RESUSCITATION 170 (2022) 115–125

Available online at ScienceDirect

Resuscitation

journal homepage: www.elsevier.com/locate/resuscitation

Clinical paper

The inflammatory response is related to circulatory failure after out-of-hospital cardiac arrest: A prospective cohort study

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Abbreviations: C3bc, complement 3 activation product, CO, cardiac output, CRP, c-reactive protein, BFGF, basic fibroblast growth factor, ECMO, extracorporeal membranous oxygenation, ICAM-1, intercellular adhesion molecule 1, ICU, intensive care unit, IFNγ, interferon gamma, IL, interleukin, IP-10, interferon-inducible protein 10, MAP, mean arterial blood pressure, mCPIS, modified Clinical Pneumonia Infection Score, MIP-1β, macrophage inflammatory protein 1 beta, OHCA, out-of-hospital cardiac arrest, PCAS, post-cardiac arrest syndrome, PDGF-BB, platelet derived growth factor-BB, Q1–Q3, first to third quartile, RANTES, regulated on activation normal *T*-cell expressed and secreted, ROSC, return of spontaneous circulation, SOFA, sequential organ failure assessment, SVR, systemic vascular resistance, TCC, terminal C5b-9 complement complex, TNF, tumor necrosis factor, VAD, ventricular assist device, VCAM-1, vascular cell adhesion molecule 1, vWF, von Willebrand factor

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https://doi.org/10.1016/j.resuscitation.2021.11.026
Received 20 September 2021; Received in Revised form 31 October 2021; Accepted 17 November 2021

Abstract

Background: Whole body ischemia and reperfusion injury after cardiac arrest leads to the massive inflammation clinically manifested in the post-cardiac arrest syndrome. Previous studies on the inflammatory effect on circulatory failure after cardiac arrest have either investigated a selected patient group or a limited part of the inflammatory mechanisms. We examined the association between cardiac arrest characteristics and inflammatory biomarkers, and between inflammatory biomarkers and circulatory failure after cardiac arrest, in an unselected patient cohort.

Methods: This was a prospective study of 50 consecutive patients with out-of-hospital cardiac arrest. Circulation was invasively monitored from admission until day five, whereas inflammatory biomarkers, i.e. complement activation, cytokines and endothelial injury, were measured daily. We identified predictors for an increased inflammatory response, and associations between the inflammatory response and circulatory failure.

Results: We found a marked and broad inflammatory response in patients after cardiac arrest, which was associated with clinical outcome. Long time to return of spontaneous circulation and high lactate level at admission were associated with increased complement activation (TCC and C3bc), pro-inflammatory cytokines (IL-6, IL-8) and endothelial injury (syndecan-1) at admission. These biomarkers were in turn significantly associated with lower mean arterial blood pressure, lower cardiac output and lower systemic vascular resistance, and increased need of circulatory support in the initial phase. High levels of TCC and IL-6 at admission were significantly associated with increased 30-days mortality.

Conclusion: Inflammatory biomarkers, including complement activation, cytokines and endothelial injury, were associated with increased circulatory failure in the initial period after cardiac arrest.

Keywords: Post-cardiac arrest syndrome, Out-of-hospital cardiac arrest, Inflammation, Biomarkers, Haemodynamic

Introduction

The inflammatory response after out-of-hospital cardiac arrest (OHCA) share many characteristics with sepsis, and is therefore described as a "sepsis-like syndrome".[1] Whole body ischemia and subsequent reperfusion injury leads to a systemic inflammation, which is, together with anoxic brain injury and myocardial dysfunction, the main elements of the post-cardiac arrest syndrome (PCAS).[2]

The balance between pro- and anti-inflammatory cytokine signalling is important for the effect of the immune system on the development of organ failure.[3] Consequently, several studies have explored the role of cytokines as biomarkers for severity, risk of organ failure and mortality in sepsis.[4] Comparatively, few studies have evaluated the complement and cytokine response in PCAS, and most evidence stems from one large trial on targeted temperature management after cardiac arrest. Findings so far indicate that high levels of interleukin 6 (IL-6) and complement factor 3 were associated with mortality, whereas high levels of IL-6 and IL-10 were associated with organ failure.[1,5–9]

PCAS is characterized by a respiratory, neurologic and circulatory failure, but only mild affection of the liver, coagulation and kidneys.[10] The circulatory failure in PCAS is currently suggested to be two-phased; first, acute myocardial stunning that is followed by superimposed vasodilatation.[11] In a study of how endothelial and inflammatory responses affect the haemodynamic in PCAS, only IL-6 was associated with vasopressor support.[12] Other studies have observed that high levels of thrombomodulin, a marker for endothelial dysfunction, is associated with multi-organ failure in PCAS.[13–15] However, some of these studies excluded patients in circulatory shock at admission and some did not examine circulatory variables in detail. Thus, our investigation, which includes patients in circulatory shock, and gives detailed information on circulatory support together with central hemodynamic variables, is warranted.

The aim of this study was to investigate the inflammatory response, including complement activation, cytokine release and endothelial biomarkers, after OHCA, and its association with circulatory failure in PCAS.

Methods

Study design

This was a pre-planned analysis of a larger prospective, observational study of 50 patients admitted to hospital with return of spontaneous circulation (ROSC) after OHCA.[16] Hemodynamic variables have been published previously.[17] Patients were included between January 2016 and November 2017.

Setting and eligibility

St. Olav's University Hospital is a 938-bed tertiary hospital in Trondheim, Norway, serving a population of ~700,000. Both comatose and awake adults admitted to the ICU with obtained ROSC after OHCA were assessed for eligibility. Exclusion criteria were age <18 years, pregnancy, assumed septic or anaphylactic aetiology of cardiac arrest, transferal from other hospitals, decision to limit life-sustaining therapy upon arrival, or acute cardiothoracic surgery, intervention with extracorporeal membranous oxygenation (ECMO) or a ventricular assist device (VAD) before arrival at the ICU.

Study procedure

Patients followed the study protocol from time of admission and the following five days, or until one of the following events occurred: the patient died; treatment with ECMO or VAD was initiated; acute cardiothoracic surgery; life-prolonging therapies were withheld; the patient was transferred to a general ward or to another hospital. The day of admission (day zero) had variable length depending on the time of inclusion, whereas day one started the following morning at 06:00.

All comatose patients, without contraindications, received a pulmonary artery catheter (Swan-Ganz CCOmbo, Edwards Lifesciences, USA) for continuous central hemodynamic measurements. All circulatory variables and drug dosages were collected from the electronic critical care information system (Picis CareSuite, Optum Inc., USA). For circulatory variables we calculated the mean value over the period starting 30 min before and ending 30 min after each blood sample collection. From the pre-hospital report and hospital record, we obtained data according to the Utstein cardiac arrest tem-

plate,[18] Charlson Comorbidity Index,[19] and clinical information on assessment and treatment.

We calculated modified Clinical Pneumonia Infection Score (mCPIS) and Sequential Organ Failure Assessment (SOFA) scores daily.[20,21] After 30 days, we obtained vital status from the medical records.

Inflammatory biomarkers

Blood sampling and plasma preparation

Blood samples were drawn at inclusion and thereafter every morning during the ICU period. After gentle mixing, the blood samples were placed vertical for 30 min in ambient temperature, and then centrifuged at 2200*g* for 10 min. EDTA-plasma was frozen to –80 °C within 1 h from sampling. C-reactive protein (CRP) and haptoglobin were analysed together with the routine blood samples drawn in the ICU.

Complement activation

Complement activation, both initial C3 activation product (C3bc) and terminal C5b-9 complement complex (TCC), was measured by ELISA, using the Complement International Standard #2.[22]

Cytokines

Plasma levels of the following inflammatory cytokines, including interleukins, interferons, chemokines and growth factors, were analysed with Bio-Plex Pro™ Human Cytokine 27-plex Assay (Bio-Rad Laboratories, Hercules, CA): tumour necrosis factor (TNF), interferon gamma (IFNγ), interleukin 1 receptor antagonist (IL-1ra), IL-6, IL-8, IL-10, interferon-inducible protein 10 (IP-10), eotaxin, macrophage inflammatory protein 1 beta (MIP-1β), regulated on activation normal *T*-cell expressed and secreted (RANTES), basic fibroblast growth factor (BFGF) and platelet derived growth factor-BB (PDGF-BB).

Endothelium and platelet markers

Plasma levels of endothelial and platelet biomarkers; intercellular adhesion molecule 1 (ICAM-1), vascular cell adhesion molecule 1 (VCAM-1), syndecan-1, vascular endothelial (VE) cadherin, p-selectin and von Willebrand factor (vWF), were measured by enzyme immunoassays in duplicate using commercially available antibodies (R&D Systems and Agilent, Minneapolis, MN) in a 384 format using a combination of a CyBi-SELMA pipetting robot (Analytik Jena, Germany) and an automatic washer-dispenser (BioTek, Winooski, VN). Absorption was read at 450 nm with wavelength correction set to 540 nm using an ELISA plate reader (BioTek). Intra- and inter-assay coefficients of variation were <10% for all enzyme immunoassays.

Measurements under lower limit of detection were set to 0.01.

Post-cardiac arrest care and cardiovascular support

Comatose patients were cooled (36 °C) for 24 h according to the hospital's standard procedure. Percutaneous coronary intervention was performed if indicated.

In the presence of hypotension and clinical signs of tissue hypoperfusion, the circulation was optimized through fluid and vasopressor administration, based on the department's guidelines on circulatory support. A detailed description of the post-cardiac arrest care in this study has been published.[16]

Statistics

To describe the circulatory effects and the risk of mortality mediated by the inflammatory response after OHCA, we divided the analysis into three steps. Firstly, the associations between Utstein variables and biomarkers were assessed applying linear regression models. Secondly, the associations between biomarker concentrations and circulatory variables (norepinephrine dose, fluid infusion, cardiac output (CO), systemic vascular resistance (SVR), and mean arterial blood pressure (MAP)) at admission and day two were assessed in linear regression models. In both analyses, the associations were assessed at day zero (i.e. admission) and on day two (after ~35–40 h) in order to capture both the immediate and a delayed inflammatory response and circulatory effects after cardiac arrest. Finally, we used logistic regression of biomarkers at admission to estimate the odds ratio for 30-day mortality.

All biomarkers were binary logarithmic ($\log_2$) transformed to obtain normal distributions. Only biomarkers consistently associated with circulatory variables (over two measurements with $p < 0.1$) in the daily univariable analysis were included in the backward selection of variables in the multivariable regression models. We used the coefficient of determination (R^2) to assess the models' explanatory capabilities. In the case of heteroscedasticity, a regression model with robust standard error was used, and strongly collinear predictors were omitted from the analysis.

To describe the biomarker alteration over time, we stratified the study population into three groups, based on whether they were dead ("status 1"), still in ICU ("status 2") or transferred to ward in stable condition ("status 3") by day five. First, we showed stratified graphs of biomarker concentrations over all days. Then, we used one-way ANOVA and Tukey's method to determine if biomarker concentrations between groups were significantly different at day zero and day two.[23]

Data were extracted with the software Matlab (Mathworks Inc., Natick, MA), and the statistical analyses were performed with Stata 16.1 (StataCorp LCC, Collage Station, TX).

Sample size

This is a descriptive study, so no formal sample size calculation was performed.[24]

Ethics

The Regional Committee for Medical and Health Research Ethics, Central Norway Health Region (REK Midt, No. 2015/1807) approved the study. Participants or their proxies provided written consent.

Results

Study population

Among 65 consecutive patients assessed for eligibility, 15 patients were excluded (seven patients due to immediate withdrawal of life-support, two had septic aetiology, two patients not in need of ICU admission, three patients received VAD or ECMO and one patient underwent immediate surgery), and 50 patients included in the study.[17] Forty-two patients were comatose at admission, 44 received bystander cardiopulmonary resuscitation and 37 had ventricular fibrillation as initial rhythm (Table 1). The median response time was 9.5 min (first to third quartile (Q1–Q3) 5–13.5). ROSC was achieved after a median of 24 min (Q1–Q3: 14–32) from the time of the emergency call. By the end of day five, 12 patients were dead (status 1),

Table 1 – Demography for all patients and subgroups.

Characteristics of patients [1]	All N = 50 (100%)	Status 1 n = 12 (24%)	Status 2 n = 22 (44%)	Status 3 n = 16 (32%)
Age, years, mean (sd)	63 (15)	63 (19)	65 (13)	59 (16)
Male sex, no (%)	40 (80)	6 (50)	21 (95)	13 (81)
Body mass index, mean (sd)	28 (6.6)	29 (12)	28 (4.3)	26 (3.5)
Charlson comorbidity index, median (Q1–Q3)	3 (2–4)	3 (1.5–5)	4 (3–4)	2 (1.5–4)
Witnessed cardiac arrest, no. (%)	42 (84)	8 (66)	19 (86)	15 (93)
Bystander CPR, no (%)	44 (88)	11 (91)	19 (86)	14 (87)
Time to ACLS, min, median (Q1–Q3)	9.5 (5–14)	14 (7–23)	10 (5–13)	6 (4–10)
Shockable initial rhythm, no. (%)	39 (78)	3 (25)	22 (100)	14 (87)
Number of defibrillations, median (Q1–Q3)	2 (1–4)	0 (0–2)	3 (1–7)	2 (1–2.5)
Time to ROSC, min., median (Q1–Q3)	24 (14–32)	27.5 (20–37)	25.5 (18–36)	14 (8–28)
Presumed cardiac etiology, no. (%)	42 (84)	6 (50)	21 (95)	15 (93)
Circulatory shock in ER [2], no. (%)	18 (36)	7 (58)	9 (40)	2 (12)
Comatose at admission [3], no. (%)	42 (84)	12 (100)	22 (100)	8 (50)
Certain pulmonary aspiration, no. (%)	9 (18)	5 (41)	2 (9)	2 (12)
Initial pH, mean (sd)	7.18 (0.14)	7.0 (0.13)	7.19 (0.14)	7.27 (0.09)
Initial base excess, mmol/L, mean (sd)	−9.4 (7.4)	−16.2 (4.9)	−9.29 (5.4)	−7.1 (4.7)
Initial lactate level, mmol/L, mean (sd)	6.7 (4.2)	11.4 (3.3)	5.5 (3.5)	4.8 (3.2)
Simplified Acute Physiology Score II, mean (sd)	62 (19)	72 (14)	68 (11)	44 (18)
30-days mortality	16 (32)	12 (100)	3 (13)	1 (6)

ACLS: advanced cardiovascular life support; CPR: cardiopulmonary resuscitation; ER: emergency room; ROSC: return of spontaneous circulation; sd: standard deviation; Q1–Q3: first to third quartile.

[1] The study population was divided into three groups, based on whether they were dead ("status 1"), still in ICU ("status 2") or transferred to ward ("status 3") by day five.

[2] Systolic blood pressure < 90 mmHg or in need of fluids and/or vasopressors to maintain systolic blood pressure > 90 mmHg.

[3] Comatose were patients that were intubated and gave no contact (GCS < 8). Awake patients were responsive and followed instructions.

22 were still in the ICU (status 2) and 16 were transferred to ward in stable circulatory condition (status 3). Three patients from status 2, and one from status 3, died within 30 days. Demographic results are given in Table 1. Mean length of day zero was 11 h (standard deviation; 5 h).

During the ICU stay, the median mCPIS score peaked on day four, when 12 of 27 patients had a score ≥6, and 26 of 27 patients received antibiotics (Supplementary Table 1).

Plasma biomarkers

The plasma concentration of the complement activation products TCC and C3bc, the cytokines IL-1ra, IL-8 and RANTES, and the endothelial cell markers syndecan-1 and VE-cadherin were highest at admission and thereafter gradually decreased (Fig. 1 and Supplementary Fig. 1), whereas IL-6 remained elevated during the study (Fig. 1). CRP increased from admission until day two (Fig. 1), whereas vWF showed a more mixed pattern (Supplementary Fig. 1). With exception of VE-cadherin and RANTES, patients in status 1 (dead by day 5) had the highest concentrations of all biomarkers, and status 3 patients (transferred to ward by day 5) had the lowest (Fig. 1 and Supplementary Table 2).

TNF, IFNγ, IL-10, IP-10, eotaxin, MIP-1β, BFGF, PDGF-BB, ICAM-1, VCAM-1 and P-selectin were elevated but not consistently associated with outcome, and thus omitted from further analyses (Supplementary Fig. 2 and Supplementary Tables 3 and 4).

The number of blood samples per day is shown in Supplementary Table 5.

Association between cardiac arrest and inflammation

The association between Utstein variables and biomarker concentrations are shown in Table 2. In the multivariable linear regression analyses, time to ROSC and high lactate concentrations at admis-

Fig. 1 – Biomarker alterations during study period. Log_2 transformed concentrations. The study population was divided into three groups, based on whether they were dead, still in ICU or transferred to ward by day five. A. Terminal complement complex (TCC), significant difference in concentration at admission between "dead" and "transferred to ward", B. Activated complement 3b (C3bc), significant difference in concentration at admission between "dead" and "transferred to ward" C. Interleukin 1 receptor antagonist (IL-1-ra), significant difference in concentration at day two between "transferred to ward" and both "still in ICU" and "dead", D. Interleukin 6 (IL-6), significant difference in concentration at admission between "dead" and both "transferred to ward" and "still in ICU", significant difference in concentration at day two between "transferred to ward" and "still in ICU", E. Interleukin 8 (IL-8), significant difference in concentration at admission between "dead" and both "still in ICU" and "transferred to ward", significant difference in concentration at day two between "transferred to ward" and "still in ICU" F. C-reactive protein (CRP), significant difference in concentration at day two between "transferred to ward" and both "dead" and "still in ICU" G. Syndecan-1. H. Vascular endothelial (VE) cadherin, significant difference in concentration at admission between "dead" and "transferred to ward".

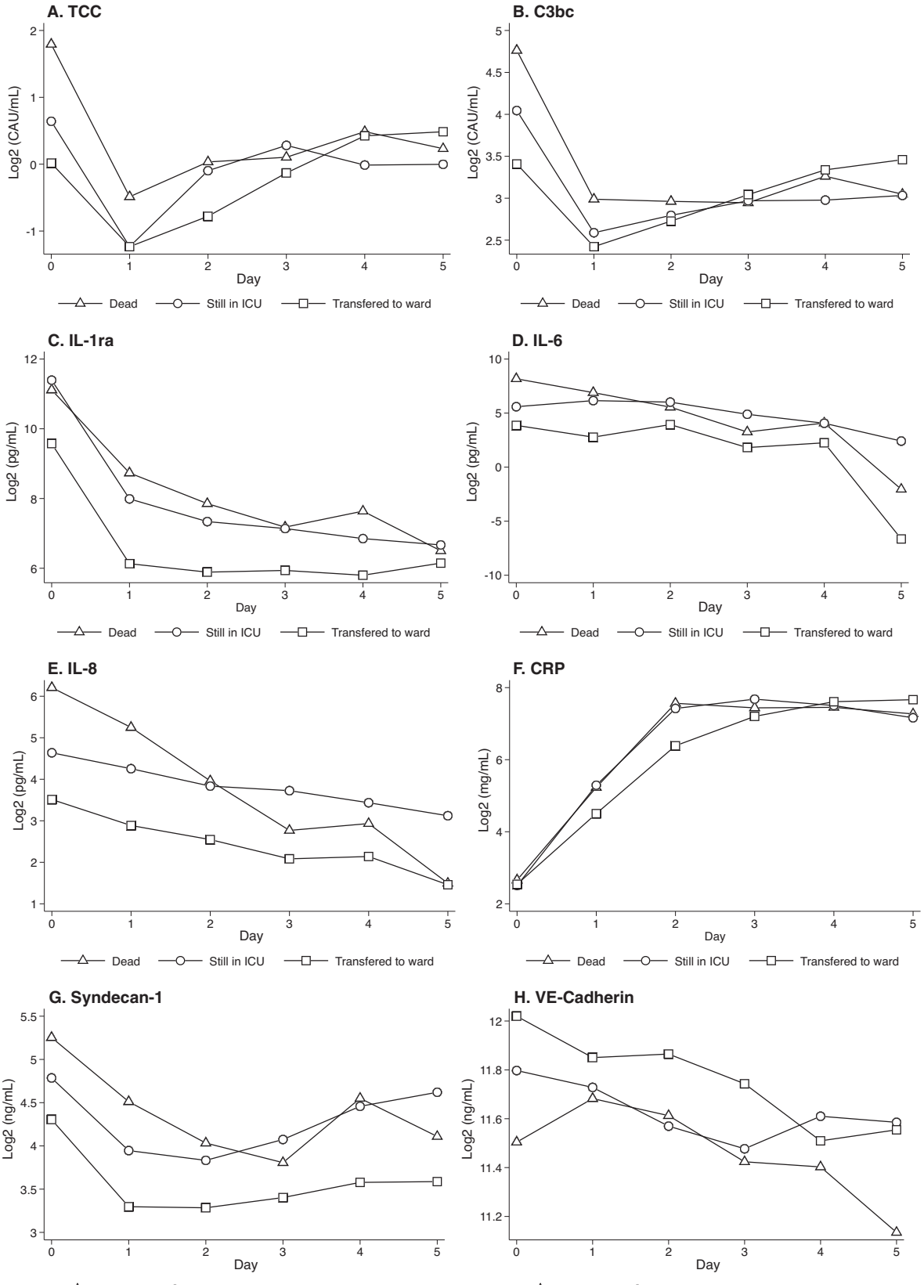
A. TCC
Log2 (CAU/mL)
Day
B. C3bc
Log2 (CAU/mL)
Day
C. IL-1ra
Log2 (pg/mL)
Day
D. IL-6
Log2 (pg/mL)
Day
E. IL-8
Log2 (pg/mL)
Day
F. CRP
Log2 (mg/mL)
Day
G. Syndecan-1
Log2 (ng/mL)
Day
H. VE-Cadherin
Log2 (ng/mL)
Day
Dead
Still in ICU
Transfered to ward

Table 2 – Association between biomarkers at admission (day 0) and Utstein cardiac arrest variables.

	TCC	C3bc	IL-1ra	IL-6	IL-8
Age, 5 years					
Univariable	0.95 (0.84–1.06)	0.99 (0.91–1.08)	1.04 (0.88–1.21)	1.00 (0.82–1.22)	0.98 (0.88–1.10)
Multivariable	–	–	–	–	–
Comorbidity score [1]					
Univariable	0.91 (0.78–1.06)	0.98 (0.87–1.09)	0.90 (0.73–1.10)	0.83 (0.65–1.07)	0.88 (0.76–1.02)
Multivariable	–	–	–	–	–
Shockable rhythm					
Univariable	0.53 (0.23–1.23)	0.54 (0.29–1.01)	1.31 (0.41–4.14)	0.17 (0.04–0.68)	0.30 (0.14–0.66)
Multivariable	–	–	–	–	–
Time to ROSC, 5 min					
Univariable	1.20 (1.08–1.33)	1.17 (1.08–1.26)	1.22 (1.05–1.41)	1.41 (1.18–1.68)	1.24 (1.13–1.37)
Multivariable	1.13 (1.01–1.26)	1.14 (1.05–1.23)	1.21 (1.05–1.40)	1.18 (1.03–1.35)	1.17 (1.08–1.27)
Lactate in ER, mmol/L					
Univariable	1.13 (1.05–1.22)	1.08 (1.02–1.14)	1.08 (0.97–1.20)	1.28 (1.16–1.41)	1.18 (1.10–1.26)
Multivariable	1.10 (1.02–1.19)	1.05 (0.99–1.11)	–	1.21 (1.10–1.33)	1.12 (1.04–1.20)
Pulmonary aspiration					
Univariable	1.92 (0.77–4.75)	1.66 (0.85–3.24)	3.15 (0.95–10.4)	6.15 (1.36–27.8)	3.37 (1.44–7.91)
Multivariable	–	–	2.83 (0.92–8.70)	3.57 (1.35–9.41)	2.71 (1.05–6.99)
R^2 Multivariable model	0.25 adjusted	0.27 adjusted	0.16 adjusted	0.47 adjusted	0.53 robust
	RANTES	**CRP**	**Syndecan-1**	**VE-cadherin**	**vWF**
Age, 5 years					
Univariable	0.95 (0.92–0.99)	0.99 (0.95–1.03)	0.98 (0.90–1.07)	0.98 (0.95–1.01)	0.98 (0.92–1.05)
Multivariable	–	–	–	–	
Comorbidity score [1]					
Univariable	0.95 (0.90–0.99)	0.98 (0.93–1.04)	0.92 (0.82–1.02)	1.00 (0.96–1.04)	0.94 (0.86–1.02)
Multivariable	–	–	–	–	–
Shockable rhythm					
Univariable	1.15 (0.85–1.55)	0.83 (0.60–1.16)	0.57 (0.30–1.06)	1.34 (1.08–1.66)	0.79 (0.49–1.27)
Multivariable	–	–	–	1.35 (1.09–1.67)	–
Time to ROSC, 5 min					
Univariable	1.02 (0.98–1.07)	1.01 (0.97–1.06)	1.16 (1.07–1.25)	0.96 (0.93–0.99)	1.07 (1.01–1.14)
Multivariable	–	–	1.12 (1.03–1.21)	0.97 (0.94–0.99)	–
Lactate in ER, mmol/L					
Univariable	1.00 (0.97–1.03)	1.00 (0.97–1.04)	1.11 (1.05–1.18)	0.97 (0.95–1.00)	1.03 (0.98–1.08)
Multivariable	–	–	1.08 (1.02–1.15)	–	–
Pulmonary aspiration					
Univariable	0.84 (0.61–1.16)	1.76 (1.28–2.41)	1.23 (0.61–2.46)	0.96 (0.75–1.24)	0.80 (0.48–1.35)
Multivariable	–	–	–	–	–
R^2 Multivariable model	–	–	0.32 adjusted	0.23 adjusted	–

C3bc: activated complement 3b; CRP: C-reactive protein; ER: emergency room; IL: interleukin; RANTES: regulated on activation normal *T*-cell expressed and secreted; ROSC: return of spontaneous circulation; TCC: terminal complement complex; VE: vascular endothelial; vWF: von Willebrand factor.

[1] Charlson Comorbidity Index.

sion were significantly associated with higher levels of TCC, C3bc, IL-1ra, IL-6, IL-8 and syndecan-1 at admission, and lower levels of VE-cadherin at admission (Table 2). In general, the clinical variables in the model predicted a substantial part of biomarker variability.

On day 2, only TCC and syndecan-1 were associated with the Utstein variables in the multivariable analysis (Supplementary Table 6).

Association between inflammation and circulation

Linear regression analysis of the associations between biomarker concentrations and circulatory variables and organ failure (SOFA score) at admission and at day two are shown in Table 3 and Table 4, respectively. A consistent finding was that higher levels of C3bc, IL-6, IL-8 and syndecan-1, and lower level of VE-cadherin, was associated with lower MAP, CO and SVR, and higher noradrenaline dosages, higher SOFA scores, and increased fluid support. The model indicates that a substantial part of circulatory variability can be explained by the biomarker concentrations.

Association between inflammation and mortality

In multivariable logistic regression analyses of admission biomarkers, the odds ratio for mortality within 30 days of admission was 1.86 and 2.01 for each two-fold increase in plasma concentration of TCC and IL-6, respectively (Table 5). Biomarker concentrations for survivors and non-survivors are shown in Supplementary Table 7.

Discussion

In this study, we found a marked and broad inflammatory response in patients after cardiac arrest, which was substantially associated with clinical outcome. Longer time to ROSC and higher lactate at admis-

Table 3 – Association between two-fold increase in biomarker concentrations and outcome at admission (day 0).

Biomarker	**MAP**, mmHg		**CO**, L/min		**SVR**, dynes/*sec*/cm^5	
2-fold increase	Univariable	Multivariable	Univariable	Multivariable	Univariable	Multivariable
TCC	−0.8 (−2.6 to 1.0)	–	−0.2 (−0.4 to 0.0)	−0.5 (−0.9 to −0.1)	25 (−81 to 131)	135 (5–266)
C3bc	−1.2 (−3.7 to 1.2)	–	−0.1 (−0.4 to 0.2)	0.5 (−0.1 to 1.1)	5 (−134 to 144)	–
IL-1ra	−1.1 (−2.4 to 0.3)	–	0.0 (−0.2 to 0.1)	–	17 (−56 to 91)	–
IL-6	−0.9 (−1.9 to 0.1)	–	0.0(−0.2 to 0.1)	–	12 (−65 to 90)	–
IL-8	−1.7 (−3.5 to 0.0)	–	−0.1 (−0.3 to 0.2)	–	9 (−91 to 109)	–
RANTES	5.9 (1.2–10)	6.9 (2.3–11)	0.2 (−0.7 to 1.2)	–	–233 (−642 to 175)	–
CRP	0.1 (−4.5 to 4.7)	–	0.1 (−0.5 to 0.6)	–	−67 (–322 to 188)	–
Syndecan-1	−2.6 (−4.9 to −0.3)	−3.0 (−5.2 to −0.9)	0.0 (−0.3 to 0.3)	–	−96 (–232 to 40)	−216 (−389 to −43)
VE-Cadherin	6.2 (−0.2 to 12)	–	0.6 (−0.3 to 1.5)	–	−203 (−620 to 213)	–
vWF	1.9 (−1.1 to 5.1)	–	−0.1 (−0.5 to 0.4)	–	−7 (−207 to 193)	–
R^2		0.22 adjusted		0.12 adjusted		0.15 adjusted
Biomarker	**Norepinephrine**, μg/kg/min		**Fluids**, mL/hr		**SOFA**, points	
2-fold increase	Univariable	Multivariable	Univariable	Multivariable	Univariable	Multivariable
TCC	0.01 (0.00–0.03)	−0.04 (−0.07 to -0.01)	120 (70–178)	95 (0–190)	0.4 (−0.1 to 1.0)	−1.1 (−2.0 to −0.1)
C3bc	0.03 (0.01–0.04)	0.05 (0.01–0.08)	144 (62–225)	–	0.9 (0.2–1.6)	1.8 (0.3–3.2)
IL-1ra	0.01 (−0.01 to 0.02)	–	−1 (−52 to 49)	−54 (−113 to 4)	0.5 (0.1–0.9)	–
IL-6	0.01 (0.01–0.02)	0.01 (0.01–0.02)	44 (6–81)	–	0.4 (0.1–0.7)	0.4 (0.1–0.7)
IL-8	0.03 (0.01–0.04)	–	98 (36–160)	81 (9–153)	0.7 (0.2–1.3)	–
RANTES	0.01 (−0.03 to 0.06)	0.03 (0.00–0.07)	176 (−13 to 364)	–	−1.2 (−2.8 to 0.4)	–
CRP	−0.02 (−0.06 to 0.02)	–	−16 (−192 to 160)	–	0.7 (−0.7 to 2.2)	–
Syndecan-1	0.02 (0.00–0.07)	–	96 (10–181)	–	0.6 (−0.1 to 1.4)	–
VE-Cadherin	−0.05 (−0.10 to 0.00)	−0.04 (−0.1 to 0.01)	−312(−548 to −77)	–	−3.1 (−5.1 to −1.1)	–
vWF	0.01 (−0.01 to 0.04)	–	107 (−9 to 222)	–	0.4 (−0.6 to 1.4)	–
R^2		0.31 adjusted		0.36 robust		0.23 robust

C3bc: activated complement 3b; CO: cardiac output; CRP: c-reactive protein; IL: interleukin; RANTES: regulated on activation normal *T*-cell expressed and secreted; MAP: mean arterial pressure; SOFA: Sequential Organ Failure Assessment; TCC: terminal complement complex; VE: vascular endothelial; vWF: von Willebrand factor.

sion was significantly associated with complement activation, cytokine release and endothelial glycocalyx injury. Which in turn were significantly associated with compromised circulation and increased need of circulatory support in the ICU. Finally, TCC and IL-6 at admission were significantly associated with 30-days mortality.

The inflammation after OHCA has previously been compared with sepsis, due to the similarity with the biochemical pattern and the typical circulatory failure; i.e. vasodilatation and capillary leakage.[25] The circulatory failure in sepsis is suggested to be caused by dysfunction of the endothelial barrier, where the endothelial glycocalyx is a central component.[26–28] Inflammation *per se*, and therapeutic volume expansion, may cause shedding of endothelial glycocalyx, leading to capillary leakage and exposure of pro-inflammatory and pro-coagulant proteins that amplifies the immune response.[29,30]

In our study, time to ROSC and initial lactate level were associated with complement activation (TCC and C3bc), pro-inflammatory cytokines (IL-6 and IL-8) and markers of glycocalyx shedding (syndecan-1). The association between these biomarkers and circulatory variables had a time-dependent pattern: Complement activation was initially associated with lower MAP, CO and SVR, and increased need of circulatory support, while pro-inflammatory cytokines showed a consistent association, and endothelial biomarkers a delayed association with the same circulatory patterns. This is in line with previous findings that IL-6 was consistently associated with vasopressor support, while thrombomodulin and syndecan-1 showed a delayed pattern.[12]

Unexpected, VE-cadherin, a marker for endothelial injury, was found in higher concentrations in patients in status 3, but was also associated with improved levels of circulatory variables and lower SOFA score. We have no explanation for this counterintuitive relationship.

However, the different biomarkers role in a clinical setting should be interpreted cautiously. Firstly, the effect of inflammatory biomarkers cannot be consistently classified as either pro- or anti-inflammatory.[31] Secondly, the effect of an individual biomarker is time- and context-dependent, and different biomarkers also work in concert as part of complex networks and cascades.[32] Finally, as therapies are given to maintain organ function and life, the untreated effects are not observed in any ethically acceptable human studies. This might result in some illogical relationships. For instance, if a biomarker is associated with low MAP and CO, and a vasopressor is given to normalize MAP, the association with MAP will be masked, and a spurious association with a *calculated* high SVR occur.

Seventy per cent of the ICU patients received antibiotics at day two, suggesting a suspected bacterial infection. At the same time, 27% had a mCPIS score above five, indicative of pneumonia. Aspiration of gastric content is common during OHCA and can cause a sterile inflammation, which subsequently may develop into a bacterial pneumonia. Thus, it is conceivable that the inflammatory

Table 4 – Association between two-fold increase in biomarker concentrations and outcome at day 2.

Biomarker	**MAP**, mmHg		**CO**, L/min		**SVR**, dynes/*sec*/cm^5	
2-fold increase	Univariable	Multivariable	Univariable	Multivariable	Univariable	Multivariable
TCC	−2.8 (−7.5 to 2.0)	–	0.0 (−0.7 to 0.7)	0.8 (0.1 to 1.4)	0 (−179 to 69)	–
C3bc	−3.3 (−10.5 to 4.0)	–	0.3 (−0.7 to 1.2)	−0.8 (−1.6 to −0.1)	−89 (−250 to 72)	–
IL-1ra	−1.8 (−4.3 to 0.8)	–	0.1 (−0.2 to 0.5)	1.5 (0.8–2.1)	−25 (−84 to 34)	−146 (−257 to −35)
IL-6	−1.7 (−3.5 to 0.01)	−1.3 (−2.4 to −2.0)	0.0 (−0.2 to 0.3)	–	−30 (−74 to 13)	−79 (−136 to −22)
IL-8	−1.6 (−4.9 to 1.6)	–	−0.1 (−0.6 to 0.3)	−1.6 (−2.1 to −1.1)	−0.1 (−78 to 77)	273 (108–439)
RANTES	5.0 (−0.4 to 10)	–	0.0 (−0.9 to 1.0)	−0.5 (−1.0 to −0.02)	97 (−61 to 256)	–
CRP	−2.9 (−7.1 to 1.3)	–	−0.2 (−1.1 to 0.7)	–	−91 (−243 to 60)	–
Syndecan-1	−3.6 (−8.6 to 1.4)	–	−0.2 (−0.8 to 0.5)	−0.8 (−1.5 to −0.01)	−17 (−136 to 103)	–
VE-Cadherin	12 (3.4–21)	11 (0.2–21)	1.3 (0.1–2.5)	1.8 (0.7–2.9)	3.1 (−231 to 238)	–
vWF	−1.8 (−4.5 to 0.9)	–	−0.2 (−0.6 to 0.2)	–	–32 (−102 to 38)	–
R^2		0.24 robust		0.69 robust		0.35 adjusted
Biomarker	**Noradrenaline**, μg/kg/min		**Fluids**, mL/hr		**SOFA**, points	
2-fold increase	Univariable	Multivariable	Univariable	Multivariable	Univariable	Multivariable
TCC	0.03 (0.00–0.06)	–	26 (3–49)	26 (3–49)	1.9 (0.3–3.6)	–
C3bc	0.00 (−0.04 to 0.05)	–	−13 (−49 to 24)	−43 (−75 to −10)	0.5 (−1.9 to 3.1)	–
IL-1ra	0.02 (0.01–0.04)	–	17 (6–29)	–	1.2 (0.4–2.1)	0.9 (0.3–1.6)
IL-6	0.02 (0.01–0.03)	0.01 (0.0–0.03)	12 (4–21)	–	0.9 (0.4–1.5)	–
IL-8	0.03 (0.01–0.05)	–	23 (8–37)	–	1.5 (0.4–2.5)	–
RANTES	−0.04 (−0.07–0.00)	–	−38 (−65 to −12)	−26 (−49 to −3)	−2.2 (−4.1 to −0.2)	–
CRP	0.04 (0.01–0.06)	–	34 (15–52)	–	2.9 (1.3–4.5)	–
Syndecan-1	0.05 (0.03–0.08)	0.04 (0.0–0.08)	34 (11–57)	28 (7–48)	2.2 (0.6–3.9)	–
VE-Cadherin	−0.06 (−0.12 to 0.00)	–	−50 (−96 to −4)	–	−4.7 (−7.9 to −1.6)	−3.6 (−6.1 to −1.0)
vWF	0.01 (0.00–0.03)	–	12 (−1 to 25)	–	1.3 (0.4–2.1)	1.0 (0.3–1.7)
R^2		0.44 robust		0.44 adjusted		0.49 adjusted

C3bc: activated complement 3b; CO: cardiac output; CRP: c-reactive protein; IL: interleukin; RANTES: regulated on activation normal *T*-cell expressed and secreted; MAP: mean arterial pressure; SOFA: Sequential Organ Failure Assessment; TCC: terminal complement complex; VE: vascular endothelial; vWF: von Willebrand factor.

Table 5 – Association between biomarkers at admission and death within 30-days.

Biomarker concentrations	Univariable analysis	Multivariable analysis
	Odds ratio (95% CI)	Odds ratio (95% CI)
TCC, per 2-fold increase	1.87 (1.21–2.89)	1.86 (1.02–3.40)
C3bc, per 2-fold increase	2.23 (1.27–3.89)	–
IL-1ra, per 2-fold increase	1.23 (0.93–1.63)	–
IL-6, per 2-fold increase	1.67 (1.20–2.32)	2.01 (1.20–3.37)
IL-8, per 2-fold increase	2.35 (1.41–3.92)	–
RANTES, per 2-fold increase	0.67 (0.26–1.75)	–
CRP, per 2-fold increase	1.28 (0.56–2.93)	–
Syndecan-1, per 2-fold increase	1.43 (0.91–2.27)	0.39 (0.15–1.00)
VE-cadherin, per 2-fold increase	0.22 (0.05–0.90)	–
vWF, per 2-fold increase	1.38 (0.76–2.53)	–
		Pseudo R^2 = 0.24

C3bc: activated complement 3b; CI: confidence interval; CRP: c-reactive protein; IL: interleukin; RANTES: regulated on activation normal *T*-cell expressed and secrete; TCC: terminal complement complex; vWF: von Willebrand factor.

response we observed is a combination of ischemia and reperfusion injury, aspiration pneumonitis and infections. However, Oppert and co-workers found that the abrupt rise in acute phase proteins after cardiac arrest was similar in patients with and without infection.[33] Bro-Jeppesen and co-workers drew a similar conclusion regarding the elevated levels of pro-inflammatory cytokines after cardiac arrest.[6] Thus, to diagnose pneumonia after OHCA using biomarkers alone may be misleading.

Complement activation products (C3bc) reflect activation of all initial pathways, whereas terminal complement complex (TCC) reflects complete activation of the terminal pathway. TCC exists in two forms; a soluble form (sC5b-9) that we measured in plasma, and in a membrane form (the membrane attack complex). Low levels of complement regulatory protein MAp19, high levels of complement C3bc and TCC, together with IL-6 have previously been shown to be associated with mortality after OHCA.[7,9,34,35] Accordingly, we found

that for every 2-fold increase in TCC and IL-6 levels at admission, the odds ratio for death within 30 days nearly doubled.

Unfortunately, therapeutic hypothermia has not been shown to alter the inflammatory response,[6] and there are currently no specific treatment for PCAS. Additionally, anti-inflammatory medications have to date not improved the outcome in critical illness.[36] However, a recent study on reducing inflammation and myocardial injury after OHCA with the IL-6 receptor blocker tocilizumab, found promising effects on biomarker release, but was underpowered for detecting change in mortality.[37] Complement inhibition might also be an alternative therapeutic approach in the future.[38] The clinical application of therapeutic complement inhibitors, has recently been extensively reviewed and seems promising.[39]

Strength and limitations

The strength of our study is that all patients were treated at one centre adhering to one protocol, which renders the use of circulatory support comparable. Furthermore, blood samples were drawn for all patients immediately after ICU admission and thereafter daily and prepared and stored according to a strict protocol to reflect *in vivo* degree of complement activation and cytokine release.[22,40] Also, the circulation was monitored, for most patients, using a Swan-Ganz catheter that provides more detailed hemodynamic measurements than routinely obtained. We acknowledge several limitations. Firstly, the generalizability might be limited by the size and the single-centre study design. Secondly, our cohort reflects a mixture of aetiologies and thus reflects a normal ICU population, but this might also make interpretation of the results more difficult than for a homogenous aetiological cohort. Thirdly, the sickest patients were more prone to aspiration and pneumonia that might affect the observed differences in biomarker concentrations. Fourthly, we chose to use a two-fold increase in concentration as the multiplicator for all biomarkers. However, the magnitude of change for the different biomarkers that reflect a physiological response is likely variable.

Conclusion

Long time to ROSC and high lactate level at admission were associated with higher levels of pro-inflammatory biomarkers, including increased complement activation (TCC and C3bc), cytokines (IL-6, IL-8) and endothelial injury (syndecan-1), in plasma at admission. These biomarkers were associated with lower MAP, CO and SVR, and increased need of circulatory support. Patients that presented with high levels of TCC and IL-6 at admission had increased 30-days mortality. Thus, this study shows that a systemic inflammatory response, including complement activation, cytokine release and endothelial glycocalyx injury, is associated with cardiac arrest and circulatory failure.

CRediT authorship contribution statement

Halvor Langeland: Conceptualization, Methodology, Investigation, Formal analysis, Writing – original draft, Project administration. **Jan Kristian Damås:** Formal analysis, Writing – original draft. **Tom Eirik Mollnes:** Formal analysis, Writing – original draft. **Judith Krey Ludviksen:** Formal analysis, Writing – review & editing. **Thor Ueland:** Formal analysis, Writing – review & editing. **Annika E. Michelsen:** Formal analysis, Writing – review & editing. **Magnus Løberg:** Methodology, Formal analysis, Writing – original draft. **Daniel Bergum:** Investigation, Writing – original draft. **Trond Nordseth:** Software, Data curation, Formal analysis, Writing – review & editing. **Nils Kristian Skjærvold:** Investigation, Writing – review & editing. **Pål Klepstad:** Conceptualization, Methodology, Investigation, Writing – original draft.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

This work is funded by a research grant from the Norwegian University of Science and Technology and St. Olav's University Hospital (Samarbeidsorganet HMN-NTNU).

We would like to thank the ICU's staff for excellent support.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.resuscitation.2021.11.026.

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