



Cardiac output during targeted temperature management and renal function after out-of-hospital cardiac arrest

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ARTICLE INFO

Keywords:

Cardiac arrest
Post cardiac arrest syndrome
Hemodynamic
Cardiac output
Acute kidney injury
Dialysis

ABSTRACT

Purpose: After resuscitation from out-of-hospital cardiac arrest (OHCA), renal injury and hemodynamic instability are common. We aimed to assess the association between low cardiac output during targeted temperature management (TTM) and acute kidney injury (AKI) after OHCA.

Materials and methods: Single-center substudy of 171 patients included in the prospective, randomized TTM-trial. Hemodynamic evaluation was performed with serial measurements by pulmonary artery catheter. AKI was the primary endpoint and was defined according to the KDIGO-criteria.

Results: Of 152 patients with available hemodynamic data, 49 (32%) had AKI and 21 (14%) had AKI with need for renal replacement therapy (RRT) in the first three days. During targeted temperature management, patients with AKI had higher heart rate (11 beats/min, $p_{\text{group}} < 0.0001$), higher mean arterial pressure (MAP) (4 mmHg, $p_{\text{group}} = 0.001$) and higher lactate (1 mmol/L, $p_{\text{group}} < 0.0001$) compared to patients without AKI. However, there was no difference in cardiac index ($p_{\text{group}} = 0.25$). In a multivariate logistic regression model, adjusting for potential confounders, MAP ($p = .03$), heart rate ($p = .01$) and lactate ($p = .006$), but not cardiac output, were independently associated with AKI.

Conclusions: Blood pressure, heart rate and lactate, but not cardiac output, during 24 h of TTM were associated with AKI in comatose OHCA-patients.

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1. Introduction

After successful resuscitation from out-of-hospital cardiac arrest (OHCA), many patients develop a sepsis-like inflammatory response with hemodynamic instability due to myocardial dysfunction and impaired vasoregulation [1–6], a condition termed the post-cardiac arrest syndrome (PCAS) [7]. PCAS is a consequence of whole-body ischemia during cardiac arrest and following reperfusion at return of spontaneous circulation (ROSC). Acute kidney injury (AKI) is present in approximately half of PCAS-patients and is associated with adverse clinical outcomes [8–12]. In severe cases of AKI, renal replacement therapy (RRT) is needed to avoid complications such as fluid overload, severe uremia or metabolic disturbances [13]. OHCA-patients often remain

hemodynamically unstable in the early post-OHCA period, during which targeted temperature management (TTM) is used to mitigate brain injury [14,15]. Vasopressors and inotropes are used to increase blood pressure and cardiac output to achieve adequate organ perfusion. The kidneys seem especially vulnerable to hypoperfusion [10], and long no- and low-flow times are associated with increased incidence of AKI and RRT [8,11]. Renal blood flow is nearly constant at MAP between 70 and 120 mmHg due to intrinsic autoregulation in healthy individuals, but after OHCA autoregulation may be impaired and optimizing blood pressure and organ blood flow could potentially improve reduce AKI [12]. We have previously reported that low mean arterial pressure (MAP) during TTM was independently associated with kidney injury and need for RRT [11]. However, blood pressure does not necessarily reflect blood flow and oxygen delivery, and there is limited knowledge regarding other hemodynamic parameters in relation to renal function. The aim of this study was to assess the relationship between renal injury and blood flow defined as cardiac output in resuscitated, comatose

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OHCA-patients undergoing 24 h of TTM. Furthermore, as exploratory analyses, we investigated other hemodynamic parameters in relation to renal injury.

2. Material and methods

We conducted a post-hoc analysis of 171 OHCA-patients prospectively and consecutively included in the TTM-trial [16] at Copenhagen University Hospital, Rigshospitalet. The TTM-trial randomized patients to a TTM-protocol of either 33 °C or 36 °C for 36h including rewarming, and the trial found no difference in terms of mortality or neurological outcome [16]. The trial included adult (aged ≥ 18 years), comatose (Glasgow Coma Score < 8) survivors of OHCA of presumed cardiac cause after sustained ROSC of at least 20 min. Main exclusion criteria included refractory shock (sustained systolic blood pressure < 80 mmHg despite treatment), unwitnessed asystole as the primary rhythm and time from ROSC to randomization exceeding four hours [17]. Prehospital data of the cardiac arrest were systematically collected according to the Utstein guidelines [18]. In Copenhagen, we recorded serial advanced hemodynamic measurements from pulmonary artery catheters (PAC), which per protocol were inserted consecutively in all patients. An analysis of the hemodynamic impact of the temperature intervention has been published previously [1]. The TTM-trial was approved by The Ethics Committee of the Capital Region of Denmark (H-1-2010-059) including the use of PAC in all patients for research purposes. A written deputy informed consent was obtained immediately from patients' next of kin and subsequently from the patient's general practitioner and from patients regaining consciousness in all cases. The study was performed according to Good Clinical Practice guidelines.

2.1. Post-cardiac arrest care

All patients were sedated, intubated, and mechanically ventilated. If needed, neuromuscular blocking agents were used to reduce shivering. Sedation was titrated with propofol and fentanyl to a Richmond Agitation-Sedation Scale score of -4 . All patients were actively cooled with a surface cooling device (Thermowrap with Allon unit, Israel). TTM was initiated immediately after randomization and maintained for 28 h followed by rewarming with 0.5 °C per hour to 37 °C.

Hemodynamic treatment goals at University Hospital of Copenhagen were defined according to international guidelines and consisted of central venous pressure (CVP) of 10 to 15 mmHg by administration of fluids. MAP ≥ 65 mmHg by administration of vasopressors and inotropes and urine output > 1.5 mL/kg/h. The main vasopressors used were norepinephrine and dopamine. As soon as possible after admission to the intensive care unit (ICU), hemodynamics were monitored with an arterial pressure catheter inserted transcutaneously in the radial artery, and a balloon-tipped, 7.5F triple lumen PAC (Swan-Ganz, Edwards Lifesciences, Irvine, CA) with CVP values attained from the proximal port. Cardiac output, pulmonary capillary wedge pressure and CVP were measured at six prespecified time points: (T0) upon insertion of the PAC, (T4) at target temperature, (T16) after 16 h, (T28) after 28 h, (T36) after 36h (at 37 °C) and (T48) after 48 h. Perfusion pressure was calculated based on MAP and CVP at each time point (MAP – CVP = perfusion pressure) [19]. Cardiac output was measured with rapid injection of cold isotonic glucose bolus using the thermodilution technique. A temperature gradient above 10 °C was required. Cardiac output was estimated as the mean of three measurements with $< 10\%$ variance [20]. Interobserver variability of cardiac output measurements showed low bias as previously reported [1]. Data from the serial PAC measurements were not part of the goals used for managing the patients and were collected for research purposes only. Arterial blood was drawn from the arterial catheter and central mixed venous blood was drawn at the previous mentioned predefined time points and analyzed for lactate concentration and mixed venous oxygen saturation (SvO₂). The mean vasopressor-load

was calculated with the formula: vasopressor-load (mcg/kg/min) = norepinephrine (mcg/kg/min) + dopamine(mcg/kg/min/2) + epinephrine (mcg/kg/min).

2.2. Renal function

Patients were classified as having AKI if they fulfilled the criteria defined by the Kidney Disease Improving Global Outcomes (KDIGO)-criteria [21]. Blood was sampled from a radial arterial line with first blood samples (T0 = baseline) obtained about 5 min after inclusion in the TTM-study in most patients. Time from ROSC to randomization was median 114 (79–149) min. Thereafter, blood was sampled at 24, 48 and 72 h after OHCA as previously described [2]. Weight and height were recorded at admission and subsequently, we calculated the estimated glomerular filtration rate (eGFR) using the Cockcroft–Gault formula [22]. RRT was recorded if it was initiated during the first 7 days after hospital admission. The creatinine-based criteria of AKI were calculated with the use of the T0 sample as the baseline value. A mean hourly urine output per kg body weight was calculated. AKI stage 1 was defined by a mean urine production < 0.5 mL/kg/h for day 1. Since patients were included at any time of day, the average length of day 1 was approximately 12 h. Periods of anuria ≥ 12 h were not used to define AKI. We divided the population according to presence of AKI at minimum one time point during the first three days. To investigate a dose-response relationship between severity of AKI and hemodynamic variables, we further stratified AKI according to the need for RRT or not (AKI without use of RRT, AKI with use of RRT).

2.3. End points

The primary endpoint was AKI developed at any time during the first 3 days after OHCA. Secondary endpoint was AKI with use of RRT.

2.4. Statistics

Baseline continuous variables are presented as mean and standard deviation (\pm SD) if data were normally distributed, and median and quartiles (q1–q3) for non-normal distributed data. Differences were tested with Students *t*-test or Mann-Whitney *U* test. Categorical variables are presented as count and percentages and differences were tested with the chi-square test or Fishers Exact Test if expected counts were less than five in the analysis. Between-group differences for continuous hemodynamic variables during TTM were evaluated with repeated-measurements mixed models with an unstructured covariance structure with time point, AKI and the interaction term of AKI with time as fixed effects. Differences between patients with or without AKI are reported as β -coefficients and *p*-values (*p*_{group}). For non-normally distributed data, logarithmic transformation was performed. Assumptions were checked and met in all cases before analysis. Output from the mixed models are reported as mean with confidence intervals (CI) and is used to describe the hemodynamic status in patients with or without AKI. Missing data for the outcome variables creatinine and AKI and the predictor variable cardiac index during TTM were all below 5%. Mortality analysis between AKI-groups was illustrated by Kaplan–Meier plots and tested with the log-rank test. Proportional hazard Cox regression was used, and results are reported as hazard ratios (HR) with 95% confidence intervals (CI). Associations between hemodynamic variables during TTM and AKI were assessed with logistic regression and results are reported as odds ratios (OR) with 95% confidence intervals. All multivariable models were adjusted for age, time to ROSC, witnessed arrest, shockable primary rhythm, lactate level at admission, level of TTM and creatinine concentration at admission. A logistic regression model with cubic smoothing splines was fitted to illustrate the risk of AKI in relation to the hemodynamic variables during TTM. We used Spearman correlation coefficients to estimate associations between predictor-variables (hemodynamic variables) with

outcomes (creatinine concentration) displayed as rho (r) and p values. All statistical analyses were performed using the SAS statistical software, version 9.4 (SAS Institute, Cary, NC) or R version 3.3.3 (R Foundation for Statistical Computing, Vienna, Austria). Graph Pad Prism version 8.0 (GraphPad Software, San Diego, CA) was used for figures. All tests are 2-sided, and statistical significance is defined as $p < .05$.

3. Results

At Copenhagen University Hospital Rigshospitalet, 171 consecutive OHCA-patients were included in the TTM-trial from November 2010 to January 2013. Invasive hemodynamic data were available from 152 patients, which constitutes the current study population. AKI was present in 49 (32%) patients (Fig. 1). Level of TTM (33 °C or 36 °C) was not associated with AKI: 24/75 (32%) had AKI in the TTM36°C-group and 25/77 (32%) in the TTM33°C-group, ($p = .95$). Patients with AKI had longer time to ROSC (AKI: 25 (19–37) min.; no AKI: 19 (12–26) min., $p = .0004$), higher lactate at hospital admission (AKI: 8.9 (7.2–13.2) mmol/L; no AKI: 5.3 (2.7–8.8) mmol/L, $p = .0002$) and received more epinephrine during resuscitation (AKI: 4 (2–6) mg.; no AKI: 1 (0–2) mg., $p < .0001$). There were no differences between groups of any comorbidities registered in this study (Table 1).

3.1. Renal function and hemodynamic status during TTM

Among the 49 patients with AKI, 21 (43%) received RRT during the ICU-stay. At ICU-admission (PAC-insertion), the two groups had similar baseline MAP, systemic vascular resistance, CVP, perfusion pressures and SvO₂ (Table 2). However, cardiac index (mean (CI): 2.6 (2.2–3.0) L/min. Per m² versus 2.2 (2.0–2.3) L/min. Per m², $p = .003$), heart rate (mean (CI): 81 (73–91) beats/min. Versus 69 (66–72) beats/min., $p < .0001$), and lactate (mean (CI): 4.2 (2.8–5.5) mmol/L versus 2.5 (1.9–2.9) mmol/L, $p = .0002$) were higher in the AKI group at baseline (Table 2). All invasive measurements after insertion of PAC are shown in Table 2. During TTM (from target temperature (T4) and the following 28 h), there was a significant overall difference in heart rate of 11 beats per minute ($p_{\text{group}} < 0.0001$, higher in AKI-group), MAP of –4 mmHg ($p_{\text{group}} = 0.01$, lower in AKI-group), perfusion pressure of –4 mmHg ($p_{\text{group}} = 0.03$, lower in AKI-group) and lactate of 1 mmol/L ($p_{\text{group}} < 0.0001$, higher in AKI-group) between the groups (Table 2). During TTM, there were no statistically significant differences between the groups regarding cardiac index, systemic vascular

Table 1

Prehospital and pre-arrest data of study population stratified according to presence of acute kidney injury (AKI) during the first three days after OHCA.

	No AKI <i>n</i> = 103 (68%)	AKI <i>n</i> = 49 (32%)	<i>p</i> -value
Demography			
Age - year (± SD)	61 (± 11)	62 (± 12)	0.39
Male sex - <i>n</i> (%)	87 (84%)	45 (92%)	0.21
Randomization			
TTM at 36 ° C - <i>n</i> (%)	51 (50%)	24 (49%)	0.95
Cardiac arrest characteristics			
Witnessed arrest - <i>n</i> (%)	93 (90%)	45 (92%)	1
Bystander CPR - <i>n</i> (%)	84 (82%)	38 (78%)	0.56
Bystander defibrillation - <i>n</i> (%)	8 (8%)	1 (2%)	0.16
Shockable primary rhythm - <i>n</i> (%)	97 (94%)	41 (84%)	0.07
Time to ROSC - min. (Q1-Q3)	19 (12–26)	25 (19–37)	0.0004
Lactate at admission - min. (Q1-Q3)	5.3 (2.7–8.8)	8.9 (7.2–13.2)	0.0002
ST-elevations at admission - <i>n</i> (%)	59 (57%)	27 (55%)	0.86
Prehospital epinephrine - mg (Q1-Q3)	1 (0–2)	4 (2–6)	<0.0001
Acute CAG	82 (80%)	38 (78%)	0.77
PCI - <i>n</i> (%)	56 (54%)	26 (53%)	0.88
Clinical shock at admission - <i>n</i> (%)	5 (5%)	7 (14%)	0.06
LVEF			
Normal or preserved (>50%)	12 (12%)	3 (6%)	
Moderately impaired (30–50%)	47 (47%)	23 (33%)	0.29
Severely impaired (<30%)	33 (33%)	14 (29%)	
Not performed	9 (9%)	9 (18%)	
Pre-arrest comorbidities			
Coronary disease - <i>n</i> (%)	23 (22%)	8 (16%)	0.39
Previous AMI - <i>n</i> (%)	17 (17%)	6 (12%)	0.49
Previous cardiac arrest - <i>n</i> (%)	1 (1%)	1 (2%)	0.54
Congestive heart failure - <i>n</i> (%)	5 (5%)	1 (2%)	0.66
Hypertension - <i>n</i> (%)	34 (33%)	13 (27%)	0.46
Previous TCI/stroke - <i>n</i> (%)	8 (8%)	2 (4%)	0.50
Previous renal failure (dialysis) - <i>n</i> (%)	0 (0%)	1 (2%)	0.32
Diabetes - <i>n</i> (%)	13 (13%)	7 (14%)	0.78
Asthma/COPD - <i>n</i> (%)	1 (1%)	1 (2%)	0.54
Alcoholism - <i>n</i> (%)	0 (0%)	1 (2%)	0.32

Abbreviations: AMI: acute myocardial infarction, AKI: Acute kidney injury, CABG: coronary artery bypass graft, 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, STEMI: ST-elevation myocardial infarction, TCI: transitory cerebral ischemia, TTM: target temperature management.

resistance index, CVP or SvO₂ (Table 2). Vasopressor load during TTM was not significantly different between groups (AKI: 3.85 ± 2.42 µg/kg/min, no AKI 3.45 ± 2.1 µg/kg/min, $p = .29$).

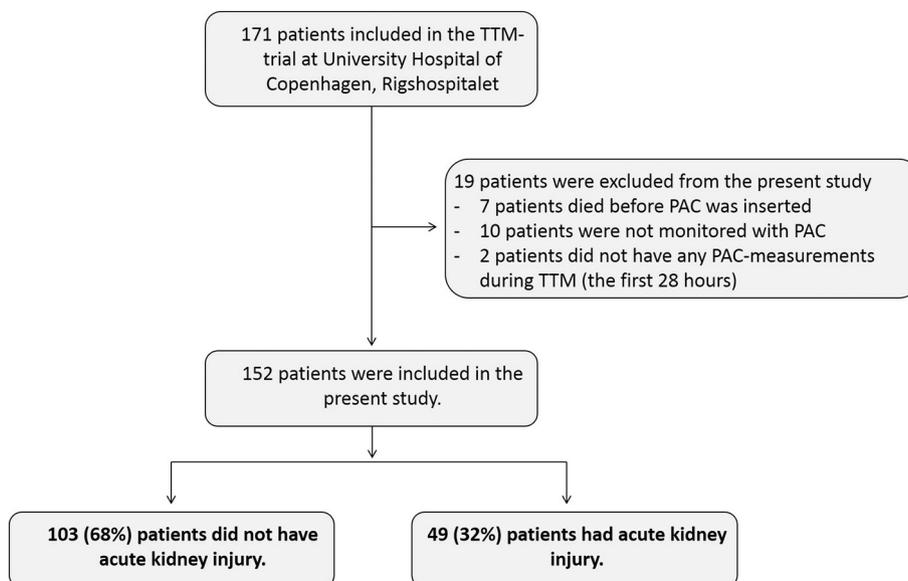


Fig. 1. Flow chart of study population.

Table 2
Hemodynamic parameters of patients with or without acute kidney injury at admission during targeted temperature management.^b

Variable	AKI group	PAC Insertion	TT	16 h	28 h	36 h	48 h	Overall difference (β-coefficient) ^a	p-group ^a
MAP, mmHg	No AKI	74 (69–79)	74 (63–83)	72 (62–75)	71 (60–82)	69 (59–80)	79 (69–90)	−4 mmHg	0.01
	AKI	71 (56–85)	70 (55–84)	68 (53–76)	67 (52–82)	69 (55–76)	78 (63–94)		
	p-value	0.46	0.09	0.08	0.08	0.89	0.46		
Heart rate, per min	No AKI	69 (66–72)	64 (59–70)	61 (55–68)	64 (58–71)	78 (71–84)	85 (78–92)	11 beats per min	<0.0001
	AKI	81 (73–91)	79 (68–91)	69 (58–82)	72 (60–85)	85 (72–98)	90 (77–103)		
	p-value	<0.0001	0.004	0.009	0.02	0.13	<0.0001		
CI, L/min per m ²	No AKI	2.2 (2.0–2.3)	2.1 (1.8–2.3)	2.2 (1.8–2.4)	2.3 (2.0–2.6)	3.0 (2.6–3.5)	3.3 (2.9–3.7)	0.1 L/min per m ²	0.22
	AKI	2.6 (2.2–3.0)	2.4 (1.8–2.9)	2.2 (1.6–2.7)	2.4 (1.8–2.9)	3.2 (2.5–4.0)	3.5 (2.8–4.2)		
	p-value	0.003	0.04	0.87	0.53	0.16	0.19		
SVRI, dynes m ² /s per cm ⁵	No AKI	2492 (2292–2692)	2591 (2256–2925)	2493 (2094–2893)	2338 (1939–2647)	1695 (1295–2094)	1755 (1350–2159)	−202 dynes m ² /s per cm ⁵	0.10
	AKI	1768 (1626–2738)	2417 (1730–3104)	2536 (1792–3282)	2153 (1496–2720)	1594 (1022–2165)	1445 (1001–2205)		
	p-value	0.09	0.33	0.81	0.16	0.25	0.11		
CVP, mmHg	No AKI	13 (12–14)	12 (11–13)	11 (9–13)	11 (9–13)	11 (9–13)	12 (10–13)	0 mmHg	0.89
	AKI	13 (10–16)	12 (10–15)	11 (8–15)	10 (8–14)	12 (9–16)	12 (8–15)		
	p-value	0.96	0.68	0.63	0.46	0.24	0.93		
PP, mmHg	No AKI	61 (56–67)	62 (51–73)	61 (50–71)	60 (49–72)	58 (47–69)	68 (56–79)	−4 mmHg	0.03
	AKI	59 (44–74)	58 (42–74)	57 (41–72)	56 (41–73)	57 (41–72)	67 (50–84)		
	p-value	0.61	0.15	0.11	0.08	0.62	0.8		
Lactate, mmol/L	No AKI	2.5 (1.9–2.9)	1.8 (0.8–2.6)	1.3 (0.3–2.3)	1.3 (0.2–2.2)	1.4 (0.2–2.3)	1.2 (0.1–2.1)	1 mmol/L	<0.0001
	AKI	4.2 (2.8–5.5)	3.0 (1.4–4.4)	2.5 (1.0–4.0)	2.2 (0.7–3.5)	2.5 (0.7–3.9)	2.1 (0.5–3.5)		
	p-value	0.0002	<0.0001	<0.0001	<0.0001	0.0006	0.0002		
SVO ₂	No AKI	72 (71–74)	71 (69–74)	72 (69–76)	73 (70–77)	75 (70–78)	73 (70–76)	−1%	0.30
	AKI	71 (67–76)	72 (67–76)	71 (65–77)	72 (67–78)	72 (64–79)	72 (66–78)		
	p-value	0.44	0.58	0.36	0.32	0.006	0.46		

Abbreviations: AKI: Acute kidney injury, TT: Target temperature, CI: Confidence interval, MAP: mean arterial blood pressure, CI: Cardiac index, SVRI: systemic vascular resistance index, CVP: Central venous pressure, PP: Perfusion pressure (MAP – CVP), SVO₂: mixed venous oxygen saturation.

^a Output from a repeated measurements mixed model.

^b From a repeated measurements mixed model with measurements at target temperature and after 16 and 28 h.

Fig. 2 illustrate the hemodynamics stratified according to severity of AKI. This shows that MAP, heart rate and lactate are significantly associated with severity of AKI, whereas cardiac index is not (Fig. 2). In an analysis of hemodynamics during TTM, comparing patients with AKI with use of RRT with the remaining population, we found a significant overall difference in heart rate of 17 beats per minute ($p_{\text{group}} < 0.0001$, higher in AKI with use of RRT), MAP of −5 mmHg ($p_{\text{group}} = 0.02$, lower in AKI with use of RRT), perfusion pressure of −5 mmHg ($p_{\text{group}} = 0.04$, lower in AKI with use of RRT) and lactate of 1 mmol/L ($p_{\text{group}} < 0.0001$, higher in AKI with use of RRT). Furthermore, systemic vascular resistance index (−337 dynes m²/s per cm⁵, $p_{\text{group}} < 0.05$) and SvO₂ (−3%, $p_{\text{group}} = 0.03$) was lower in the AKI with use of RRT. No statistically significant differences regarding cardiac index ($p_{\text{group}} = .25$) or CVP ($p_{\text{group}} = 0.70$). Sensitivity-analysis of the two TTM-groups separately showed similar results.

We used the mean hemodynamic variables during TTM (T4, T16 and T28) as continuous variables in univariate logistic regression models. Mean cardiac index during TTM was not associated with AKI (OR for AKI: 1.36 [0.81–2.29], $p = .25$ per 1 L/min. Per m² increase) (Table 3). We identified four variables associated with AKI: (1) Mean MAP during TTM (OR for AKI: 0.69 [0.52–0.91] per 5 mmHg increase, $p = .008$), (2) mean heart rate during TTM (OR for AKI: 1.05 [1.03–1.08] per 1 beat/min. Increase, $p = .0001$), (3) mean perfusion pressure during TTM (OR for AKI: 0.77 [0.61–0.98] per 5 mmHg increase, $p = .03$) and (4) mean lactate during TTM (OR for AKI: 1.67 [1.25–2.22] per 1 mmol/L increase, $p = .0005$) (Table 3). For MAP, heart rate and lactate, these associations remained significant after adjusting for potential confounders in multivariate analysis (Table 3). As a sensitivity analysis, we furthermore assessed the relationship between mean cardiac index and severe AKI needing RRT. Cardiac index was not associated with severe AKI (OR: 1.73 [0.89–3.36], $p = .11$), but in multivariate analyses, higher CI tended to associate with severe AKI, however not statistically significant (OR: 1.98 [0.81–3.62], $p = .06$).

Fig. 3 illustrate the associations between risk of AKI and level of MAP, cardiac index, heart rate and lactate.

Correlations between mean hemodynamic variables during TTM with creatinine measured at admission and after 28 and 48 h are shown in Table 4. Creatinine at 28 h correlated weakly with mean cardiac index during TTM ($r = 0.17$; $p = .03$) and mean pulmonary artery wedge pressure ($r = 0.17$; $p = .04$) and correlated inversely with mean MAP during TTM ($r = -0.17$; $p = .03$) and mean SVO₂ ($r = -0.18$; $p = .03$). There was an even stronger correlation between creatinine at 28 h and mean heart rate ($r = 0.41$; $p < 0.0001$) and mean lactate ($r = 0.27$; $p = .001$) (Table 4).

3.2. Interaction between heart rate, MAP and cardiac output

We stratified patients into four groups according to cardiac index (above/below median) and heart rate (above/below median). Patients with low cardiac output and high heart rate had the highest incidence of AKI (18/32 (56%), $p = .001$). Patients with low heart rate had low incidence of AKI whether cardiac output was high or low (Fig. 4). We also stratified the population according to MAP (above/below median) and cardiac output, which showed an equal distribution of AKI between the four MAP/cardiac index-groups (Fig. 4).

3.3. AKI and mortality

The 180-day mortality for patients with and without AKI is illustrated in Fig. 5. AKI was associated with mortality (HR: 2.64 [1.44–4.83], $p = .0002$). After adjusting for potential confounders, there still was a trend, but not statistically significant (HR: 1.98 [0.99–3.93], $p = .05$).

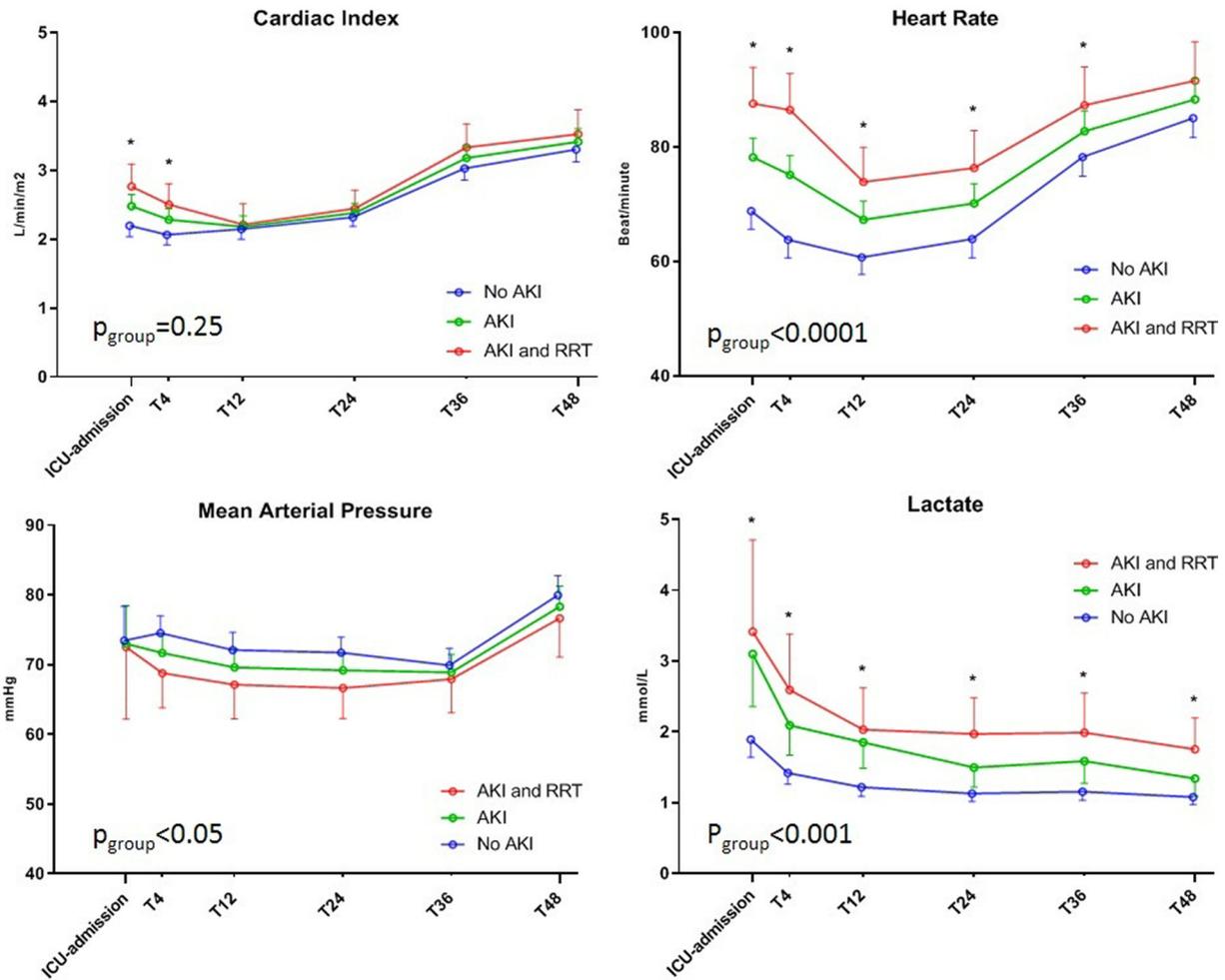


Fig. 2. Median lactate, heart rate, cardiac index and mean arterial pressure at admission and after 12 and 28 h stratified according to severity of acute kidney injury (AKI). 25th and 75th percentiles are represented by the lower and upper error bars.

4. Discussion

In this analysis of advanced hemodynamics during TTM and renal function in 152 comatose OHCA-patients, we found that 1) cardiac index during TTM and AKI are not associated, 2) however, heart rate, MAP and lactate during TTM were independently associated with AKI.

To our knowledge, this is the first study assessing the association between cardiac output and renal function after OHCA. We hypothesized that low cardiac output would be associated with decreased renal

function since the kidneys are vulnerable to hypoperfusion [23]. Moreover, it has been shown, in 154 patients with cardiogenic shock, that decreased cardiac output was associated with AKI [23]. Interestingly, in this study of OHCA-patients there was no association between decreased cardiac index and AKI. In fact, cardiac index at admission was significantly higher among the patients developing AKI, although this difference did not persist during the TTM-period (Table 2). OHCA-patients seem to have a different hemodynamic profile compared to cardiogenic shock-patients in general [24]. In cardiogenic shock, low

Table 3

Association between hemodynamic variables during targeted temperature management and Acute Kidney Injury (AKI) assessed by univariable and multivariable logistic regression models.

	Odds ratios for AKI			
	Univariable OR (95%CL)	p-value	Multivariable ^a OR (95%CL)	p-value
Mean CI during TTM / L/min/m ²	1.36 (0.81–2.29)	0.25	1.74 (0.87–3.48)	0.12
Mean MAP during TTM /5 mmHg	0.69 (0.52–0.91)	0.008	0.70 (0.51–0.98)	0.04
Mean CVP during TTM /mmHg	1.01 (0.91–1.12)	0.83	1.02 (0.91–1.14)	0.80
Mean PP during TTM /5 mmHg	0.77 (0.61–0.98)	0.03	0.83 (0.63–1.08)	0.17
Mean Heart rate during TTM /min	1.05 (1.03–1.08)	0.0001	1.23 (1.05–1.45)	0.01
Mean SVRI during TTM /10 dyn·s·cm ⁻⁵	1.00 (0.99–1.01)	0.28	0.99 (0.98–1.00)	0.14
Mean central venous saturation during TTM /%	0.97 (0.91–1.02)	0.25	1.01 (0.94–1.08)	0.82
Mean lactate during TTM /mmol/l	1.67 (1.25–2.22)	0.0005	1.59 (1.14–2.21)	0.006 ^b

OHCA = Out-of-hospital cardiac arrest, OR = odds ratio, CL = confidence limit, MAP = mean arterial pressure, TTM = targeted temperature management, ROSC = return of spontaneous circulation, CPR = cardiopulmonary resuscitation. Boldface values signify statistically significant (p < .05).

^a Adjusted for known confounding factors in a multivariable logistic regression model: age, time to return of spontaneous circulation, witnessed arrest, vasopressor_load, shockable primary rhythm, lactate level at admission, creatinine level at admission and level of TTM.

^b lactate level at admission was left out of the model due to risk of multicollinearity.

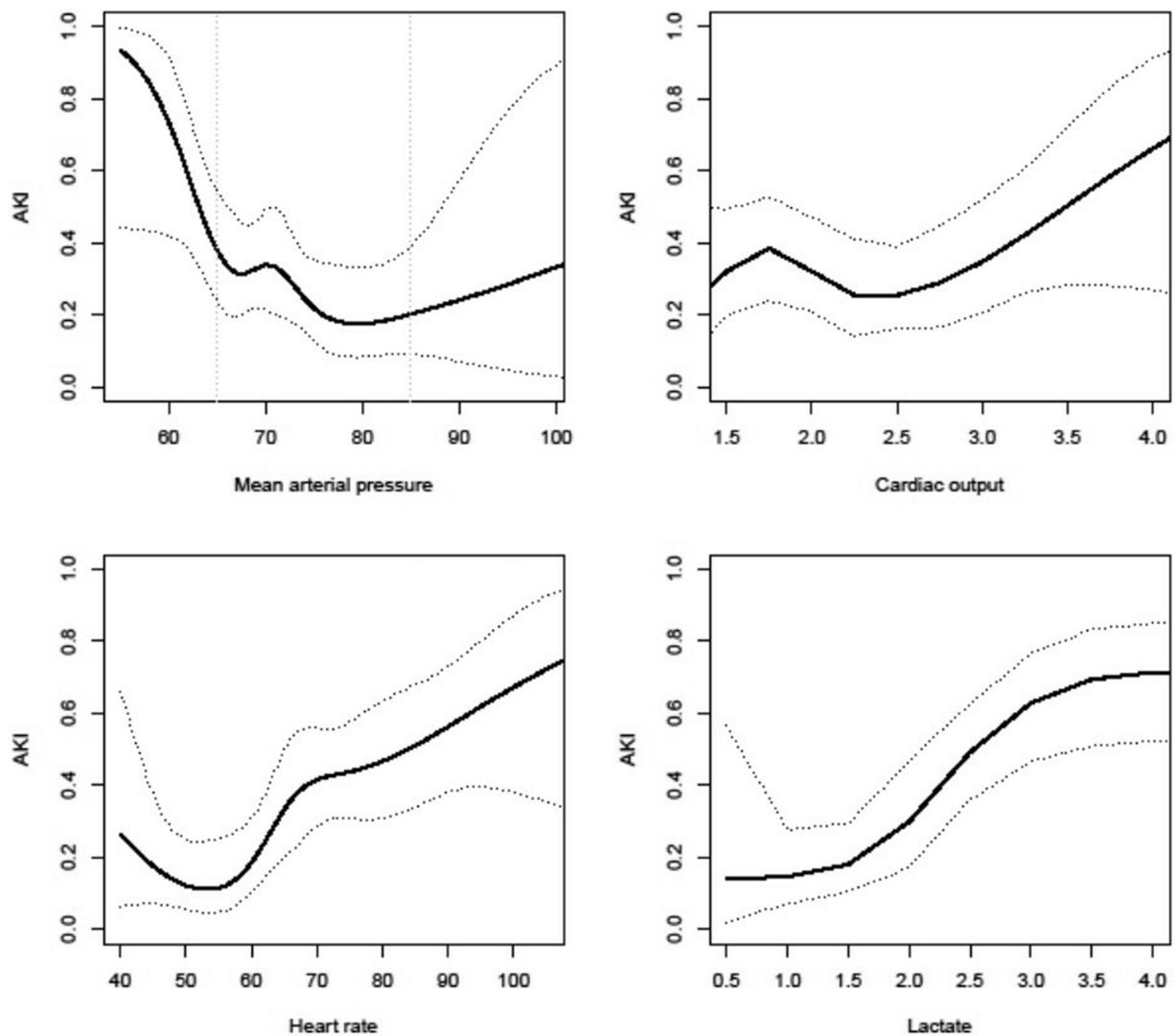


Fig. 3. Risk of acute kidney injury (AKI) as a function of (1) mean arterial pressure, (2) cardiac index, (3) heart rate, and (4) lactate values during targeted temperature management illustrated by a logistic regression model with cubic smoothing splines. The dotted lines indicate the 95% confidence interval. The vertical lines represent the limits of the normal MAP-interval according to international guidelines.

cardiac output is leading to decreased tissue perfusion. In contrast, OHCA-patients exhibit an initial low cardiac output followed by vasodilation with normal or high cardiac output, increased need of vasopressor support in response to endothelial injury [6] and increased inflammation [4] as part of the PCAS [3,4,6,25]. Due to peripheral vasodilatation, fluid administration is often well tolerated and should be considered first line treatment in PCAS. In contrast fluid administration

may increase CVP above the preload dependent zone of the Frank–Starling curve and could worsen venous congestion in cardiogenic shock. Therefore, hypovolemia is poorly tolerated, and the optimal CVP is difficult to define in cardiogenic shock as well as in PCAS. In this study of PCAS-patients, CVP was not associated with AKI, however prospective trials of CVP-goals should be a priority, since this central hemodynamic variable have been poorly investigated previously. This

Table 4
Correlations Between Hemodynamic Variables During Targeted Temperature Management and Creatinine by Spearman correlation coefficients (r).

	Creatinine					
	Admission		Day 1		Day 2	
	r	p-value	r	p-value	r	p-value
Mean MAP during TTM /mmHg	−0.09	0.24	−0.17	0.03	−0.16	0.05
Mean CVP during TTM /mmHg	−0.008	0.93	0.16	0.05	0.1	0.22
Mean heart rate during TTM /min	0.17	0.03	0.41	<0.0001	0.29	0.0005
Mean CI during TTM / L/min/m ²	−0.04	0.59	0.17	0.03	0.03	0.77
Mean SVRI during TTM /dyn·s·cm ^{−5}	0.1	0.21	−0.13	0.12	−0.02	0.85
Mean PCWP during TTM /mmHg	0.12	0.15	0.17	0.04	0.1	0.23
Mean SVO ₂ during TTM /%	−0.2	0.004	−0.18	0.03	−0.25	0.003
Mean lactate during TTM /mmol/l	0.16	0.05	0.27	0.001	0.35	<0.0001

Abbreviations: TTM: Target temperature Management, MAP: mean arterial blood pressure, CI: Cardiac index, SVRI: systemic vascular resistance index, CVP: Central venous pressure, SVO₂: mixed venous oxygen saturation, PCWP: pulmonary capillary wedge pressure.

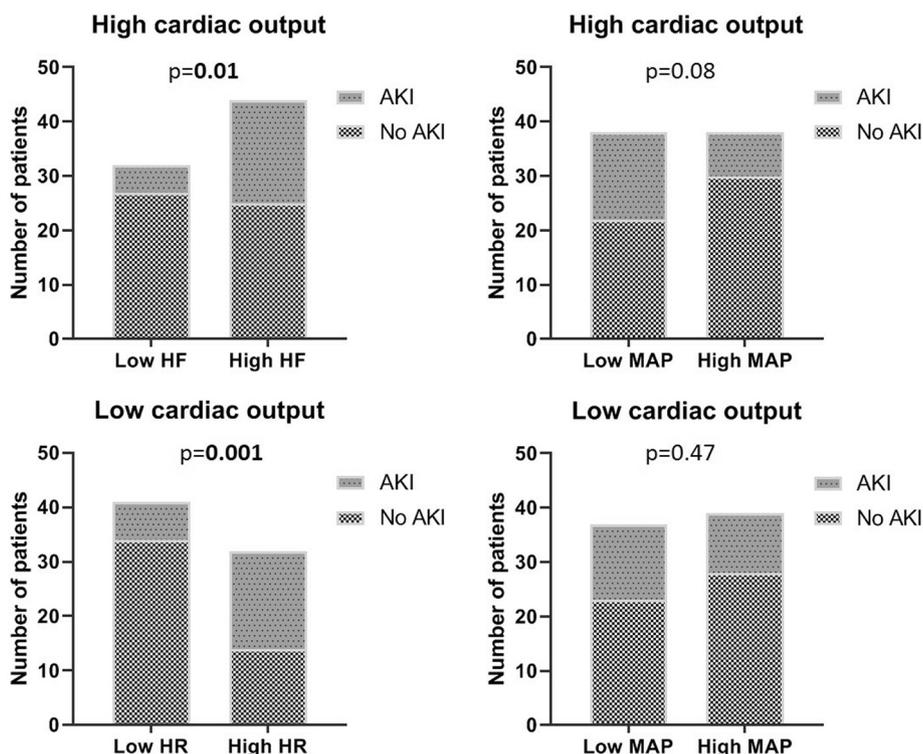


Fig. 4. Bar chart depicting the incidence of AKI in the study population. The population is stratified by mean cardiac index above or below the median. In the two left graphs patients were stratified by heart frequency (HF) above or below the median during TTM. In the right graphs, patients were stratified mean arterial pressure (MAP) above or below 2 mmol/L.

study suggests that low MAP but not low cardiac index is associated with AKI in PCAS. Since patients with severely impaired left ventricular ejection fraction (LVEF) was not overrepresented in the AKI-group, low LVEF at admission after OHCA seems not to be associated with AKI during TTM. These results should be confirmed by future studies.

It is intuitively better for the kidneys to have more perfusion (more cardiac output) and according to current guidelines, inotropic support may be indicated due to low cardiac output and myocardial dysfunction in PCAS-patients [14]. Based in the results of this study, low cardiac output after cardiac arrest is not necessarily a risk factor of AKI if heart rate, MAP and lactate are normal, however this needs to be tested in future prospective studies. Low cardiac index after OHCA may reflect low oxygen demand during TTM, where patients in are deeply sedated. This

may explain, why low cardiac output in relation to renal function seems benign. However, since low MAP is independently associated with AKI [11], hypotension should be avoided during TTM. There are a limited number of trials on hemodynamics and renal function in OHCA-patients. A recent trial by Jakulla et al. [26] randomized 120 patients to low normal (65–75 mmHg) or high-normal (80–100 mmHg) MAP, and a trial by Ameloot et al. [27] randomized 112 OHCA patients to a MAP-target of 85–100mmHg or 65 mmHg without differences in mortality or neurological outcomes. In the trial by Ameloot et al., creatinine and urine output were reported, which showed a significantly higher urine output in the high-MAP group, but no difference in creatinine [27]. In septic shock, Asfar et al. randomized 776 patients to an open-label MAP-target of either 80 to 85 mmHg or 65 to 70 mmHg with no difference on mortality as primary outcome [28]. In a subgroup analysis of patients with known arterial hypertension, significantly fewer patients needed RRT in the higher MAP-target group. These findings indicate a potential for less renal injury if hemodynamic treatment goals are enhanced after resuscitation from OHCA and because AKI is associated with unfavorable outcome in OHCA patients this may have implications for overall mortality. Whether increasing MAP with vasopressors during TTM could mitigate renal injury should be investigated in prospective preferably blinded studies [11,29].

Lower heart rate during TTM is a known early marker of low mortality and favorable neurological outcome after OHCA [30,31], which may reflect higher cardiovascular reserve and less sympathoadrenal activation. The findings of our study verify that low heart rate in addition is an early and easily obtainable marker of favorable renal function, since heart rate during TTM was more strongly correlated with renal function assessed by creatinine than any other hemodynamic marker evaluated in this study.

Macrocirculatory and microcirculatory dysfunction is thought to contribute concomitantly in the pathophysiology of organ failure during sepsis [32]. The present study has investigated macrocirculation, and since no association was found between cardiac output and AKI the question is if impaired microcirculation could be a target to improve

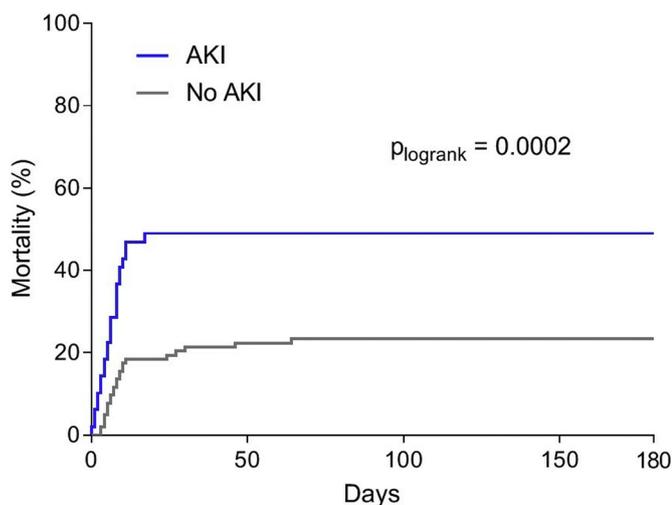


Fig. 5. Survival at 180 days of study population stratified according to presence of acute kidney injury.

outcome after OHCA. However, only few studies have investigated this area in OHCA-patients in relatively small sample sizes [33]. Future studies should investigate other aspects of the hemodynamic system, such as microcirculatory mechanism during TTM in relation to organ function after OHCA.

4.1. Limitations

Several limitations to the present study must be acknowledged. First, we classified patients into having AKI or not based on urine output, creatinine and need for RRT [21]. This may not be the optimal assessment of renal injury or long-term renal outcome since creatinine is a somewhat unspecific marker of renal function. Future studies could assess renal function with more specific biomarkers [34]. However, AKI was strongly associated with mortality indicating, that this condition is of clinical importance. Second, we performed the hemodynamic measurements on several predefined time points during the post-resuscitation care. This method may not be completely representative of the actual hemodynamics since fluctuations between measurements were missed. Third, this study only reports associations, and the implications of its findings on causality is to be hypothesis generating, only. Fourth, this study is based on a database from one of the largest clinical OHCA-trials, but the present analysis is post-hoc and the results should be tested in other cohorts and, if feasible, targeted in prospective trials. Fifth, even though this was a prospectively collected, consecutive cohort, we excluded 19 patients due to missing PAC-measurements. It is likely, that these patients may have been hemodynamically different from the rest of the cohort, and therefore limiting the present study's external validity. Finally, we did not use the anuria criterium for defining AKI in this analysis, why we potentially have missed some patients with AKI due to anuria.

5. Conclusions

Blood pressure, heart rate and lactate, but not cardiac output, during 24 h of TTM were associated with AKI in comatose OHCA-patients. Low cardiac output during TTM after OHCA is seemingly not a risk factor of renal injury.

Funding

The research fund Gangstedfonden and the Research fund of Rigshospitalet has supported this study with unrestricted salary in Dr. Grand's PhD project.

JK was supported by unrestricted grants from the Novo Nordisk Foundation: NNF170C0028706.

The TTM-trial was supported by independent research grant from TrygFonden (Denmark) (grant no: 7-12-0454).

Declaration of Competing Interest

The authors have no conflicts of interests regarding the submitted work.

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