OPEN

Decreased human leukocyte antigen-D–related expression on CD14$^+$ monocytes in patients with out-of-hospital cardiac arrest provided target temperature management therapy: a prospective observational study

Huan Shao[a,b], Wei Yuan[a,b], Ziren Tang[a,b], Zhijiang Qi[a,b], Le An[a,b], Qiang Zhang[a,b], Chunsheng Li[a,b,*]

Abstract

Background: Post–cardiac arrest syndrome involves systemic inflammation, which causes subsequent neurological impairments. We investigated the influence of targeted temperature management (TTM) therapy in patients with out-of-hospital cardiac arrest (OHCA) after return of spontaneous circulation (ROSC) by observing the changes in circulating CD14$^+$ monocytes and the expression of human leukocyte antigen D–related (HLA-DR) and programmed cell death ligand 1 (PD-L1) in CD14$^+$ monocytes.

Methods: Adult patients admitted to the emergency department of Beijing Chao-Yang Hospital after OHCA between January 2017 and March 2018 were included in this study. Thirty control subjects, 10 patients with OHCA, and 37 patients with OHCA who received 72 hours of TTM therapy were enrolled. Peripheral blood samples of patients in the OHCA and TTM groups were collected on Days 1 and 3 (D1 and D3) after ROSC and evaluated for HLA-DR and PD-L1 expression on CD14$^+$ monocytes using flow cytometry.

Results: Compared with control subjects, the percentage of circulating CD14$^+$ monocytes, HLA-DR$^+$/CD14$^+$ monocyte ratios, and mean fluorescence intensity were significantly decreased in patients with OHCA. After ROSC, HLA-DR expression in CD14 $^+$ monocytes in the TTM group was lower than that in patients with OHCA. However, there were no significant differences in the percentage of PD-L1$^+$/CD14$^+$ monocytes or the mean fluorescence intensity between patients with OHCA and healthy volunteers.

Conclusion: After ROSC, circulating CD14$^+$ monocytes and HLA-DR$^+$/CD14$^+$ monocyte ratios decreased significantly in patients with OHCA. Human leukocyte antigen D–related expression in CD14$^+$ monocytes was lower in patients treated with TTM.

Keywords: Human leukocyte antigen D–related, Monocytes, Out-of-hospital cardiac arrest, Target temperature management

Introduction

Approximately 10% of patients with out-of-hospital cardiac arrest (OHCA) survive in North America.[1] Those who are comatose after return of spontaneous circulation (ROSC) are admitted to the intensive care unit for further treatment. Whole-body ischemia and reperfusion in patients with OHCA lead to "post–cardiac arrest syndrome"[2] whose pathophysiology involves systemic inflammation with increased circulating inflammatory mediators leading to a sepsis-like syndrome secondary to generalized ischemia/reperfusion.[1,3] This pathophysiological reaction is also one of the factors that cause subsequent neurological impairments following OHCA.[4]

Targeted temperature management (TTM) is used to attenuate post–cardiac arrest syndrome–related neurological injuries and improve outcomes.[5–8] Maintaining a constant target temperature (32–36 °C) for at least 24 hours delays the induction of proinflammatory cytokines in human peripheral blood mononuclear cells.[9] In addition, TTM can impair neutrophil and macrophage function, decrease white blood cell counts, and inhibit complement system activation.[10] Diminished monocyte human leukocyte antigen D–related (HLA-DR) expression on the cell surface reflects immunosuppression in critically ill patients and can be used to determine its magnitude and persistence over time.[11] However, the main functions of monocyte phagocytosis, antigen expression, and cytokine production are mediated by surface molecules, such as CD14 and major histocompatibility complex class II HLA-DR; their roles in patients with TTM have not yet been clarified.

Moreover, programmed cell death receptor 1 and its ligand (PD-L1) are coinhibitory receptor molecules that play major roles in sepsis-induced immunosuppression. The programmed cell death receptor 1/PD-L1 pathway exerts inhibitory effects by regulating T-cell activation, tolerance, and immunopathology.[12,13] However, the role of this pathway in TTM remains unclear. In this study, we investigated the influence of TTM therapy at 33 °C for 72 hours in patients with OHCA after ROSC by observing changes in circulating CD14$^+$ monocytes and the expression of HLA-DR and PD-L1 on CD14$^+$ monocytes.

HS and WY contributed equally to this article.

All data generated or analyzed during this study are included in this published article.

[a] Department of Emergency Medicine, Beijing Chao-Yang Hospital, Capital Medical University, Beijing, China, [b] Beijing Key Laboratory of Cardiopulmonary Cerebral Resuscitation, Beijing Chao-Yang Hospital, Capital Medical University, Beijing, China.

** Corresponding author. Address: Department of Emergency Medicine, Beijing Chao-Yang Hospital, Capital Medical University, 8# Worker's Stadium South Road, Chaoyang District, Beijing 100020, China. E-mail address: lcscyyy@163.com (C. Li).*

Emergency and Critical Care Medicine (2024) 4:1

Received: 17 July 2023; Accepted: 3 January 2024

Published online: 29 February 2024

http://dx.doi.org/10.1097/EC9.0000000000000118

Materials and methods

Study population

This prospective clinical observational study was approved by the Medical Ethics Committee of Beijing Chao-Yang Hospital. The study conformed to the guidelines of the Declaration of Helsinki. Adult patients admitted to the emergency department of Beijing Chao-Yang Hospital after OHCA between January 2017 and March 2018 were included in this study. The inclusion criteria were ROSC >24 hours and a Glasgow Coma Scale score <8 after ROSC. Exclusion criteria were as follows: age younger than 18 years, terminal stage of a disease (eg, malignant cancer of any type or AIDS), or receipt of immunosuppressive therapy in the last 3 months. The OHCA group included patients with ROSC, whose family members refused TTM. To reduce bias, all patients who met the inclusion criteria were recommended TTM by the same physician. The TTM group included patients with ROSC treated with therapeutic hypothermia (33 °C) for 72 hours. Patients treated with therapeutic hypothermia were actively cooled using a surface-cooling device. Active cooling was initiated immediately after the patient was admitted to the emergency department. There was an induction period of 4 hours to achieve the target temperature, followed by a maintenance period of 72 hours with subsequent rewarming at no more than 0.5 °C per hour to 37 °C. Thirty age- and sex-matched control subjects with no history of or current clinical disease were enrolled in this study. Written informed consent was obtained from all the patients (when possible) and volunteers. Consent for patients who were unable to respond was obtained from their first-degree relatives. All patients were treated according to the 2015 International Consensus on Cardiopulmonary Resuscitation guidelines.

Data collection

Demographic, resuscitation, and clinical and laboratory data were collected upon admission. Clinical data included age, sex, comorbidities, and the causes and characteristics of cardiac arrest. Laboratory data were collected at 2 time points: Day 1 (D1) (24 ± 4 hours after OHCA) and D3 (72 hours after OHCA). Healthy volunteers donated samples for laboratory analysis only once under fasting state at 8 AM. The Acute Physiology and Chronic Health Evaluation II and Sequential Organ Failure Assessment scores were calculated to assess the severity of cardiac event.[14]

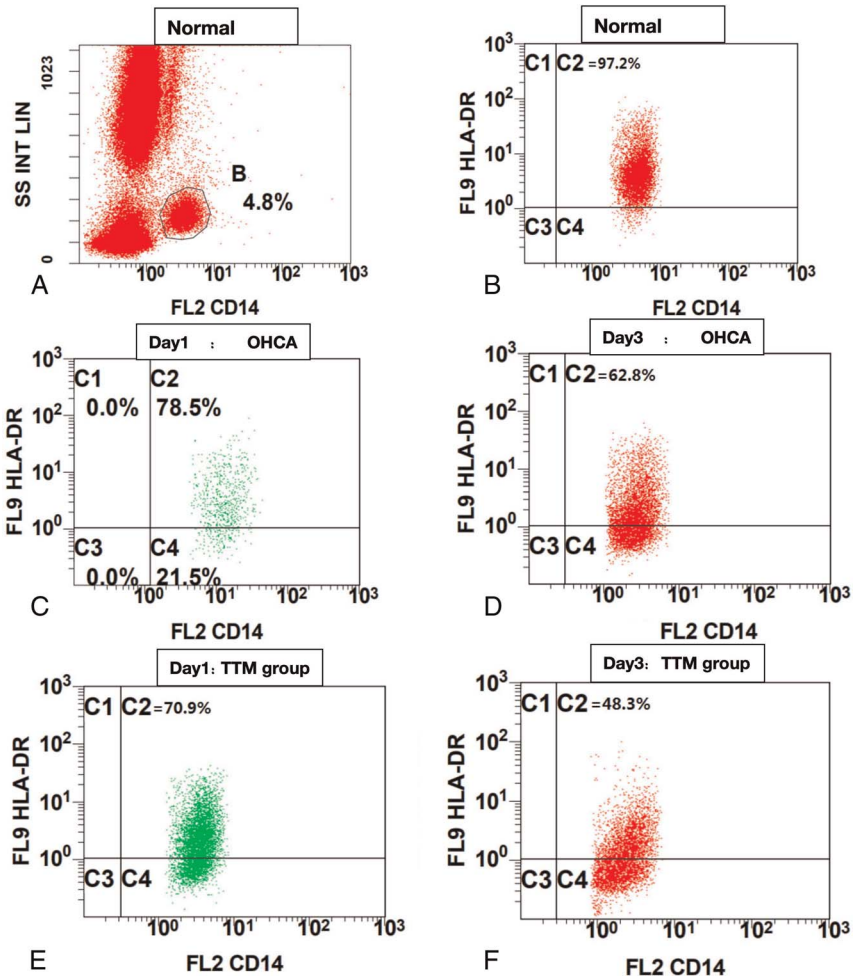

Figure 1. Representative flow dot plots of HLA-DR expression on CD14+ monocytes. (A) The monocyte population of CD14+in the healthy group. (B) HLA-DR expression in health group. (C) HLA-DR expression in OHCA group Day 1. (D) HLA-DR expression in OHCA group Day 3. (E) HLA-DR expression in TTM group Day 1. (F) HLA-DR expression in TM group Day 3. CD: cluster-of-differentiation; HLA-DR: human leucocyte antigen-D related. OHCA, out-of-hospital cardiac arrest; TTM, targeted temperature management.

Flow cytometry

Peripheral blood samples were collected in heparin tubes, transported, and immediately processed in a research laboratory. The expression of HLA-DR and PD-L1 in $CD14^+$ monocytes was measured using flow cytometry, according to the manufacturer's recommendations. Briefly, erythrocytes were lysed in a 100 μL peripheral blood sample for 12 minutes, and the debris was removed. The cells were then stained for 20 minutes in the dark and evaluated by a researcher blinded to the clinical data. The following monoclonal antibodies and their isotype controls were used: eFluor 450-labeled anti-HLA-DR (2 μL; Thermo Fisher Scientific, Waltham, MA, USA) and PE-labeled anti-CD14 (2 μL; BD Bioscience, Beijing, China). Samples were run on a Gallios Flow Cytometer (Beckman Coulter, Brea, CA, USA) and analyzed using Gallios Software Version 1.0 (Beckman Coulter). Lymphocytes were gated using forward- and side-scatter techniques. Monocytes were identified using $CD14^+$ staining (Fig. 1). At least 3000 cells were analyzed for each sample. The thresholds for HLA-DR and PD-L1 expression for $CD14^+$ monocyte gating were defined using isotype controls. The results are expressed as percentages and mean fluorescence intensity (MFI).

Statistical analyses

Statistical analyses were performed using the SPSS version 24.0 software (IBM Corp, Chicago, IL). For skewed distribution data, variables were expressed as the median and 25th and 75th percentiles. The Kruskal-Wallis test was applied for multigroup comparisons, and the Mann-Whitney *U* test was used to compare 2 groups. Wilcoxon signed-rank test was used to compare the differences in variables at different time points. Qualitative parameters were analyzed using χ^2 tests. Continuity correction or Fisher exact test was used for further analyses. All statistical tests were 2-tailed, and statistical significance was set at $P < 0.05$.

Results

Patient characteristics

In this study, 47 patients with OHCA and 30 control subjects were enrolled. Patients with OHCA were divided into 2 subgroups: 10 patients in the normal-temperature group and 37 in the TTM group. There were no significant differences in age, sex, or correlative diseases among the patients in the 3 groups. Detailed demographics, comorbidities, and prehospital data are shown in Table 1. In this study, 1 of 10 patients in the OHCA group and 4 of 37 patients in the TTM group who died within 3 days after ROSC were analyzed only on D1.

Circulating $CD14^+$ monocytes and programmed cell death ligand 1 expression in control subjects and the out-of-hospital cardiac arrest group

Compared with control subjects (5.9 [5.1, 6.5]), the percentage of circulating $CD14^+$ monocytes ($CD14^+$ %) was significantly decreased on D1 in patients with OHCA (3.3 [3.2, 3.7], $P = 0.026$). Between patients with OHCA and TTM, those with TTM showed a lower percentage (2.8 [1.5, 3.5], $P < 0.001$) on D1. Similar results were observed for D3.

There were no significant differences in the percentages of PD-$L1^+/CD14^+$ monocytes between patients with OHCA and healthy volunteers ($P > 0.05$). In addition, there was no statistically significant difference in the MFI of PD-L1 expression on $CD14^+$ monocytes between patients with OHCA and TTM ($P > 0.05$). Table 2 presents the results of the study.

Table 1

Patient Characteristics of the Study Population

	Healthy Control Group (n = 30)	OHCA Group (n = 10)	OHCA With TTM Group (n = 37)	*P*
Age, y	57.0 (42.0, 71.7)	61.0 (50.2, 74.5)	65.0 (53.5, 76.5)	0.243
Male	18 (60%)	7 (70%)	24 (64.8%)	0.831
Comorbidities				
Hypertension	8 (26.7%)	5 (50%)	19 (51.4%)	0.106
Diabetes	2 (6.7%)	3 (30%)	12 (32.4%)	0.033
Coronary artery disease	1 (3.3%)	3 (30%)	8 (21.6%)	0.030
Congestive heart failure	0	1 (10%)	6 (16.2%)	0.624
COPD	1 (3.3%)	1 (10%)	4 (10.8%)	0.466
Renal failure	0	1 (10%)	9 (24.3%)	0.326
Previously cerebral stroke	0	0	2 (5.4%)	0.585
Cardiac arrest cause				
Cardiac		3 (30%)	10 (27.0%)	0.852
Respiratory		5 (50%)	19 (51.4%)	0.940
Cerebral		1 (10%)	6 (16.2%)	0.624
Others		1 (10%)	2 (5.4%)	0.521
Initial resuscitation				
Time to ROSC, min		16.5 (5.0, 22.5)	18.0 (12.0, 30.0)	0.252
Adrenaline, mg		3 (1, 5)	3 (2, 5)	0.513
Initial rhythm				
Ventricular arrhythmia		3 (30%)	11 (30%)	0.987
Asystole and pulseless activity		7 (70%)	26 (70%)	0.987
APACHE II score		31.5 (28.5, 36.2)	33.0 (28.5, 36.5)	0.808
SOFA score		11.0 (9.0, 13.2)	11.0 (10.0, 12.5)	0.808
Day 28 mortality		6 (60%)	22 (59.5%)	0.975

Data are n (%) and median (interquartile range). Other cardiac arrest causes included poisoning and unexplained causes.

APACHE II, Acute Physiology and Chronic Health Evaluation II; COPD, chronic obstructive pulmonary disease; OHCA, out-of-hospital cardiac arrest; ROSC, return of spontaneous circulation; SOFA, Sequential Organ Failure Assessment; TTM, targeted temperature management.

Table 2

The Demographic and Clinical Characteristics of the 3 Groups of Patients at Day 1 and Day 3

	Healthy Group (n = 30)	Day 1 of OHCA Group (n = 10)	P^*	Day 3 of OHCA Group (n = 9)	$P^\dagger$	Day 1 of TTM Group (n = 37)	$P^\ddagger$	Day 3 of TTM Group (n = 33)	$P^\S$
Age, y	57.0 (42.0, 71.7)	61.0 (50.2, 74.5)	0.345	65.0 (49.5, 75.0)	0.276	65.0 (53.5, 76.5)	0.814	65.0 (53.5, 77.5)	0.876
Male	18 (60%)	7 (70%)	0.819	6 (66.7%)	0.862	24 (64.9%)	0.917	20 (60.6%)	0.892
WBCs, $\times 10^9$/L	5.8 (4.3, 6.7)	10.1 (7.3, 15.8)	<0.001	11.4 (8.1, 19.0)	<0.001	11.9 (7.7, 15.9)	0.532	9.7 (6.8, 16.9)	0.197
Monocytes, $\times 10^9$/L	0.44 (0.33, 0.62)	0.27 (0.09, 0.85)	0.881	0.55 (0.26, 0.74)	0.788	0.44 (0.20, 0.59)	0.750	0.31 (0.24, 0.43)	0.136
$CD14^+$ monocyte ratio (%)	5.9 (5.1, 6.5)	3.3 (3.2, 3.7)	0.026	2.7 (2.6, 3.0)	<0.001	2.8 (1.5, 3.5)	<0.001	1.9 (1.4, 2.4)	<0.001
Percentage of PD-L1$^+$/$CD14^+$ monocytes	7.4 (3.8, 15.9)	9.5 (3.4, 19.1)	0.097	3.4 (1.1, 14.3)	0.102	5.0 (2.5, 10.2)	0.952	3.6 (1.8, 11.2)	0.434
MFI of PD-L1 on $CD14^+$ monocytes	1.4 (1.3, 1.5)	1.5 (1.4, 1.7)	0.307	1.5 (1.4, 1.9)	0.162	1.5 (1.4, 1.7)	0.983	1.6 (1.4, 1.9)	0.872
Percentage of HLA-DR$^+$/$CD14^+$ monocytes	96.7 (93.8, 98.0)	72.1 (70.0, 77.7)	<0.001	63.2 (60.2, 67.2)	<0.001	67.3 (61.7, 70.1)	0.035	49.1 (43.6, 52.2)	0.012
MFI of HLA-DR on $CD14^+$ monocytes	7.4 (6.7, 8.7)	6.7 (5.3, 7.4)	0.017	6.1 (5.3, 6.3)	<0.001	4.7 (4.2, 5.2)	<0.001	2.9 (2.2, 3.4)	<0.001

Data are n (%) and median (interquartile range).

HLA-DR, human leukocyte antigen D relation; MFI, mean fluorescence intensities; OHCA, out-of-hospital cardiac arrest; PD-L1, programmed death ligand 1; TTM, targeted temperature management; WBCs, white blood cells.

P^* means Day 1 of OHCA group versus healthy group.

$P^\dagger$ means Day 3 of OHCA group versus healthy group.

$P^\ddagger$ means Day 1 of TTM group versus OHCA group.

$P^\S$ means Day 3 of TTM group versus OHCA group.

Human leukocyte antigen D–related expression on circulating CD14$^+$ monocytes

The median levels of HLA-DR expression in circulating $CD14^+$ monocytes in each group are shown in Table 2. The median percentage of HLA-DR$^+$/$CD14^+$ monocytes in the healthy volunteers was 96.7 (93.8, 98.0). There was a significant decrease in the HLA-DR$^+$/$CD14^+$ monocyte ratio in the OHCA group on both D1 and D3 compared with that in the control subjects (D1: 96.7 [93.8, 98.0] vs 72.1 [70.0, 77.7], $P < 0.001$; D3: 96.7 [93.8, 98.0] vs 63.2 [60.2, 67.2], $P < 0.001$). Interestingly, on both D1 and D3, the difference in the expression of HLA-DR on $CD14^+$ monocytes between the TTM and OHCA groups was statistically significant (TTM group vs OHCA group, D1: 67.3 [61.7, 70.1] vs 72.1 [70.0, 77.7], $P = 0.035$; D3: 49.1 [43.6, 52.2] vs 63.2 [60.2, 67.2], $P = 0.012$). Similar results were observed when expressed as MFI (all $P < 0.001$). In the TTM group, the $CD14^+$ %, HLA-DR$^+$/$CD14^+$ monocyte ratio, and MFI values were lower on D3 than on D1 ($P_{CD14} = 0.048$, $P_{HLA} < 0.001$, $P_{MFI} = 0.040$). Changes in the circulatory $CD14^+$ monocyte ratio and the percentage and MFI of HLA-DR$^+$ on $CD14^+$ monocytes in the 3 patient groups are shown in Fig. 2.

Discussion

The results of the present study showed that the $CD14^+$ % and HLA-DR$^+$/$CD14^+$ monocyte ratios in patients with OHCA were lower than those in healthy patients, indicating that cardiac arrest decreased HLA-DR expression.

Patients successfully resuscitated after OHCA were exposed to whole-body ischemia during the period of cardiac arrest until reperfusion upon ROSC. Ischemia/ischemia/reperfusion injury is partially related to the activation of neutrophils with the release of proinflammatory cytokines.[14] After cardiac arrest, patients commonly exhibit a modest systemic inflammatory response syndrome.[15,16] This condition has many features in common with sepsis, including enhanced leukocyte apoptosis, defective lymphocyte proliferation in response to recall antigens or mitogens, and deactivation of monocyte function by downregulation of HLA-DR expression in antigen-presenting cells.[15–19] Monocyte antigen presentation, assessed by surface HLA-DR expression, is a significant component of the early innate immune response. Our previous research has demonstrated that HLA-DR expression is reduced on circulatory monocytes and B and T lymphocytes after ROSC.[20] However, as a hallmark of immunoparalysis, a decrease in HLA-DR expression on the membranes of circulating monocytes is associated with a greater likelihood of secondary infections.[21] Lower HLA-DR expression indicates attenuated lymphocyte antigen presentation and impaired immune response initiation. Our current research further shows that cardiac arrest may inhibit the response of monocytes by downregulating the expression of HLA-DR, which then causes immune paralysis. Moreover, immunosuppression induced by ischemia/reperfusion injury is closely related to 28-day mortality in patients with OHCA. However, further research is needed to investigate the relationship between paralysis and systemic inflammatory response after cardiac arrest.

In contrast, TTM has become the recommended treatment for comatose patients with spontaneous circulation after OHCA because of its neuroprotective effects.[5,6] After ROSC, HLA-DR expression in $CD14^+$ monocytes was lower in patients with TTM. This result indicates that monocyte HLA-DR expression may be suppressed by hypothermia (33 °C).

In patients with OHCA, the effect of hypothermia on the immune response is a "double-edged sword." In vitro studies and clinical observations have suggested that TTM has a strong immunosuppressive

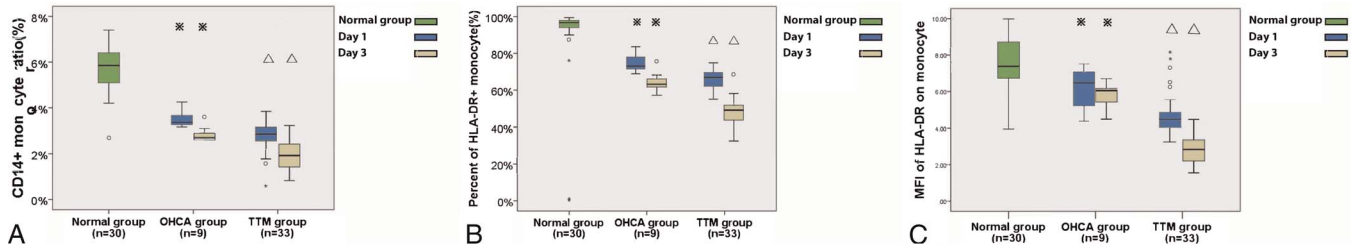

Figure 2. Changes in circulatory CD14$^+$ monocyte ratios, percentages, and MFI of HLA-DR$^+$ on CD14$^+$ monocytes in the normal, OHCA, and TTM groups. $P < 0.05$ compared with healthy control group; $\triangle P < 0.05$ compared with OHCA control group. CD, cluster of differentiation; HLA-DR, human leukocyte antigen D–related; MFI, mean fluorescence intensity; OHCA, out-of-hospital cardiac arrest; TTM, targeted temperature management.

effect, including a decrease in white blood cell count[10,22] and blocking the release of proinflammatory cytokines.[9,23,24] This action may buffer excessive inflammatory reactions caused by cardiac arrest, which can play a neuroprotective role. Hypothermia can also impair neutrophil and macrophage function. The suppression of inflammatory responses occurs in all organs and may lead to an increased risk of secondary infections, especially pneumonia.[25] Indeed, many clinical studies have reported high infection rates in patients treated with prolonged (>24 hours) therapeutic cooling.[26] Owing to these conflicting results, identifying appropriate methods to dynamically monitor the balance between immune function and inflammatory mediators in patients with TTM may be an ideal approach for future clinical treatment.

Limitations

This study had several limitations. First, the sample size was relatively small. This was a single-center study, and the findings need to be confirmed in a multicenter study. The lack of randomization against clinically relevant controls introduces the risk of confounding factors. Second, this study had a potential selection bias due to subgrouping after OHCA. In this study, the advanced care protocol and decision to implement TTM were usually determined by both the physician's preference and the willingness of the family or caregiver to pay TTM fees. These clinical and cultural selection factors may have biased TTM results. Finally, as this study was observational, we only observed early changes and did not perform dynamic observations on subsequent days. Dynamic observations of a longer duration would be helpful in evaluating the immunity of patients with OHCA with normal temperature and TTM.

Conclusion

After ROSC, circulating CD14$^+$ monocytes and HLA-DR$^+$/CD14$^+$ monocyte ratios decreased significantly in patients with OHCA. Human leukocyte antigen D–related expression in CD14$^+$ monocytes was lower in patients treated with TTM.

Conflict of interest

Chunsheng Li is an Associate Editor of *Emergency and Critical Care Medicine*. The article was subject to the journal's standard procedures, with peer reviews handled independently of this Associate Editor and their research groups. The authors declare no conflict of interest.

Author contributions

Shao H contributed to the study design, method development, data interpretation, and manuscript writing. Yuan W, Tang Z, Qi Z, An L, and Zhang Q contributed to the experimental design of the studies and conducted experiments. Li C conceived the study design, coordinated the experiments, helped draft the manuscript, and finalized the manuscript. All the authors have read and approved the final version of the manuscript.

Funding

This work was supported by the National Natural Science Foundation of China (Grant No. 81372025).

Ethical approval of studies and informed consent

The study followed the principles of the Declaration of Helsinki as revised in 2013. This study was approved by the Medical Ethics Committee of the Beijing Chao-Yang Hospital (No. 2013-KE-1). Approval date: January 10, 2013. Written informed consent was obtained from all the patients (when possible) and volunteers. Consent for patients who were unable to respond was obtained from their first-degree relatives. This manuscript obtains the consent of the patient for the use of their data and the publication of the data that appear in the article.

Acknowledgments

None.

References

[1] Wissenberg M, Lippert FK, Folke F, et al. Association of national initiatives to improve cardiac arrest management with rates of bystander intervention and patient survival after out-of-hospital cardiac arrest. *JAMA*. 2013;310(13):1377–1384. doi:10.1001/jama.2013.278483
[2] Stub D, Bernard S, Duffy SJ, Kaye DM. Post cardiac arrest syndrome: a review of therapeutic strategies. *Circulation*. 2011;123(13):1428–1435. doi:10.1161/CIRCULATIONAHA.110.988725
[3] Peigne V, Azoulay E, Coquet I, et al. The prognostic value of ADAMTS13 (a disintegrin and metalloprotease with thrombospondin type 1 repeats, member 13) deficiency in septic shock patients involves interleukin-6 and is not dependent on disseminated intravascular coagulation. *Crit Care*. 2013;17(6):R273. doi:10.1186/cc13115
[4] Samaniego EA, Persoon S, Wijman CA. Prognosis after cardiac arrest and hypothermia: a new paradigm. *Curr Neurol Neurosci Rep*. 2011;11(1):111–119. doi:10.1007/s11910-010-0148-9
[5] Taccone FS, Picetti E, Vincent JL. High quality targeted temperature management (TTM) after cardiac arrest. *Crit Care*. 2020;24(1):6. doi:10.1186/s13054-019-2721-1
[6] Hosseini M, Wilson RH, Crouzet C, Amirhekmat A, Wei KS, Akbari Y. Resuscitating the globally ischemic brain: TTM and beyond. *Neurotherapeutics*. 2020;17(2):539–562. doi:10.1007/s13311-020-00856-z
[7] Mody P, Kulkarni N, Khera R, Link MS. Targeted temperature management for cardiac arrest. *Prog Cardiovasc Dis*. 2019;62(3):272–278. doi:10.1016/j.pcad.2019.05.007

[8] Granfeldt A, Holmberg MJ, Nolan JP, Soar J, Andersen LW, International Liaison Committee on Resuscitation (ILCOR) Advanced Life Support Task Force. Targeted temperature management in adult cardiac arrest: systematic review and meta-analysis. *Resuscitation*. 2021; 167:160–172. doi:10.1016/j.resuscitation.2021.08.040

[9] Kimura A, Sakurada S, Ohkuni H, Todome Y, Kurata K. Moderate hypothermia delays proinflammatory cytokine production of human peripheral blood mononuclear cells. *Crit Care Med*. 2002;30(7):1499–1502. doi:10.1097/00003246-200207000-00017

[10] Polderman KH. Mechanisms of action, physiological effects, and complications of hypothermia. *Crit Care Med*. 2009;37(7 suppl):S186–S202. doi:10.1097/CCM.0b013e3181aa5241

[11] de Roquetaillade C, Dupuis C, Faivre V, Lukaszewicz AC, Brumpt C, Payen D. Monitoring of circulating monocyte HLA-DR expression in a large cohort of intensive care patients: relation with secondary infections. *Ann Intensive Care*. 2022;12(1):39. doi:10.1186/s13613-022-01010-y

[12] Okazaki T, Honjo T. PD-1 and PD-1 ligands: from discovery to clinical application. *Int Immunol*. 2007;19(7):813–824. doi:10.1093/intimm/dxm057

[13] Nurieva RI, Liu X, Dong C. Yin-yang of costimulation: crucial controls of immune tolerance and function. *Immunol Rev*. 2009;229(1):88–100. doi:10.1111/j.1600-065X.2009.00769.x

[14] Lee JT, Mikkelsen ME. Risk stratification tools in sepsis: from Acute Physiology and Chronic Health Evaluation to quick Sequential Organ Failure Assessment. *Crit Care Med*. 2019;47(8):1159–1161. doi:10.1097/CCM.0000000000003859

[15] Czerwińska-Jelonkiewicz K, Grand J, Tavazzi G, et al. Acute respiratory failure and inflammatory response after out-of-hospital cardiac arrest: results of the post–cardiac arrest syndrome (PCAS) pilot study. *Eur Heart J Acute Cardiovasc Care*. 2020;9(4_suppl):S110–S121. doi:10.1177/2048872619895126

[16] Grimaldi D, Sauneuf B, Guivarch E, et al. High level of endotoxemia following out-of-hospital cardiac arrest is associated with severity and duration of postcardiac arrest shock. *Crit Care Med*. 2015;43(12): 2597–2604. doi:10.1097/CCM.0000000000001303

[17] Mongardon N, Perbet S, Lemiale V, et al. Infectious complications in out-of-hospital cardiac arrest patients in the therapeutic hypothermia era. *Crit Care Med*. 2011;39(6):1359–1364. doi:10.1097/CCM.0b013e3182120b56

[18] Beurskens CJ, Horn J, de Boer AM, et al. Cardiac arrest patients have an impaired immune response, which is not influenced by induced hypothermia. *Crit Care*. 2014;18(4):R162. doi:10.1186/cc14002

[19] Su C-P, Wu J-H, Yang M-C, et al. Demographics and clinical features of postresuscitation comorbidities in long-term survivors of out-of-hospital cardiac arrest: a national follow-up study. *Biomed Res Int*. 2017;2017:9259182. doi:10.1155/2017/9259182

[20] Qi Z, An L, Liu B, et al. Patients with out-of-hospital cardiac arrest show decreased human leucocyte antigen-DR expression on monocytes and B and T lymphocytes after return of spontaneous circulation. *Scand J Immunol*. 2018;88(4):e12707. doi:10.1111/sji.12707

[21] Leventogiannis K, Kyriazopoulou E, Antonakos N, et al. Toward personalized immunotherapy in sepsis: the PROVIDE randomized clinical trial. *Cell Rep Med*. 2022;3(11):100817. doi:10.1016/j.xcrm.2022.100817

[22] Polderman KH, Herold I. Therapeutic hypothermia and controlled normothermia in the intensive care unit: practical considerations, side effects, and cooling methods. *Crit Care Med*. 2009;37(3):1101–1120. doi:10.1097/CCM.0b013e3181962ad5

[23] Dietrich WD, Chatzipanteli K, Vitarbo E, Wada K, Kinoshita K. The role of inflammatory processes in the pathophysiology and treatment of brain and spinal cord trauma. *Acta Neurochir Suppl*. 2004;89:69–74. doi:10.1007/978-3-7091-0603-7_9

[24] Suehiro E, Fujisawa H, Akimura T, et al. Increased matrix metalloproteinase-9 in blood in association with activation of interleukin-6 after traumatic brain injury: influence of hypothermic therapy. *J Neurotrauma*. 2004;21(12):1706–1711. doi:10.1089/neu.2004.21.1706

[25] Polderman KH. Hypothermia, immune suppression and SDD: can we have our cake and eat it?. *Crit Care*. 2011;15(2):144. doi:10.1186/cc10080

[26] Polderman KH. Induced hypothermia and fever control for prevention and treatment of neurological injuries. *Lancet*. 2008;371(9628):1955–1969. doi:10.1016/S0140-6736(08)60837-5

How to cite this article: Shao H, Yuan W, Tang Z, et al. Decreased human leukocyte antigen-d–related expression on cd14$^+$ monocytes in patients with out-of-hospital cardiac arrest provided target temperature management therapy: a prospective observational study. *Emerg Crit Care Med*. 2024;4(1):16–21. doi: 10.1097/EC9.0000000000000118