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Original Article

Clinical observation of different targeted temperature management methods in patients with cardiac arrest

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Abstract: Objective: To explore the clinical value of extracorporeal cardiopulmonary resuscitation (ECPR) combined with different targeted temperature management (TTM) for the treatment of cardiac arrest. Methods: From January 2018 to September 2020, ECPR was initiated in patients with cardiac arrest who did not have their spontaneous circulation restored after 20 minutes of traditional cardiopulmonary resuscitation (CPR). A total of 22 patients (observation group) given TTM were treated with Hico-variotherm 550 (HU 550) and 30 patients (control group) not given TTM were treated with a medical water circulation cooling blanket. The Glasgow Coma scale (GCS) score, serum neuron-specific enolase (NSE), survival rate and neurological prognosis after ECMO weaning were compared between the two groups. Results: There was no significant difference between the two groups in GCS score on the third and seventh days after resuscitation and serum NSE on the first and third day after treatment ($P>0.05$). Compared with the control group, the survival rate (40.91% vs 33.33%) and favorable neurological outcome (36.36% vs 26.67%) of patients in the observation group were slightly higher, but the differences were not statistically significant (all $P>0.05$). The incidence of shivering and body temperature fluctuation during rewarming in the observation group was lower than that in the control group ($P<0.05$). Conclusion: HU550 poikilothermia water cabinet combined with ECMO can better control the targeted temperature of patients in a more accurate range and improve the survival rate; however, it exerts no statistical improvement in the incidence of complications.

Keywords: Extracorporeal membrane oxygenation, targeted temperature management, cardiac arrest

Introduction

Cardiac arrest refers to the sudden stop of the heart caused by a variety of reasons, the disappearance of effective pumping function, resulting in severe hypoxia and ischemia. Target temperature management (TTM) is an effective therapy, which can physically lower the patient's body temperature to a desired level. In recent years, the Consensus of French experts have recommended TTM [1]. TTM is also recommended as a main neuroprotective approach, and it is widely used in intensive care units to enhance the survival rate of cardiac arrest patients with good neurological outcomes. The Consensus of French experts recommended to maintain the body temperature within 32-36°C. TTM can significantly reduce the body's metabolism and inflammatory response. Each 1°C decrease in temperature can cause a 13% decrease in the metabolic rate of the whole body and 5% decrease in oxygen consumption. When the body temperature drops to 34°C, the metabolic rate of the whole body drops by about 39% and oxygen consumption decreases by 15% [2, 3].

Interpretations by the 2019 American Heart Association updated the guidelines for cardiopulmonary resuscitation and emergency cardiovascular care regarding adult basic and advanced life support and first aid: with the rapid implementation and support of a skilled ECPR (extracorporeal membrane oxygenation) team, for patients who have not responded to traditional cardiopulmonary resuscitation (CPR), ECPR can be considered as a rescue method (recommendation level 2b; level of evidence C-LD) [4]. Using target temperature management (TTM) as the main neuroprotective meth-

Table 1. Baseline characteristics of the two groups

Subgroup	Observation group (n=22)	Control group (n=30)	χ^2/t	P
Age (y)	44.68±18.46	42.90±16.15	0.370	0.713
Gender			0.164	0.685
Male, n (%)	15 (68)	22 (73)		
Female, n (%)	7 (32)	8 (27)		
Previous disease status, n (%)				
Cardiac disease	4 (18)	6 (20)	-	1.000
PE	1 (5)	2 (7)	-	1.000
DM	4 (18)	5 (17)	-	1.000
HBP	8 (36)	9 (30)	0.234	0.629
Hyperlipidemia	1 (5)	1 (3)	-	1.000
AMI	4 (18)	13 (43)	2.595	0.107
Cancer	3 (14)	2 (7)	0.134	0.714
Viral myocarditis	4 (18)	3 (10)	0.196	0.658

Note: PE, Pulmonary Embolism; DM, Diabetes Mellitus; HBP, High Blood Pressure; AMI, Acute Myocardial Infarction.

od can improve the survival rate of patients and improve the neurological function of patients after ECMO weaning [5, 6]. This study retrospectively analyzed the data of critically ill patients undergoing TTM with ECPR, and explored the application effect and clinical value of different TTM methods in ECPR patients.

Methods

Study design and patients

From January 2018 to September 2020, the clinical data (**Table 1**) of hospitalized patients with cardiac arrest who underwent ECPR after failing to achieve ROSC (return of spontaneous circulation), hemodynamic instability or autonomic rhythm maintenance after 20 min of traditional CPR were retrospectively analyzed [7].

Exclusion criteria: patients who underwent traditional CPR performed by non-professionals; patients who had contraindications of target temperature management, severe coagulation dysfunction, severe craniocerebral injury; and patients whose families were unwilling to continue further treatment. The patients' family members signed the informed consent, and this study was approved by the Ethical Committee of Jiangsu Province Hospital (approval number: 2021-NT-40).

Establishment of the ECMO team

The ECMO team was made up of 8 ICU physicians with rich experience in ECMO catheterization. The physicians had received training in the arteriovenous puncture technique under Doppler ultrasound to ensure the success arteriovenous puncture and therefore shorten the waiting time for ECMO. Nursing staff were comprised of 10 ICU nurses (ICU years >10 years in charge of nurses) who were trained in ECMO prefilling theory and operation every month and regularly participated in the assessment of the ECMO quality management to ensure the one-time success of ECMO circulating line prefilling. An aseptic diagnosis and treatment environment was maintained during the ECMO catheterization, all personnel strictly followed aseptic operation instructions, and all materials were provided by the specialized ECMO catheterization vehicle.

Establishment of ECMO circulation circuit

Immediately after the patients had cardiac arrest, the ECMO team started the ECPR process upon receiving the consultation. While giving high-quality CPR, venous-arterial (V-A) ECMO circulation was established at the bedside. During the establishment of ECMO, continuous extra-thoracic heart compression, appropriate fluid replacement, supplementation of red blood cells, plasma, albumin and other colloids, and vasoactive drugs were applied to maintain the average arterial pressure of 60-80 mmHg.

Targeted temperature management

Current guidelines recommend a temperature range of 32.0-36.0°C for targeted temperature management [8, 9]. After the ECMO assisted circulation was established, the temperature measurement silicone urinary catheter with a thermal probe instead of the ordinary latex uri-

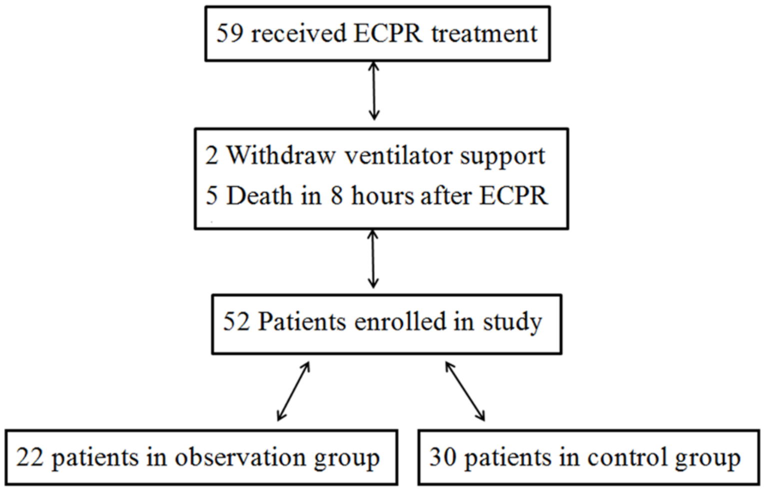

Figure 1. Flowchart of patient inclusion. ECPR: extracorporeal cardiopulmonary resuscitation.

nary catheter was used to monitor the bladder temperature. In the observation group, the patient's core temperature was lowered to the bladder temperature of 34.0°C with a fluctuation of <1°C by adjusting the temperature of the HU550 poikilothermia water cabinet by adjusting the ECMO, and maintaining it for about 24 hours [10, 11]. Patients in the control group were provided medical water circulation cooling blankets to lower the patient's core body temperature to 34.0°C and maintain it for 24 hours. During the resuscitation phase of the targeted body temperature, the bladder temperature was slowly increased to 36.0-37.0°C at a rate of 0.2°C/h.

Fluid management

During the operation of ECMO, the patient was fully sedated. Daily Doppler ultrasound was used to check the vascular volume and elasticity, cardiac ejection fraction, and the cardiac function of the patients was evaluated. The 24-hour fluid in and out of the patients was strictly controlled to maintain the circulating cardiac blood volume and reduce the cardiac overload, so as to ensure the high blood flow perfusion in ECMO. The flow rate was maintained at 3-4 L/min, and the average arterial pressure of patients was controlled at 60-80 mmHg. Patients with respiratory failure were connected to a ventilator to assist their breathing. Intra-aortic balloon pump (IABP) was used to assist heart function in patients with severe left ventricular insufficiency, and continuous renal replacement therapy (CRRT) was used to treat the patients with renal failure to maintain water electrolyte and acid-base balance.

Data collection

The basic data and postoperative indices, including survival rate (90 days after treatment), favorable neurological prognosis, percentage of ECMO+IABP assistance, ECMO+CRRT assistance and ECMO+IABP+CRRT assistance, ECMO auxiliary time (h) and ICU hospital stay(d), were collected and compared between the two groups. The incidence of complications was also compared between the two groups.

The nervous system indicators of the two groups of patients were recorded, including Glasgow Coma scale (GCS) score on the first and third day of CPR and serum neuron-specific enolase (NSE) on the third and seventh day of CPR. For GCS, we accessed and patients were scored for the eye-opening response, verbal response and body movement. The higher the score, the better the state of consciousness. As for NSE, 5 ml fasting blood was obtained from each patient, and the serum NSE level was detected by Electrochemiluminescence Kit and automatic immunoanalyzer (Roche, Germany).

Statistical analysis

Statistical analysis was performed using IBM SPSS 25.0 software. Continuous data were presented as mean ± SD and analyzed using independent sample t test or paired t test. Categorical variables were expressed as number (%) and analyzed by Pearson chi-squared test, chi-squared test combined with Yate's correction or Fisher's exact test. P value <0.05 indicated a statistically significant difference.

Results

General information

A total of 52 patients were enrolled in this study (**Figure 1**). In the observation group, 22

Table 2. Laboratory tests of the two groups

Laboratory indications	NSE 1* (ng/mL)	NSE 3* (ng/mL)	GCS 3*	GCS 7*
Observation group	105.01±57.11	121.73±96.79	4.50±3.26	5.91±5.08
Control group	131.25±120.09	155.28±126.01	4.80±3.24	6.87±5.47
T value	1.046	1.042	0.329	0.643
P value	0.301	0.302	0.744	0.523

Note: NSE 1* refers to the serum neuro-specific enolase value (ng/ml) on the first day of CPR, and NSE 3* refers to the serum neuro-specific enolase value (ng/ml) on the third day of CPR, GCS 3* refers to the GCS score on the third day of CPR, and GCS 7* refers to the GCS score on the seventh day of CPR.

Table 3. Postoperative indices in the two groups

Postoperative indices	Observation group (n=22)	Control group (n=30)	χ^2/t	P
Survival rate, n (%)	9 (40.91%)	10 (33.33%)	0.314	0.575
Favorable neurological prognosis, n (%)	8 (36.36%)	8 (26.67%)	0.560	0.454
ECMO+IABP assistance, n (%)	5 (22.73%)	11 (36.67%)	1.158	0.282
ECMO+CRRT assistance, n (%)	15 (68.18%)	22 (73.33%)	0.164	0.685
ECMO+IABP+CRRT, n (%)	5 (22.73%)	8 (26.67%)	0.105	0.746
ECMO auxiliary time (h)	144.73±156.34	153.57±146.93	0.209	0.837
ICU hospital stay (d)	11.5±10.75	12.03±11.36	0.171	0.865

patients used HU550 poikilothermia water cabinet for TTM, and there were 15 males and 7 females with an average age of 44±18 years old. Thirty patients who underwent TTM with medical water circulation cooling blanket were recruited in the control group, including 22 males and 8 females, with an average age of 43±16 years old (See **Table 1**).

Laboratory test results

Initially for ECMO treatment the patients were treated with sedatives, and the GCS score was evaluated at the third and seventh day after resuscitation. The results showed that the GCS scores of the observation group on the 3rd and 7th day after CPR were (4.50±3.26) and (5.91±5.08) while that of the control group were (4.80±3.24) and (6.87±5.47) (all P>0.05). The value of serum NSE in the observation group and control group on the first day was [(105.01±57.11) ng/mL vs (131.25±120.09) ng/mL], and the value of serum NSE in the observation group and control group on the third day was [(121.73±96.79) ng/mL vs (155.28±126.01) ng/mL], and there was no statistical difference between the two groups (all P>0.05) (**Table 2**).

Postoperative indices in the two groups

There were no statistical differences in ECMO operation time, IABP assisted myocardial contraction, CRRT assisted renal function, survival rate after extubation and favorable neurological function prognosis between the two groups (all P>0.05). In this study, the ECMO auxiliary time [(144.73±156.34) h vs (153.57±146.93) h] and the ICU hospital stay [(11.5±10.75) d vs (12.03±11.36) d] were relatively close in the two groups of patients. However, the survival rate of patients in the observation group was higher than that in the control group (40.91% vs 33.33%), and the rate of good prognostic neurological function in the observation group was higher than that in the control group (36.36% vs 26.67%). In this study, the IABP assistance rate (22.73% vs 36.67%), the CRRT assistance rate (68.18% vs 73.33%) and the combined IABP and CRRT assistance rate (22.73% vs 26.67%) in patients of the observation group were all lower than those in the control group, although with no statistical difference (**Table 3**).

Complications in the two groups

Comparison of postoperative complications showed that there was no statistical difference in the incidence of diarrhea, coagulation dysfunction, and the incidence of core body temperature change more than 1°C every 4-6 h during rewarming, but the incidence of shivering and body temperature fluctuation during rewarming in the observation group was low-

Table 4. Complications in the two groups

Incidence of complications	Shivering	Diarrhea	Coagulation disorders	Body temperature fluctuation during rewarming*
Observation group	0	2 (9.09%)	5 (22.73%)	0
Control group	7 (23.33%)	8 (26.67%)	7 (23.33%)	6 (20.00%)
χ^2 value	-	1.519	0.003	-
P value	0.016	0.218	0.959	0.033

Note: Body temperature fluctuation during rewarming* refers to the change of core temperature of patients in the resuscitation stage by more than 1°C every 4-6 h.

er than that in the control group (P<0.05, **Table 4**).

Discussion

Neuron-specific enolase (NSE) is a macromolecular protein substance unique to neurons and neuroendocrine cells. Under normal circumstances, there is almost no NSE in the serum and cerebrospinal fluid. Relevant studies in recent years have found that cerebral ischemia and hypoxia can cause the death and disintegration of some neurons, and damage the integrity of the cell membrane of neurons, forcing NSE in nerve cells to diffuse into the cerebrospinal fluid and intercellular space. Due to the destruction of the blood-brain barrier caused by the injury, its integrity is destroyed or permeability is enhanced, and the natural barrier function of the brain tissue is weakened, causing some protein components to be released into the blood and cerebrospinal fluid through the blood-brain barrier [12]. A prospective observational study in South Korea showed that the NSE concentration on the first day after cardiopulmonary resuscitation is highly correlated to a poor 6-month prognosis of neurological function [13]. Previous studies have shown that the NSE concentration at 48 h and 72 h after cardiopulmonary resuscitation is a strong predictor of neurological prognosis after cardiac arrest, and can be used to predict the neurological prognosis of patients with cardiac arrest [14-17].

TTM in patients undergoing ECPR can reduce the degree of ischemia-reperfusion injury, improve CPR survival rate and reduce sequelae, especially neurological sequelae. TTM has the following characteristics: (1) Reducing the oxygen consumption of brain tissue and reducing the accumulation of lactic acid in brain tissue. (2) Protecting the blood-brain barrier and reducing cerebral edema [18, 19]. The results of this study showed that on the first day of CPR, the serum NSE value of the observation group was (105.01±57.11), and that of the control group was (131.25±120.09). On the third day of CPR, the serum NSE value of the observation group was (121.73±96.79) and that of the control group was (155.28±126.01), the serum NSE value of the observation group was slightly lower than that of the control, although there was no statistical difference.

In this study, 19 (36.54%) out of 52 patients who had ECPR survived after TTM therapy, of which 16 patients were conscious upon discharge, and the rate of good neurological function was (30.77%). Further analysis showed that the survival rate of patients in the observation group was higher than that in the control group (40.91% vs 33.33%), and the rate of good neurological function in the observation group was higher than that in the control group (36.36% vs 26.67%), which suggests that the implementation of TTM using HU550 Hico-variotherm can improve the survival rate of patients, improve the prognosis of patients, and increase the social reintegration rate of patients, although the differences were not statistically significant. Results suggest that ECPR patients using HU550 poikilothermia water cabinet, for temperature fluctuation can quickly control the patients' core body temperature to the target temperature, keep the core temperature fluctuation <1°C and lower the incidence of adverse reactions (**Figure 2**), facilitating clinical nursing staff to implement operation and monitoring [20, 21].

In this study, more patients died than survived. The rate between death and survival in the observation group was similar. This is possibly because TTM therapy reduced ischemia-reperfusion, the heart work is significantly reduced,

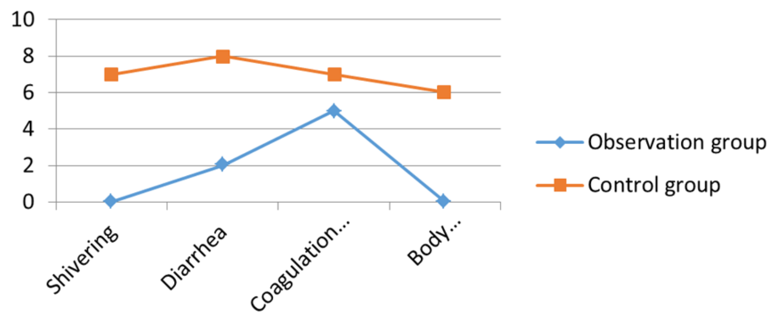

Figure 2. Comparisons of total incidence of complications of the two groups.

and it can improve the survival rate of CPR and reduce disease sequelae.

TTM can decrease the myocardial oxygen consumption of patients, slow the rate of consumption of adenosine triphosphate and lactate build-up during myocardial ischemia, reduce myocardial damage caused by hypoperfusion, and provide favorable conditions for the recovery of cardiac function and clinical outcomes [22, 23]. Some studies have reported that TTM combined with CRRT or IABP can effectively improve the circulatory function of patients, and shorten the length of hospital stay [24, 25].

In conclusion, HU550 poikilothermia water cabinet can further improve the prognosis and increase the survival rate on the basis of assisting ECMO. However, the application of TTM combined with ECMO in the treatment of patients with cardiopulmonary resuscitation in China is still in its initial stages. This study is a single-center, retrospective study with a small sample size and limited indicators, so the results need to be further verified by expanding the sample size and follow-up time.

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Disclosure of conflict of interest

None.

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