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Mean arterial pressure during targeted temperature management and renal function after out-of-hospital cardiac arrest

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ABSTRACT

Purpose: This study investigates the association between mean arterial pressure (MAP) and renal function after out-of-hospital cardiac arrest (OHCA).
Materials and methods: Post-hoc analysis of 851 comatose OHCA-patients surviving >48 h included in the targeted temperature management (TTM)-trial.
Results: Patients were stratified by mean MAP during TTM in the following groups; <70 mmHg (22%), 70–80 mmHg (43%), and > 80 mmHg (35%). Median (interquartile range) eGFR (ml/min/1.73 m^2) 48 h after OHCA was inversely associated with MAP-group (70 (47–102), 84 (56–113), 94 (61–124), $p < .001$, for the <70-group, 70–80-group and > 80-group respectively). After adjusting for potential confounders, in a mixed model including eGFR after 1, 2 and 3 days this association remained significant ($p_{group\_adjusted} = 0.0002$). Higher mean MAP was independently associated with lower odds of renal replacement therapy (odds $ratio_{adjusted} = 0.77$ [95% confidence interval, 0.65–0.91] per 5 mmHg increase; $p = .002$]).
Conclusions: Low mean MAP during TTM was independently associated with decreased renal function and need of renal replacement therapy in a large cohort of comatose OHCA-patients. Increasing MAP above the recommended 65 mmHg could potentially be renal-protective. This hypothesis should be investigated in prospective trials.

1. Introduction

Acute kidney injury (AKI) is common after out-of-hospital cardiac arrest (OHCA) [1,2], and is associated with increased mortality [1,3], morbidity and financial costs. To mitigate ischemic injury of the organs, hemodynamic monitoring and support in addition to targeted temperature management (TTM) have been implemented as central facets of post-resuscitation care [4-6]. Published protocols have targeted MAP of >65 mmHg, however a specific MAP is not identified in international guidelines, recommending that adequate measures of organ perfusion (decreasing lactate and adequate urine output) should be achieved by administration of fluids and norepinephrine (NE) with or without inotropes [5,6]. Improved organ perfusion and oxygen delivery in the hours and days after OHCA can potentially mitigate organ injury, however clinical evidence regarding optimal hemodynamic targets after OHCA is sparse. The kidneys are vulnerable to hypotension and hypoperfusion [7-10] and in patients with intrinsic renal failure, urine output is an unreliable reflection of end-organ perfusion [1,11]. In the absence of clinical evidence, the renal perfusion-pressure could potentially be improved by a higher MAP after OHCA [8,12]. Furthermore, preexisting patient-characteristics may influence the optimal perfusion-pressure of the kidneys [13].

We hypothesized that a higher MAP after OHCA was associated with improved renal function, which we investigated in the cohort of the Targeted Temperature Management (TTM)-Trial. Accordingly, we assessed the association between mean MAP during TTM with renal

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function, defined as estimated glomerular filtration rate (eGFR) and need for renal replacement therapy. Secondly, we assessed the effect of pre-existing hypertension, heart failure, ischemic heart disease and age on the association between mean MAP and renal function.

2. Methods

This sub-study is a post-hoc analysis of the investigator-initiated, multicenter, randomized, parallel-group, and assessor-blinded clinical TTM-trial, which randomly assigned comatose OHCA-patients in a 1:1 ratio to a TTM protocol of either 33 °C or 36 °C for 24 h. Primary endpoint was all-cause mortality and no differences between allocated groups were seen [14,15]. Prehospital data were collected according to the Utstein guidelines [16]. The TTM-trial was approved by the ethics committees in each country and informed consent was obtained or waived in accordance with local regulations. The TTM-trial is registered at ClinicalTrials.gov (identifier: NCT01020916) and complies with the Declaration of Helsinki. Good Clinical Practice was followed.

2.1. Patients

From November 2010 to January 2013, 950 patients were included in 36 intensive care units in Europe and Australia. Informed consent was withdrawn in 4 patients and 7 patients were excluded after randomization, resulting in 939 patients in the modified intention-to-treat population. Comatose adult patients admitted after OHCA of presumed cardiac cause were eligible for inclusion. Patients were excluded if unwitnessed asystole was the primary rhythm, the time between ROSC and randomization exceeded four hours, suspected or confirmed intracranial bleeding or initial core temperature on admission was <30 °C [14,17].

2.2. Post–cardiac arrest care and hemodynamic management

All patients were sedated, intubated and mechanically ventilated and active cooling was initiated immediately after randomization. Target temperature was induced and maintained for 28 h after randomization, followed by active rewarming of no >0.5 °C/h to 37 °C. Sedation was tapered and the patients recovered spontaneously after 36 h. No treatment goals regarding MAP, central venous pressure, heart rate, urine output or other hemodynamics were pre-specified by the study protocol and were left at the discretion of the treating physicians at each site due to the pragmatic study design. MAP-targets ranged from 65 to 75 mmHg and dopamine and/or norepinephrine were the main vasopressors. MAP was measured by an arterial line in all patients and MAP during TTM until rewarming was mandatorily reported at 0, 4, 12, 20 and 28 h after randomization. A total of 32 patients were excluded due to missing MAP-measurements and 56 patients died within the first 48 h and were excluded to limit effects of extreme hemodynamic instability on renal function assessment (Fig. 1). Moderate shock on admission was defined as signs of hypoperfusion (cool extremities, urine output below 30 ml/h) and need of supportive measures (fluid loading, vasopressors, inotropic drugs and/or mechanical support) to maintain a systolic blood pressure > 90 [18], and randomization in the TTM trial was withheld until shock resolved.

2.3. Data collection

The mean MAP-data for all patients were normally distributed. For each patient, the mean MAP during TTM (from randomization to 28 h) was calculated by averaging all obtained MAP-values during TTM. Mean MAP was examined as: 1) a continuous variable depicting risk of needing renal replacement therapy (RRT), and 2) a categorical

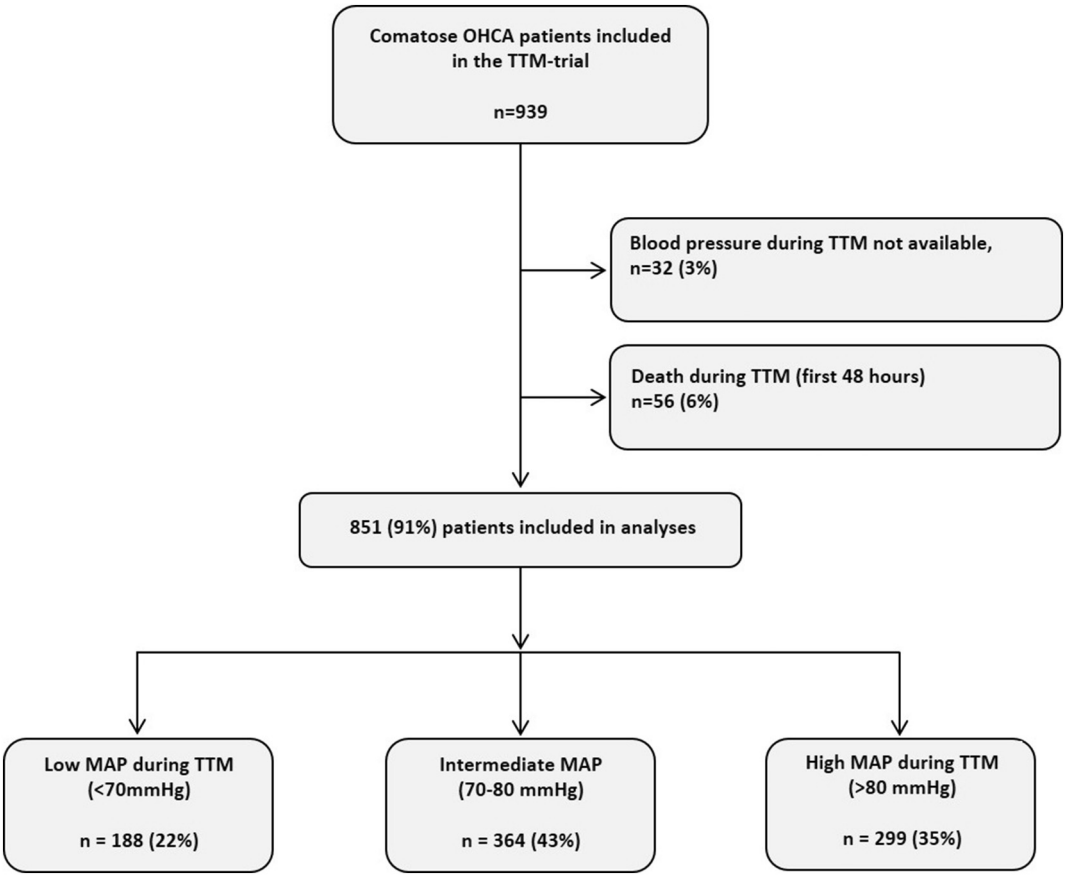

Fig. 1. Flowchart depicting study population stratified in three groups according to mean arterial pressure during targeted temperature management. OHCA = out-of-hospital cardiac arrest, TTM = targeted temperature management, MAP = mean arterial pressure.

variable stratifying patients into three groups using pre-specified MAP-strata: <70 mmHg, 70 to 80 mmHg, and > 80 mmHg. These strata are clinically relevant ranges in the intensive care unit (ICU) and were chosen based on approximations of the 25th and 75th percentiles of mean MAP as have been described in previous smaller studies [12]. Following, a sensitivity-analysis was performed stratifying patients by mean MAP into tertiles. Lastly, the influence of preexisting comorbidity on the association of blood pressure and need for RRT was assessed, focusing on hypertension, heart failure, ischemic heart disease and age. An assessment of blood pressure and mortality of the entire TTM-population have previously been performed [19]. The maximum dose of vasopressor was reported daily as the cardiovascular subscore of sequential organ failure assessment (SOFA) [19]. Patients with a cardiovascular SOFA score recorded of 4 (Dopamine >15 μg/kg/min and/or Epinephrine/Norepinephrine >0.1 μg/kg/min) at any time during ICU-stay were in the high vasopressor-group. Patients with a cardiovascular SOFA score <4 were in the low vasopressor group.

2.4. Endpoints

The primary endpoint of this study, was estimated glomerular filtration rate (eGFR). The secondary endpoints were need for RRT and mortality.

2.5. Renal function assessment

We assessed renal dysfunction by 1) eGFR, which we considered a marker of renal function, 2) need for RRT and 3) patients having AKI according to the Kidney Disease Improving Global Outcomes (KDIGO)-criteria [20].

Creatinine measurements were performed in local hospital laboratories and the admission-creatinine and highest measurement per day in addition to weight and height were reported by the including center. Subsequently estimated glomerular filtration rate (eGFR) was calculated using the Cockcroft–Gault formula [21]. Initiation of RRT was defined as any kind of dialysis during the first 7 days after OHCA. For the creatinine-based criteria of AKI, we used the admission creatinine-value as the baseline value. A mean hourly urine output per day was calculated and adjusted for body weight. We did not grade stages of AKI, we simply divided the population into having AKI or not.

2.6. Statistics

Mean with standard deviation (SD) and median with quartiles (Q1-Q3) were used to present the data according to distribution. Categorical data was compared using chi-square test or the Cochran-Armitage Trend Test for ordinal data such as the three blood pressure groups. The Kruskal–Wallis test was used for continuous data. Factors associated with low mean MAP (i.e. <70 mmHg) and the association between mean MAP and renal replacement therapy were assessed with logistic regression and results are reported as odds ratios (OR). In multivariable models, we adjusted for baseline eGFR, allocated randomization group (TTM at 33 °C or 36 °C), witnessed cardiac arrest, time to ROSC, bystander CPR, admission-lactate level, sex, age, ST-elevations at admission, shockable first rhythm, shock at admission and furthermore adjusted for including hospital (dichotomized into large ($n = 431$) or small centers ($n = 420$)). For the model including RRT and death, we reduced the number of covariates by a stepwise backward elimination, with a significance level below 0.05 to stay in the model. The proportional hazards assumption was checked and confirmed. Collinearity diagnostics were performed to confirm stability of the model: A variance inflation factor above than 5 were used to indicate collinearity problems. To quantify model-discrimination, we calculated a C-statistics. C-statistics is a value between 0.5 and 1, with higher values indicating better performance. Goodness-of-Fit was tested with the Hosmer-Lemeshow test. Values <0.05 indicate poor calibration. Between MAP-group differences in eGFR measured at 24 h, 48 h, 72 h were assessed by repeated-measurements mixed models with an unstructured covariance structure. MAP-group and time point were fixed effects. The interaction term of MAP-group with time (24 h, 48 h, 72 h) was included. *p*-values are denoted p_{group}. Following adjustments for confounders were made as previously mentioned. Logarithmic transformation for skewed data was performed and assumptions were checked and met in all cases before analysis. In addition, multivariable models were assessed for a potential interaction of preexisting comorbidities on the relationship between mean MAP and renal function. Mortality analysis between MAP-groups was illustrated by Kaplan–Meier plots and the log-rank test. Missing data regarding eGFR, dialysis and MAP was <5%, thus we did not use imputations. For illustration of the relationship between hazard of RRT in relation to mean MAP, an additive multivariable proportional hazard model with cubic smoothing splines was fitted. Whether death influenced hazard of renal replacement therapy was tested by performing a competing risk regression with death as competing risk to renal replacement therapy. A two-sided *p*-value of <0.05 was considered statistically significant. 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).

3. Results

Of the 939 included patients in the TTM-trial, 851 patients (91%) had available blood pressure measurements and survived 48 h after admission, thus constituting the current study population. Mean MAP during TTM was <70 mmHg in 188 (22%) patients, 70–80 mmHg in 364 (43%) patients and > 80 mmHg in 299 (35%) patients (Fig. 1). Patients treated with TTM at 33 °C versus 36 °C were evenly distributed between the MAP-strata ($p = .81$). Patients with mean MAP<70 mmHg were significantly older ($p = .03$), a shockable primary rhythm was more frequent ($p = .005$), and so was ST-elevations in first ECG ($p < .001$), they had a higher frequency of performed acute coronary angiographies ($p = .005$), primary percutaneous coronary interventions ($p = .01$) and clinical shock upon admission ($p = .009$). Furthermore, left ventricular ejection fraction was more impaired ($p < .0001$) and previous myocardial infarction was more common ($p = .01$). Preexisting arterial hypertension ($p = .007$) and alcoholism ($p = .04$) was significantly less common in patients with mean MAP<70 mmHg. eGFR at admission was not significantly different between the MAP-groups (Table 1). Factors independently associated with mean MAP<70 mmHg during TTM were increasing age ($p_{adjusted} = 0.0003$), shockable primary rhythm ($p_{adjusted} = 0.04$), ST-elevations in first ECG ($p_{adjusted} < 0.0001$), clinical shock at admission ($p_{adjusted} = 0.02$) and including site ($p_{adjusted} < 0.0001$) (Table 2).

3.1. Renal function

eGFR during the first 3 days after OHCA stratified according to MAP-group is illustrated by Fig. 2. Lower MAP-group was associated with decreased eGFR in the mixed model ($p_{group} = 0.0002$) (Fig. 2A). After adjusting for potential confounders, MAP-group remained independently associated with eGFR ($p_{group\_adjusted} = 0.0003$). Preexisting arterial hypertension ($p_{interaction\_MAP*hypertension} = 0.88$), chronic heart failure ($p_{interaction–MAP*heart\_failure} = 0.28$), ischemic heart disease ($p_{interaction\_MAP*IHD} = 0.88$), level of target temperature ($p_{interaction–MAP*TTM} = 0.09$) or age ($p_{interaction–MAP*age} = 0.39$) did not statistically significant interact with MAP-group regarding the outcome eGFR.

The high vasopressor-group was associated with decreased eGFR ($p_{group} < 0.0001$) (Fig. 2D) and this association remained in the multivariate model ($p_{group\_adjusted} < 0.0001$). Renal replacement therapy was needed significantly more in the high vasopressor-group (high group = 14%, low group = 5%; $p_{chi\text{-}square} < 0.0001$).

Table 1
Baseline characteristics and demographics and prehospital data of study population stratified in three groups according to mean arterial pressure during targeted temperature management.

	Low MAP (<70 mmHg)	Intermediate (70–80 mmHg)	High MAP (>80 mmHg)	*p*-value
	***n* = 188 (22%)**	***n* = 364 (43%)**	***n* = 299 (35%)**	
Demography				
Age - year (±SD)	66 (±12)	63 (±13)	63 (±12)	**0.03**
Male gender - n (%)	162 (86%)	299 (82%)	238 (80%)	0.07
Randomization				
TTM at 36° C - n (%)	94 (50%)	179 (49%)	147 (50%)	0.81
Cardiac arrest characteristics				
Witnessed arrest - n (%)	174 (93%)	331 (91%)	261 (87%)	0.05
Bystander CPR - n (%)	145 (77%)	271 (74%)	208 (70%)	0.06
Bystander defibrillation - n (%)	18 (10%)	36 (10%)	32 (11%)	0.66
Shockable initial rhythm - n (%)	161 (87%)	298 (84%)	227 (77%)	**0.005**
Time to ROSC - min. (Q1-Q3)	25 (17–38)	25 (16–37)	25 (16–39)	0.97
Lactate at admission - min. (q1-q3)	6 (3–9)	6 (3–9)	5 (3–9)	0.19
ST-elevations at admission - n (%)	108 (58%)	142 (40%)	105 (35%)	<**0.001**
Acute CAG - n (%)	138 (73%)	223 (61%)	179 (60%)	**0.005**
PCI - n (%)	100 (53%)	160 (44%)	117 (39%)	**0.01**
Clinical shock at admission - n (%)	34 (18%)	44 (12%)	29 (10%)	**0.009**
eGFR at admission - ml/min/1.73m^2 (±SD)	73 (±30)	77 (±31)	77 (±31)	0.46
LVEF				
Normal or preserved (>50%)	14 (8%)	49 (14%)	56 (19%)	<**0.001**
Moderately impaired (30–50%)	70 (38%)	108 (30%)	57 (19%)	
Severely impaired (<30%)	36 (19%)	55 (15%)	40 (14%)	
Not performed	65 (35%)	147 (41%)	142 (48%)	
Pre-arrest comorbidities				
Chronic dialysis - n (%)	2 (1%)	3 (1%)	1 (0%)	0.33
Coronary disease - n (%)	54 (29%)	105 (29%)	68 (23%)	0.1
Previous AMI - n (%)	45 (24%)	88 (24%)	46 (15%)	**0.01**
Previous cardiac arrest - n (%)	3 (2%)	9 (2%)	6 (2%)	0.84
Congestive heart failure - n (%)	13 (7%)	26 (7%)	17 (6%)	0.52
Hypertension - n (%)	61 (33%)	139 (38%)	134 (45%)	**0.007**
Previous TCI/stroke - n (%)	16 (9%)	25 (7%)	25 (8%)	0.96
Diabetes - n (%)	29 (16%)	49 (14%)	44 (15%)	0.91
Asthma/COPD - n (%)	15 (8%)	40 (11%)	31 (10%)	0.47
Alcoholism - n (%)	1 (1%)	16 (4%)	13 (4%)	**0.04**
Hemodynamic status during TTM				
MAP during TTM - mmHg (Q1-Q3)	66 (64–68)	75 (73–77)	86 (82–92)	<**0.001**
High Vasopressor need during TTM - n (%)	91 (49%)	172 (48%)	125 (42%)	0.24

Abbreviations: MAP: Mean Arterial Pressure, SD: Standard Deviation, TTM: Targeted Temperature Management, CPR: cardiopulmonary resuscitation, Q1-Q3: interquartile range, ROSC: return of spontaneous circulation, CAG: coronary angiography, PCI: Primary Coronary Intervention, LVEF: Left Ventricular Ejection Fraction, AMI: Acute Myocardial Infarction, TCI: Transitory Cerebral Ischemia, COPD: Chronic Obstructive Pulmonary Disease.

AKI was present in 392 (46%) patients in the current study-population and was more present in the low MAP-groups ($p = .01$) (Table 3). AKI was significantly associated with 180-day mortality (hazard ratio = 2.03 [95% confidence interval, 1.65–2.49], $p_{log\text{-}rank} < 0.0001$).

RRT was initiated in a total of 81 (10%) patients and was significantly associated with 180-day mortality (hazard ratio = 1.99 [95% confidence interval, 1.48–2.67], $p_{log\text{-}rank} < 0.0001$). RRT was needed significantly more in the two lowest MAP-groups (<70 mmHg = 13%, 70–80 mmHg = 12%, and > 80 mmHg = 4%; $p = .0007$) (Table 3). Increasing mean MAP was independently and inversely associated with initiation of RRT ($OR_{adjusted} = 0.77$ [95% confidence interval, 0.65–0.91] per 5 mmHg increase; $p = .002$) (Table 4). This association remained after excluding patient with pre-existing renal disease ($n = 6$). Other factors independently associated with initiation of RRT were higher lactate level at admission ($p < .0001$), ST-elevation in initial ECG ($p = .03$), pre-randomization eGFR ($p = .03$) and shock at admission ($p = .007$) (Table 4). Survival at 180 days after OHCA was similar in all three MAP-groups (< 70 mmHg = 54%, 70–80 mmHg = 56%, and > 80 mmHg = 54%; $p_{log\text{-}rank} = 0.93$) (Fig. 3).

An additive multivariable proportional hazard model with cubic smoothing splines is shown in Fig. 4 and illustrates that increasing mean MAP in the entire normal range of MAP (65 mmHg – 85 mmHg) was associated with less need for RRT.

Level of TTM ($p_{interaction\_MAP*TTM} = 0.55$), pre-existing arterial hypertension ($p_{interaction\_MAP*hypertension} = 0.06$), heart failure ($p_{interaction\_MAP*heart\_failure} = 0.69$), ischemic heart disease ($p_{interaction\_MAP*IHD} = 0.46$) or age ($p_{interaction\_MAP*age} = 0.06$) did not statistically significant interact with MAP-group regarding the outcome RRT.

A sensitivity-analysis, stratifying patients in tertiles (tertil 1 < 72 mmHg, tertil 2 = 72–80 mmHg, tertil 3 > 80) instead of the three pre-specified strata of mean MAP, was performed, which did not change the results regarding the primary endpoint, eGFR (Tertiles: $p_{group} = 0.0005$; MAP-groups; $p_{group} = 0.0003$). Furthermore, we assessed the association between RRT and MAP at single time points during TTM. This analysis showed, that mean MAP during TTM was stronger associated with RRT than MAP at any single time point.

4. Discussion

In this post-hoc analysis of MAP during TTM and renal function in 851 patients randomized in the TTM-trial, we report that 1) mean MAP<70 mmHg compared with 70–80 mmHg and > 80 mmHg was independently associated with decreased renal function measured by eGFR, 2) mean MAP was independently and inversely associated with odds of renal replacement therapy, 3) renal replacement therapy was associated with mortality, however 4) low MAP was not associated with mortality in this study, where we excluded patients dying in the first 48 h.

In the early period following resuscitation from OHCA, the blood pressure is unstable and low in some patients as a consequence of the post-cardiac arrest syndrome, characterized by myocardial dysfunction, vasodilatation, systemic inflammation and anoxic brain injury [22]. Consequently, hemodynamic monitoring and infusion of vasoactive and inotropic drugs are often needed [5]. To guide drug-infusion, a blood pressure target of at least 65 mmHg is suggested, but this has not been investigated in clinical trials [23]. The MAP-target depends on the treating physician's choice or hospital guidelines. This is confirmed by our study, where inclusion at a small hospital was independently associated with higher odds of low MAP. In search of an optimal blood pressure target in septic shock, Asfar et al. randomized 798 patients to a MAP-target of 65 to 70 mmHg (low-target group) or 80 to 85 mmHg (high-target group) in the first five days of septic shock in the ICU and found no difference in mortality between the groups [24]. Several observational studies have investigated mean MAP after OHCA and have found conflicting results; a systematic review

Table 2
Predictors of low mean arterial pressure during targeted temperature management.

	Odds ratios for low MAP during TTM after OHCA			
	Univariate	***p*-Value**	**Multivariate**	***p*-Value**
	OR (95%CI)		**OR (95%CI)**	
Age at arrest/year	1.02 (1.00–1.03)	**0.009**	1.03 (1.01–1.05)	**0.0003**
Sex, male	1.46 (0.93–2.31)	0.10	1.23 (0.75–2.03)	0.41
Time to ROSC/min	1.00 (0.99–1.01)	0.96	0.99 (0.99–1.01)	0.67
Initial lactate/mmol/L	1.03 (0.99–1.07)	0.21	1.03 (0.99–1.08)	0.14
Witnessed arrest	1.49 (0.82–2.71)	0.19	1.51 (0.77–2.95)	0.23
Bystander CPR	1.29 (0.89–1.89)	0.18	1.29 (0.83–2.03)	0.26
Bystander defibrillation	0.93 (0.54–1.59)	0.78	0.78 (0.42–1.45)	0.43
Shockable primary rhythm	1.55 (0.97–2.46)	0.07	1.78 (1.03–3.06)	**0.04**
ST-elevations at admission	2.29 (1.65–3.20)	<**0.0001**	2.29 (1.56–3.33)	<**0.0001**
Clinical shock at admission	1.78 (1.15–2.78)	**0.01**	1.81 (1.09–2.99)	**0.02**
Including hospital (small versus large)	0.35 (0.25–0.49)	<**0.0001**	0.33 (0.23–0.48)	<**0.0001**

Hosmer and Lemeshow Goodness-of-Fit test: p = .18. C-statistics: AUC = 0.66.
Abbreviations: TTM = Targeted Temperature Management, OHCA: Out-of-Hospital Cardiac Arrest, OR = odds ratio, CI = confidence interval, ROSC = return of spontaneous circulation, CPR: cardiopulmonary resuscitation.
Boldface values signify statistically significance (p <0 .05).

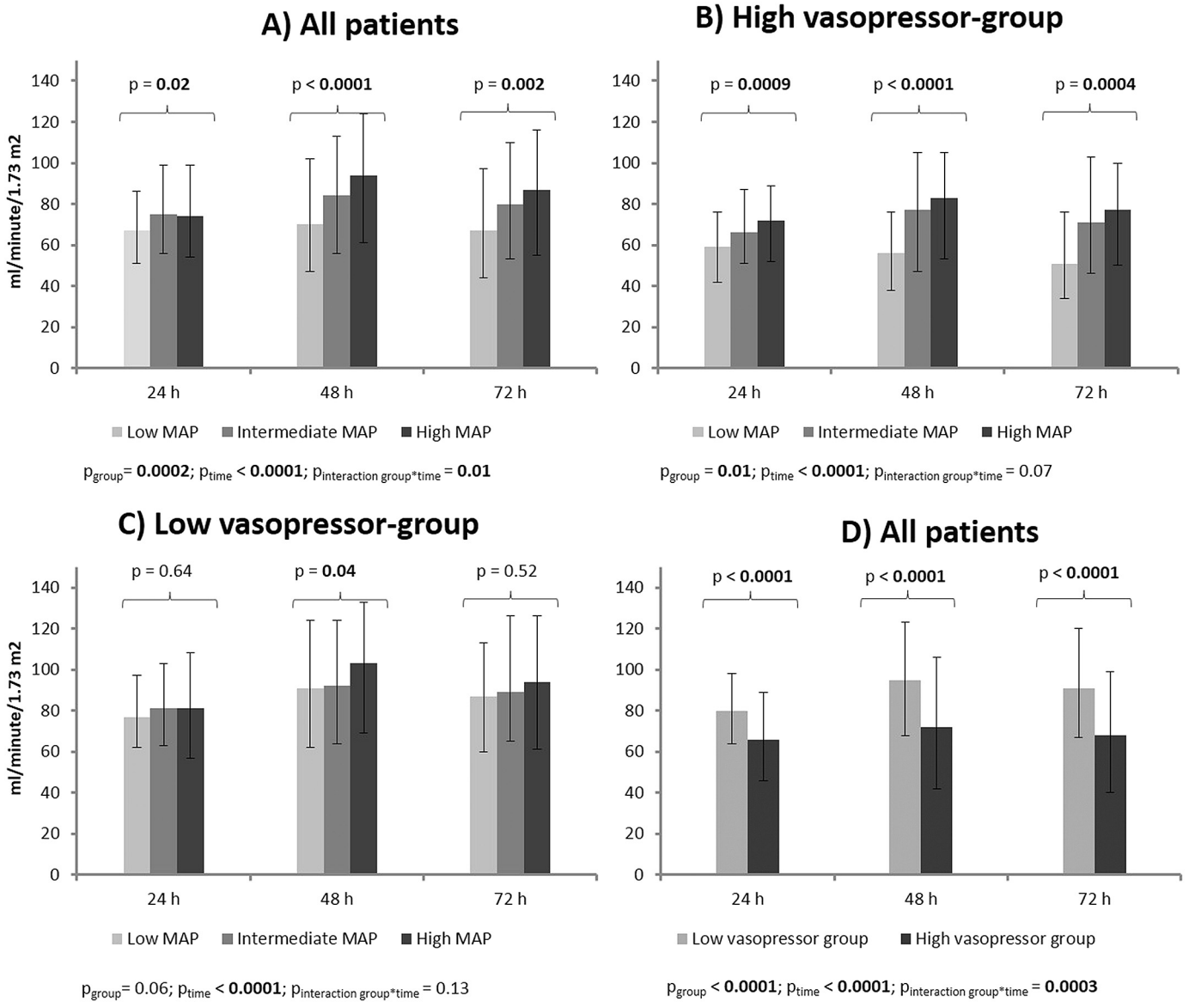

Fig. 2. Median estimated glomerular filtration rate (eGFR) after 24, 48 and 72 h. Error bars depicts the 25th and 75th percentiles. A) All patients stratified by MAP-group (<70 mmHg; 70–80 mmHg; <80 mmHg), B) The high vasopressor-group stratified by MAP-group, C) The low vasopressor-group stratified by MAP-group, D) All patients stratified by vasopressor-group.

Table 3
Clinical Outcome of Study Population Stratified According to mean arterial pressure during targeted temperature management. Data are presented as mean ± SD or median and (interquartile range) as appropriate. The *p*-value represents comparison between groups. High vasopressor is defined by cardiovascular Sequential Organ Failure Assessment = 4 versus ≤3. Renal replacement therapy is defined as initiation of any kind of dialysis during the first 7 days after OHCA. Boldface values signify statistically significant ($p < .05$).

	Low MAP (<70 mmHg)	Intermediate (70–80 mmHg)	High MAP (>80 mmHg)	p-Value
	n = 188 (22%)	n = 364 (43%)	n = 299 (35%)	
Clinical outcome				
Heart rate during TTM - min^{-1} (±SD)	76 (±15)	74 (±14)	77 (±14)	0.17
Lactate during TTM - mmol/L (Q1-Q3)	2.2 (1.5–3.2)	1.9 (1.3–2.9)	1.9 (1.3–3.1)	**0.02**
Survival - n (%)	102 (54%)	202 (56%)	162 (54%)	0.92
Atrial fibrillation during TTM - n (%)	38 (20%)	88 (24%)	54 (18%)	0.15
Ventricular fibrillation during TTM - n (%)	15 (8%)	15 (4%)	20 (7%)	0.14
Renal function during TTM				
eGFR relative to baseline - (%)				
Day 1	94%	103%	101%	
Day 2	99%	116%	127%	
Day 3	95%	110%	118%	
Urine output - mL/kg/h (Q1-Q3)				
Day 1	1.3 (0.5–2.2)	1.2 (0.6–2.1)	1.3 (0.7–2.1)	0.57
Day 2	1.1 (0.6–1.7)	1 (0.6–1.5)	1 (0.6–1.5)	0.69
Day 3	1.3 (0.6–1.8)	1.1 (0.7–1.6)	1.1 (0.7–1.7)	0.80
Acute kidney injury (any stage) - n (%)	102 (54%)	164 (45%)	126 (42%)	**0.01**
Renal replacement therapy - n (%)	25 (13%)	43 (12%)	13 (4%)	**0.0004**

Abbreviations: MAP = mean arterial pressure, TTM = targeted temperature management, Q1-Q3 = interquartile range, OHCA = Out-of-hospital cardiac arrest, OR = odds ratio, MAP = mean arterial pressure, eGFR = estimated glomerular filtration rate, ROSC = return of spontaneous circulation, CPR = cardiopulmonary resuscitation.

from 2015 found that 7 of 9 studies reported associations between higher blood pressure and improved outcomes [25], whereas a systematic review from 2017 did not find evidence to support a higher MAP-target in critically ill patients requiring vasopressor therapy [26]. So far, the largest observational study of vasopressors and MAP after OHCA is an analysis from the same cohort as in the present study including patients dying within 48 h ($n = 920$). Here we found that higher mean MAP during TTM was associated with reduced risk of death (30-day mortality), HR = 0.90 [95% CI, 0.85–0.95] per 5 mmHg increase; $p = .0008$) [19]. Our current study found no association between MAP and mortality, probably because this association found in previous studies is driven by patients dying from cardiogenic shock during TTM [27]. Low MAP does not seem to affect mortality in patients surviving >2 days. Since our aim was to assess the optimal MAP-target regarding renal perfusion, it we excluded this group of patients.

5. MAP and renal function

Observational studies of septic patients have found associations between MAP below 75 mmHg and increased need for renal replacement therapy [9], whereas a study of shock concluded that a MAP of 72 to 82 mmHg might be necessary to avoid AKI because of disturbance in renal autoregulation [8]. Our study is, to the best of our knowledge, the first study to investigate an association between renal function and hemodynamic variables in OHCA-patients. Our findings agree with the septic shock-studies; patients with a mean MAP above 80 mmHg had significantly less need for renal replacement therapy. Furthermore, using logistic regression analysis adjusted for potential confounders and study site, increasing MAP during TTM remained independently associated with less need for renal replacement therapy. In the absence of clinical evidence of optimal blood pressure targets in

Table 4
Univariable and multivariable logistic regression models of study population. The models include factors known for influencing mortality after OHCA in addition to mean arterial pressure during TTM. Data are presented as odds ratios with 95% confidence limits. Renal failure is defined as initiation of any kind of dialysis during the first 7 days after OHCA. Boldface values signify statistically significance ($p < .05$).

	Odds ratios for death 180 days after OHCA				Odds ratios for renal replacement therapy			
	Univariable	*p*-Value	Multivariable*	*p*-value	Univariable	*p*-Value	Multivariable*	*p*-Value
	OR (95%CL)		OR (95%CL)		OR (95%CL)		OR (95%CL)	
Mean MAP during TTM/5 mmHg	0.98 (0.92–1.06)	0.63	1.01 (0.92–1.120)	0.85	0.69 (0.59–0.82)	<**0.0001**	0.77 (0.65–0.91)	**0.002**
Age at arrest/year	1.07 (1.05–1.08)	<**0.0001**	1.08 (1.06–1.09)	<**0.0001**	1.01 (0.99–1.03)	0.34	–	–
Sex, male	0.67 (0.47–0.96)	**0.03**	–	–	0.95 (0.53–1.72)	0.87	–	–
Time to ROSC/min	1.03 (1.02–1.04)	<**0.0001**	1.03 (1.02–1.04)	<**0.0001**	1.01 (1.00–1.02)	**0.02**	–	–
Witnessed arrest	0.54 (0.33–0.81)	**0.008**	0.50 (0.29–0.88)	**0.02**	1.19 (0.53–2.68)	0.67	–	–
Bystander CPR	0.53 (0.39–0.72)	<**0.0001**	–	–	0.70 (0.43–1.14)	0.16	–	–
Bystander defibrillation	0.47 (0.29–0.77)	**0.003**	0.55 (0.32–0.96)	**0.04**	0.56 (0.22–1.42)	0.22	–	–
Shockable primary rhythm	0.13 (0.09–0.20)	<**0.0001**	0.17 (0.10–0.28)	<**0.0001**	0.79 (0.45–1.41)	0.44	–	–
Lactate level at admission per mmol/L	1.09 (1.06–1.13)	<**0.0001**	1.06 (1.02–1.11)	**0.004**	1.15 (1.09–1.21)	<**0.0001**	1.13 (1.07–1.19)	<**0.0001**
ST-elevations at admission	0.76 (0.58–1.01)	0.05	–	–	1.93 (1.18–3.14)	**0.009**	1.75 (1.04–2.93)	**0.03**
Shock at admission	2.42 (1.59–3.69)	<**0.0001**	–	–	4.02 (2.39–6.77)	<**0.0001**	2.26 (1.25–4.07)	**0.007**
Including site (small versus large)	1.16 (0.88–1.52)	0.29	–	–	0.76 (0.48–1.20)	0.24	–	–
Pre-randomization eGFR	0.98 (0.97–0.98)	<**0.0001**	–	–	0.99 (0.98–0.99)	0.003	0.99 (0.98–0.99)	**0.03**
TTM at 36° C versus 33° C	0.95 (0.73–1.25)	0.74	–	–	1.21 (0.77–1.92)	0.41	–	–

Abbreviations: 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.

* Adjusted for known confounding factors in a model assessing all variables from the univariable models followed by stepwise backwards elimination to reduce numbers of covariates in the final models. *Mortality: Hosmer and Lemeshow Goodness-of-Fit test: $p_{mortality} = 0.79$. C-statistics: AUC = 0.81. Renal replacement therapy: Hosmer and Lemeshow Goodness-of-Fit test: p_{rrt}: $p = .34$. C-statistics: AUC = 0.77.*

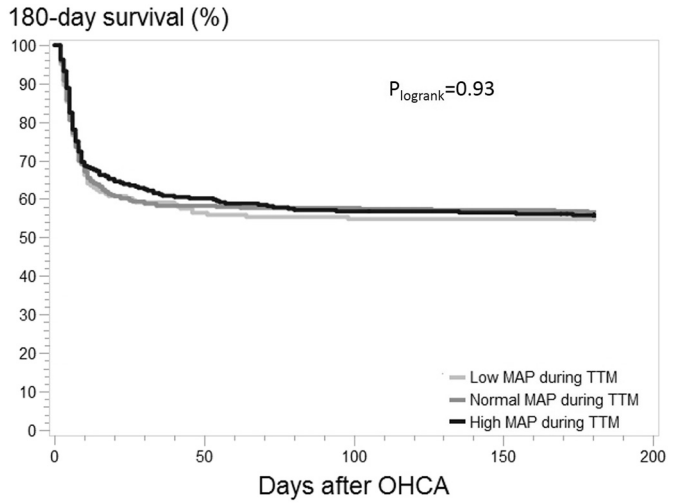

Fig. 3. Survival at 180 days in comatose out-of-hospital cardiac arrest (OHCA) patients treated with targeted temperature management at 33 °C and 36 °C. Patients were stratified by mean arterial pressure during TTM (<70 mmHg, 70–80 mmHg, and > 80 mmHg).

OHCA-patients, current guidelines are extrapolated from studies in sepsis [5,6,28]. In a subgroup of OHCA-patients, however, the lower threshold of organ autoregulation is shifted rightwards and these patients may benefit from a higher MAP in the hours and days after the primary insult [13,29,30]. Furthermore, studies of physiological mechanisms of chronic arterial hypertension have demonstrated a rightward-shift in cerebral pressure-flow autoregulation [24,31]. In a fitted spline plot (Fig. 4) we illustrate a decreased risk of needing RRT with increasing mean MAP. Based on our findings, we propose the hypothesis that a higher MAP-target can improve renal function after OHCA limiting patient-morbidity and treatment-costs. This hypothesis should be investigated in prospective trials and is supported by the findings of Asfar et al., where a subgroup-analysis of patients with arterial hypertension showed that the high-target group required less renal-replacement therapy than did those in the low-target group [24]. We did, however, not find a statistically significant interaction of preexisting arterial hypertension, with the association between mean MAP and eGFR, however a trend was seen ($p = .06$). In our study, we defined AKI according to the KDIGO-criteria [20] to increase sensitivity for smaller changes in renal function. Using the same dataset, Bro-Jeppesen et al. have reported AKI according to the sub-score of SOFA, resulting in a smaller number of AKI cases [19].

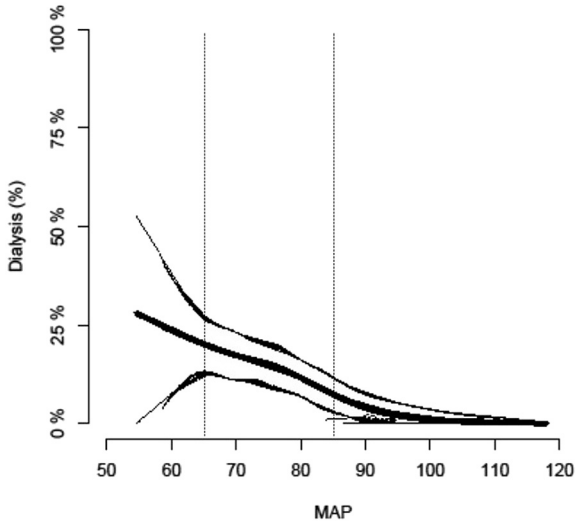

Fig. 4. Hazard of dialysis at different mean arterial pressure (MAP) values during targeted temperature management illustrated by a proportional hazard model with cubic smoothing splines. Whether death influenced hazard of dialysis was tested by performing a competing risk regression with death for 180 days as competing risk to dialysis. The vertical lines represent the limits of the normal MAP-interval according to international guidelines. Dialysis is defined as initiation of any kind of renal replacement therapy in the first 6 days after cardiac arrest.

5.1. Limitations

Although the present study has several advantages being a large analysis of MAP-data prospectively collected in a randomized, international, clinical multicenter-trial, some limitations are acknowledged. First, we omitted patients dying within 48 h, and therefore the results of this study are not applicable to these patients, which often are characterized by severe hemodynamic instability. Second, MAP-measurements at the predefined time points in this analysis may not be completely representative of the actual mean MAP during TTM since fluctuations in MAP between measurements were not reported. Third, eGFR may not be the optimal method of assessing renal dysfunction, therefore future prospective studies of kidney injury after OHCA could include other biomarkers of renal injury [32]. Fourth, the present analysis is based on a database from a clinical trial, on which previous reports on the impact of level of target temperature has been published. We did not adjust for multiple comparisons and the results should, as with any post hoc analysis, be considered hypothesis-generating and not conclusive. Fifth, several factors, such as depth of sedation and precise vasopressor dose, may be important during TTM and were not assessed in the current analysis due to the pragmatic nature of the trial by which the administration of sedation and other drugs was at the discretion of the treating physician and not reported in detail. Future studies could clarify the interaction between sedative drugs and MAP. Sixth, the focus of this study was the hemodynamics during TTM. Hemodynamics after rewarming were not assessed and could influence renal function in the days after rewarming.

5.2. Conclusions

This study of comatose, resuscitated OHCA-patients, finds an independent association between low mean MAP and decreasing renal function, defined as more need for renal replacement therapy and short term lower eGFR in patients surviving at least 48 h. Renal function after OHCA could potentially benefit from a higher MAP-target during TTM than currently suggested by international guidelines. This hypothesis should be investigated in prospective clinical trials of MAP-targets after OHCA.

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