiography; COPD: chronic obstructive pulmonary disease; CPR: cardiopulmonary resuscitation; Q1–Q3: interquartile range; LVEF: left ventricular ejection fraction; *n*: number; PCI: percutaneous coronary intervention; ROSC: return of spontaneous circulation; SD: standard deviation; TCI: transitory cerebral ischemia; TTM: target temperature management; SVO_2 = mixed venous oxygen saturation; LAD = left anterior descending coronary artery; LCX = left circumflex coronary artery; LM = left main coronary artery; RCA = right coronary artery. Bold values signify statistical significance at the 5 percent level.

required. The mean of three measurements with less than 10% variance was used.[28] We have previously reported that interobserver variability of cardiac output measurements was low.[1] The cardiac index was calculated by dividing the cardiac output with the body surface area. Arterial blood and central venous blood were drawn at the previous mentioned predefined time points and analyzed for arterial lactate concentration and central venous oxygen saturation (S_VO_2). Data from the right heart catheterizations were not used to define treatment goals or optimize the hemodynamic status.

All patients were sedated with propofol and fentanyl to a Richmond Agitation-Sedation Scale score of −4, intubated, and mechanically ventilated. Neuromuscular blocking agents were occasionally used to reduce shivering. All patients were cooled actively with surface cooling (Thermowrap with Allon unit, Israel). TTM was initiated immediately post-randomization. The allocated target temperature was maintained for 28 h before rewarming to 37 °C with a 0.5 °C per hour to 37 °C. Hemodynamic treatment goals were CVP of 10–15 mmHg by fluid administration, MAP ≥65 mmHg by vasopressors and inotropes and urine output >1.5 mL/kg/h. The vasopressors norepinephrine and dopamine were the first-line agents, and epinephrine was used secondarily. The accumulated dose of vasopressors/inotropes was calculated for the first 36 h after ICU-admission. The mean vasopressor-load was calculated using the formula: vasopressor-load (μg/kg/min) = norepinephrine (μg/kg/min) + dopamine(μg/kg/min/2) + epinephrine (μg/kg/min).[29] No goals for targeting cardiac indexes were set, however S_VO_2-targets were >55%. Primary percutaneous interventions (PCI) were performed for all patients presenting with ST-elevation in initial ECG. Extend of coronary artery disease and primary diseased coronary artery, was defined by the PCI-operator.

Outcome measures

We have previously reported that TTM at 33 °C compared to TTM at 36 °C significantly lowers cardiac index.[1] To account for this previous finding in the current analysis, we defined low cardiac index with different cut off values based on the lowest quartiles in each TTM-group (Fig. 1).

We wanted to assess cardiac index during TTM until rewarming. We assessed the cardiac index during TTM of each patient in this cohort by visual inspection of spaghetti plots of cardiac index during TTM. We confirmed, that cardiac index is consistent during TTM in most patients, and therefore, to produce a measure of mean cardiac index, we averaged measurements from each patient from time point T4 (target temperature), T16 and T28 (before rewarming). The same procedure was used for other hemodynamic variables. We defined high heart rate as the upper quartile in each TTM-group and we defined high lactate as a mean lactate level during TTM above 2 mmol/L.

After 180 days, survival-status was reported and if the patient was deceased, two experts categorized patients dying from anoxic brain injury (cerebral death). In this study, all other causes of death are termed “non-neurological deaths”.

Endpoints

The primary endpoint was 180-day mortality. Secondary endpoint was mortality stratified according to cause of death.

Statistic

Baseline continuous variables are presented according to distribution as either mean and standard deviation (SD) if data were normal distributed, or median and quartiles (q1–q3). Students T-test and Kruskal–Wallis tests were applied. Categorical variables are presented as count with proportions (%). Chi-square test (or Fishers exact test if expected counts are less than five) was applied. Mortality analysis was illustrated by Kaplan–Meier plots. Furthermore, univariable and multivariable proportional hazard Cox regression was used to adjust for potential confounders. Results are reported as hazard ratios (HR) with 95% confidence intervals (CI) for mortality. Assumptions of proportional hazards and linearity was confirmed. Multivariable models were adjusted for age, time to ROSC, witnessed arrest, cardiopulmonary resuscitation by bystander, shockable primary rhythm, lactate level at admission, randomization group (TTM at 33 °C or 36 °C) and vasopressor load. Between-group differences in hemodynamic variables measured during TTM were assessed by repeated-measurements mixed models with an unstructured covariance structure. Group and time point were fixed effects. The interaction term of group with time was included. Output from the model is used to illustrate the hemodynamic status during TTM and rewarming. p-values are denoted p_{group}. Skewed data were log-transformed before analysis. There was no missing data regarding outcome variables (mortality), and missing data of the predictor variable, cardiac index, were <5%. Statistical analyses are made using the SAS statistical software, version 9.4 (SAS Institute, Cary, NC). Figures are made in Graph Pad Prism version 8.0 (GraphPad Software, San Diego, CA). All tests are 2-tailed, and statistical significance is defined as $p < 0.05$.

Results

We included 171 consecutive OHCA-patients at Copenhagen University Hospital Rigshospitalet, between November 2010 to January 2013 in the TTM-Trial. Invasive hemodynamic data during TTM was available from 151 patients (Fig. 1). The 20 excluded patients had longer time to ROSC (31 (19–57) versus 23 (14–30), $p = 0.01$) and tended to have less primary shockable rhythms ($p = 0.09$) compared to the rest of the population. There were no other differences in baseline characteristics. Baseline data of study population stratified according to low or normal cardiac index during TTM are presented in Table 1. Low cardiac index-patients tended to be older (64 ± 10 versus 60 ± 12 years, $p = 0.09$), were more often men (37 (97%) versus 95 (83%), $p = 0.03$) and tended to more often have impaired myocardial function (ejection fraction <30%) (31 (28%) versus 16 (42%), $p = 0.08$). There were no differences in comorbidities or cardiac arrest-characteristics between low cardiac index and normal cardiac index patients (Table 1).

Hemodynamic status during TTM according to cause of death

After 180 days, 101 (67%) patients were alive and 50 (33%) were deceased. Of the deceased patients, 34 (23% of total population, 68% of deceased) were in the cerebral death group, 16 (11% of total population, 32% of deceased) were in the non-neurological death.

Fig. 2 shows the hemodynamic status during TTM of the study population stratified according to cause of death. Overall, the

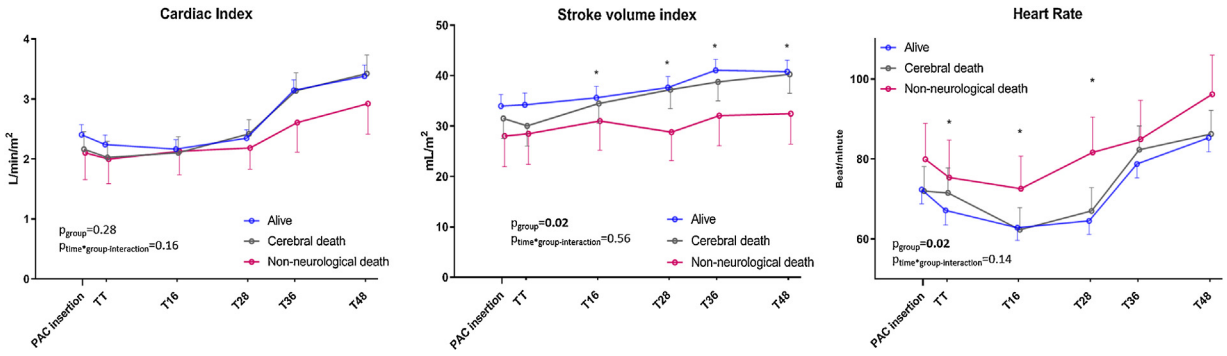

Fig. 2 – Hemodynamic status during targeted temperature management in three groups according to survival status and cause of death. Error bars represent 95% confidence intervals. Data and *p*-values are from a repeated-measures mixed model. p_{group} represents the overall difference between the groups until 48 h after randomization. Boldface represents statistical significance. PAC = pulmonary artery catheter; TT = target temperature.

hemodynamics were similar between long-term survivors and cerebral death-patients. However, non-neurological death-patients had significantly different hemodynamics (Fig. 2). After 24 h of TTM, cardiac index was 2.4 [95% CI, 2.0–2.5], 2.4 [95% CI 2–2.9] and 2.2 [95% CI 1.6–2.8] L/min/m^2 ($p = 0.37$) for the survivors, cerebral death and non-neurological death, respectively. There was no overall difference in cardiac index during TTM between death-groups; cerebral death: $\beta = -0.04$, [95% CI, −0.27 to 0.19] L/min/m^2, non-neurological death: $\beta = -0.25$ [95% CI −0.57 to 0.08] L/min/m^2 ($p_{group} = 0.28$) compared to survivors (Fig. 2). Furthermore, there were no differences between groups regarding MAP ($p_{group} = 0.51$), SvO_2 ($p_{group} = 0.32$) or CVP ($p_{group} = 0.24$), but the non-neurological death group had a significantly higher heart rate ($\beta = 9$ [95% CI 2–16] beats/min; $p_{group} = 0.02$), lower stroke volume index $\beta = -7$ [95% CI −12 to −2] mL/m^2; $p_{group} = 0.02$), and higher lactate ($\beta = 2.0$ [95% CI 1.5–2.6] mmol/L; $p_{group} < 0.0001$) compared to survivors.

Associations between hemodynamic variables and mortality

There was no significant difference in mortality of patients with low cardiac index compared to normal cardiac index-patients in univariate analysis (HR: 0.90 [0.47–1.72], $p = 0.75$) (Fig. 3) or after adjusting for potential confounders ($HR_{adjusted}$: 1.09 [0.49–2.38], $p = 0.83$). Low cardiac index was also not associated with non-neurological death ($HR_{adjusted}$: 1.67 [0.37–7.49], $p = 0.50$), or cerebral death ($HR_{adjusted}$: 0.99 [0.40–2.48], $p = 0.99$).

Cardiac index during TTM as a continuous variable in a Cox regression-model was not significantly associated with mortality in univariate (HR: 0.84 [0.54–1.31], $p = 0.59$) or multivariate analyses ($HR_{adjusted}$: 1.03 [0.57–1.83], $p = 0.93$) (Table 2). Cardiac index during TTM and TTM-group did not significantly interact regarding mortality ($p = 0.09$). Cardiac index values at each time point were also not associated with mortality (At target temperature: HR: 0.69 [0.46–1.06], $p = 0.09$, after 12 h: HR: 0.94 [0.65–1.37], $p = 0.76$, after 24 h: HR: 0.99 [0.66–1.50], $p = 0.98$). Higher heart rate during TTM (HR: 1.02 [1.00–1.04], $p = 0.03$), and lower stroke volume index (HR: 0.97 [0.94–0.99], $p = 0.04$) was significantly associated with mortality, however these associations disappeared after adjusting for confounders (heart rate: $p_{adjusted} = 0.46$, stroke volume index: $p_{adjusted} = 0.74$). MAP during TTM ($p_{adjusted} = 0.78$), CVP ($p_{adjusted} = 0.29$), SvO_2 during TTM ($p_{adjusted} = 0.28$) and vasopressor load during TTM (μg/kg/min) ($p_{adjusted}$: 0.69) were not associated with mortality but increasing lactate during TTM ($HR_{adjusted}$: 1.65 [1.16–2.33], $p = 0.005$) was significantly associated with mortality.

Cardiac index during TTM was not significantly associated with non-neurological death in univariate (HR: 0.84 [0.39–1.84], $p = 0.67$) or multivariate analyses ($HR_{adjusted}$: 1.25 [0.43–3.59], $p = 0.68$). However, lactate during TTM ($HR_{adjusted}$: 2.15 [1.19–3.85], $p = 0.01$) and MAP during TTM ($HR_{adjusted}$: 0.89 [0.81–0.97], $p = 0.008$) were independently associated with non-neurological death. None of the hemodynamic variables assessed in this population were significantly associated with death from anoxic brain injury.

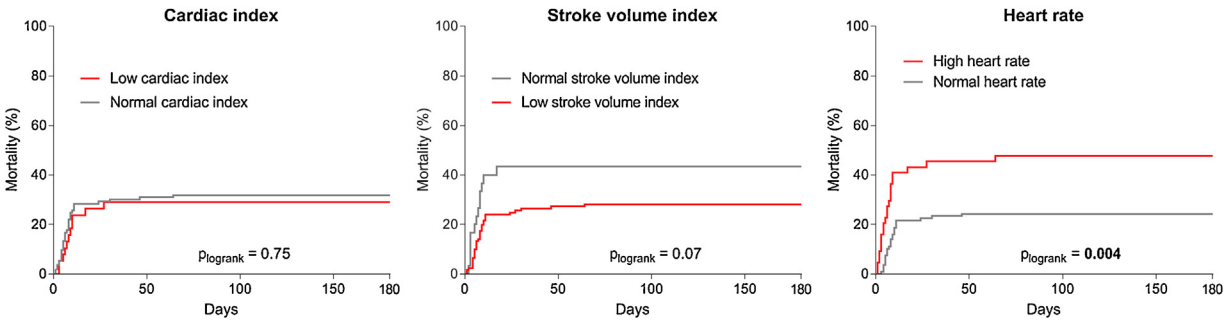

Fig. 3 – 180-days mortality of study population. Patients were stratified by the lowest quartile of cardiac index and stroke volume and highest quartile of heart rate in each TTM-group. Time zero is the day of cardiac arrest.

Table 2 – Association between cardiac index during targeted temperature management (TTM) and mortality assessed by univariable and multivariable cox regression models. the cumulated dose of epinephrine, norepinephrine and dopamine during the first 36 h are reported.

	Hazard ratios for 180-day mortality			
	Univariable HR (95%CL)	*p*-value	Multivariable[a] HR (95%CL)	*p*-value
Cardiac index during TTM (L/min/m^2)	0.84 (0.54–1.31)	0.44	1.03 (0.57–1.83)	0.93
Age at arrest (year)	1.05 (1.02–1.07)	**0.0003**	1.04 (1.00–1.07)	**0.03**
Time to ROSC (min)	1.02 (1.01–1.03)	**<0.0001**	1.02 (1.00–1.03)	**0.03**
Witnessed arrest (yes/no)	0.25 (0.12–0.49)	**<0.0001**	0.27 (0.10–0.68)	**0.006**
Bystander CPR (yes/no)	1.11 (0.56–2.24)	0.76	0.60 (0.20–1.45)	0.26
Shockable primary rhythm (yes/no)	0.24 (0.12–0.48)	**<0.0001**	0.28 (0.11–0.69)	**0.006**
Lactate level at admission (mmol/L)	1.08 (1.02–1.14)	**0.01**	1.05 (0.97–1.14)	0.23
TTM at 36 °C (yes/no)	0.67 (0.38–1.18)	0.17	0.76 (0.35–1.68)	0.49
Vasopressor load during TTM (μg/kg/min)	1.07 (0.91–1.25)	0.42	1.04 (0.86–1.25)	0.69

Abbreviations. TTM: targeted temperature management, CL: confidence limit, CPR: cardiopulmonary resuscitation, HR: Hazard ratio, ROSC: return of spontaneous circulation. Bold values signify statistical significance at the 5 percent level.

[a] Adjusted for age, time to ROSC, witnessed arrest, cardiopulmonary resuscitation by bystander, shockable primary rhythm, lactate level at admission, randomization group (TTM at 33 °C or 36 °C) and inotropic vasopressor load.

Coronary artery disease and cardiac index

Left anterior descending coronary artery disease was present in 48 (32%) patients, left circumflex coronary artery disease was present in 26 patients (17%), left main coronary artery disease was present in 2 (1%) patients and right coronary artery disease was present in 36 (24%) patients. However, affected coronary artery was not associated with low cardiac output (Table 1). Furthermore, number of coronary stenoses was also not associated with low cardiac output (Table 1). PCI was performed in 81 (54%) patients and treatment with PCI was not associated with overall mortality or non-neurological death ($p = 0.78$).

Cardiac index and lactate

As illustrated in Fig. 4, we stratified patients into four groups according to cardiac index (low or normal) and lactate during TTM (above/below 2 mmol/L). Patients with low cardiac index combined with increased lactate had the highest mortality, whereas patients with low cardiac index and normal lactate had the lowest mortality (Fig. 4).

Discussion

We report, that low cardiac index during TTM is not associated with overall mortality or death from cerebral or non-neurological cause. However, lactate is increased as a sign of hypoperfusion, the mortality is high in both normal and low cardiac index-states. If lactate is normal, low cardiac index during TTM seems benign and not associated with mortality. Low cardiac index is possibly a symptom of hemodynamic instability only in a subgroup of OHCA-patients but is not in general a marker of organ hypoperfusion since neither lactate or mortality was associated with low cardiac output.

Cardiac index in OHCA-patients undergoing TTM have been investigated previously. One of the first studies was performed by Bernard et al. in 2002, who reported that cardiac index was 2.5–3.0 L/min/m^2 in the normothermia group and 2.0–2.5 L/min/m^2 in the hypothermia group.[30] In 47 selected patients from a large cohort, Oksanen et al. reported that low cardiac index (<1.5 L/min/m^2) after cardiac arrest was not associated with neurological outcome.[20] In another selected group of 333 patients with PAC-measurements from a registry of 8736 cardiac arrest-patients, Trzeciak et al. reported that

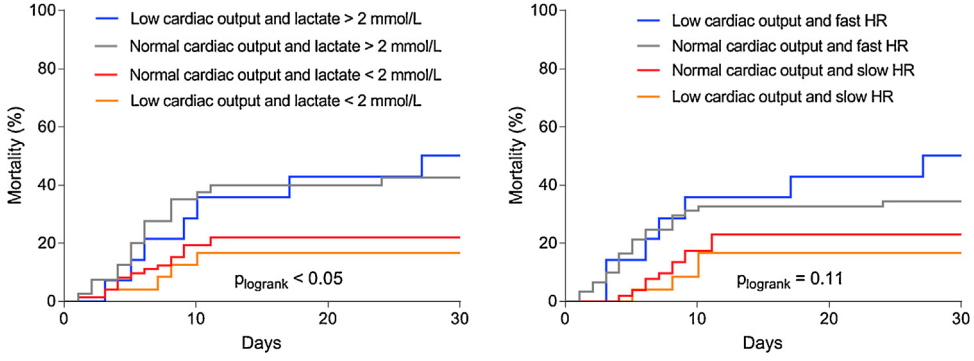

Fig. 4 – 30-days mortality of study population. In the left graph, patients were stratified by low cardiac output (lowest quartile in each TTM-group) and lactate above or below 2 mmol/L. In the right graph, patients were stratified by low cardiac output and mean heart rate above (fast) or below (slow) the median during TTM.

cardiac index was low (<2 L/min/m^2) in 28% without association with mortality.[24] Torgersen et al. found, in 54 selected patients with PAC-measurements, that a higher cardiac index during 24 h post-resuscitation, was weakly associated with adverse neurological outcome.[31] In contrast, a prospective study of 95 consecutive cardiac arrest (both in-hospital and out-of-hospital)-patients by Huang et al., found that low cardiac index (<2.5 L/min/m^2) after 12 h was associated with in-hospital mortality but not with neurological outcome at hospital discharge. One limitation to that study was the cardiac index assessment by transpulmonary thermodilution (PICCO) instead of PAC.[12] According to the cut-off values for low cardiac index used in previous studies, we confirmed that low cardiac index is frequent during TTM. However, low cardiac index during TM was not associated with mortality in this study. After OHCA, systemic inflammation and vasodilation (i.e. decreasing SVR) may lead to a compensatory increase in cardiac index and therefore low cardiac index may be a marker of relatively low systemic inflammation and low oxygen demand rather than a marker of myocardial infarction and dysfunction. Furthermore, we showed, that extend of coronary artery disease or diseased coronary artery was not associated with low cardiac index. We found that SvO2 was significantly decreased in patients with low cardiac index, which may indicate that these patients compensate for the reduced cardiac output by increased oxygen extraction. This is plausible because lactate levels are not increased in patients with low cardiac output.[15]

Cardiac index was not associated with non-neurological or cerebral causes of death. After OHCA different mechanism may be the cause of deterioration and ultimately death. We have showed that the hemodynamic profile is different between patients dying of non-neurological or cerebral causes, while patients dying from cerebral causes had similar hemodynamic status compared to survivors (Fig. 2). In a multivariate logistic regression model with hemodynamic variables during TTM, we identified MAP and lactate during TTM as factors independently associated with non-neurological causes of death. However, no hemodynamic variable in this study was associated with cerebral death. One limitation to this assessment is the bias of competing risks, since some patients dying hemodynamically likely would have died a cerebral death, if they survived the initial hemodynamic instability. However, it is interesting that the cerebral death-patients in this study, who represents a large group of patients with fatal anoxic brain injury, had similar hemodynamics as survivors. In this cohort, we did not find any association between vasopressor load and mortality, which may be confounded by the fact, that some of the most hemodynamical unstable patients were excluded. However, the finding agrees with the study by Laurikkala et al., who also used vasopressor load as a marker of overall vasopressor usage during TTM.[29]

Limitations

We acknowledge several limitations to this study. We used PAC-measurements for cardiac index-assessment, which we consider to be the golden standard. However, 20 patients had to be excluded from analysis due to missing PAC-measurements and these patients had longer time to ROSC compared to the included patients. Furthermore, patients with persistent shock was excluded. Therefore, it is not certain that our results are representative of the most hemodynamically unstable OHCA-patients. However, we prospectively and consecutively included all eligible patients without exclusion criteria and therefore, we consider the external validity of our results to be fair. Second, because this is an observational study, we can report associations, which does not prove a causal relation. Future studies are needed to confirm our results. Third, even though our sample size is larger than previous studies of cardiac index and mortality after OHCA, our study is possibly underpowered to assess important associations between hemodynamic variables and clinical outcomes. Third, the method of averaging hemodynamic values over three time points is a limitation since fluctuations between the values are not recorded. Finally, this was a single center study, and results cannot necessarily be extrapolated to other centers.

Conclusions

Low cardiac index during TTM was frequent after resuscitation from OHCA but was not associated with mortality or lactate. Furthermore, low-cardiac index combined with normal lactate and/or slow heart rate seemed especially benign.

Conflicts of interest

On behalf of all authors, the corresponding author states that there is no conflict of interest.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.resuscitation.2019.07.024.

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