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Effects of early hemodynamics, oxygen metabolism, and lactate dynamics on prognosis of post-cardiac arrest syndrome

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With an annual incidence of 0.5 to 1.5/1000, cardiac arrest (CA) has emerged as a major global public health concern.[1] Although the American Heart Association (AHA)-International Liaison Committee on Resuscitation updates the cardiopulmonary resuscitation (CPR) guidelines every 5 years, the survival rate and percentage of patients with good neurologic outcomes post-CA after hospital discharge have been relatively low. Therefore, the AHA 2010 CPR guidelines mention the treatment of post-cardiac arrest syndrome (PCAS) in the intensive care unit (ICU) as the fifth link in the CA survival chain. PCAS is a pathophysiological process that includes (1) brain injury, (2) myocardial dysfunction leading to hemodynamic instability, and (3) systemic ischemia/reperfusion response leading to lactate accumulation.[2] These key factors affect the survival and neurological prognosis of CA patients in the early stages. We assessed the effects of early hemodynamics, oxygen metabolism, and lactate dynamics during PCAS on a 28-day survival rate and neurological outcomes.

This study was approved by the Ethics Committee of Beijing Chaoyang Hospital, Capital Medical University (No. 2011-med-42). We analyzed the data of patients admitted to the ICU of Beijing Chaoyang Hospital from January 2012 to July 2019. We used the following inclusion criteria: (1) patients with successful resuscitation after out-of-hospital cardiac arrest (OHCA), (2) age ≥18 years, (3) serum lactate levels measured within 2 hours after return of spontaneous circulation (ROSC). We excluded patients who were pregnant, had malignant tumors, survived for <2 hours, or suffered from a CA caused by major trauma.

We collected data on patient demographics, resuscitation, and clinical treatment. All patients with OHCA were monitored by continuous electrocardiography, pulse oximetry, and continuous systemic arterial blood pressure measurement. All patients were treated according to the AHA 2010 CPR guidelines.

Vital signs and arterial blood gas analysis, including the mean arterial pressure (MAP), heart rate (HR), serum lactate levels, arterial pH, partial oxygen pressure (PaO_2), and partial carbon dioxide pressure ($PaCO_2$) at admission (within 2 hours after ROSC, day one) and three days later (72 hours after ROSC), were recorded. Lactate clearance was calculated as (lactate levels at admission – lactate levels at 72 hour)/lactate levels at admission × 100%. All patients were followed until death or up to 28 days. An experienced neurologist assessed the patients' neurological prognosis using a cerebral performance category (CPC) score. A favorable neurologic outcome was defined as a CPC score of 1 to 2.

Baseline characteristics and index events were described for both groups. Continuous data are presented as means with standard deviations or medians with interquartile range, depending on the normality of the data. The categorical variables are expressed as numbers and percentages. Differences in the variables were assessed using Student's *t* test, the Wilcoxon rank-sum test, or the Chi-squared test, as appropriate. Univariate and multivariate Cox regression analyses were performed to identify the risk factors of 28-day mortality and the predictors of good neurological functions. All tests were two-tailed and a $P < 0.05$ was considered statistically significant. Statistical analyses were performed using IBM SPSS Statistics 22 (IBM, Armonk, NY, USA).

A total of 1383 patients with ROSC after CA were recruited in the study. Overall, among 233 patients excluded, 133 patients survived for <2 hours, 59 patients

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had incomplete test data, and 41 patients were lost to follow-up. Finally, 1150 patients were enrolled in the study, out of which 476 patients belonged to the 28-day survival group and 674 patients belonged to the non-survival group. In addition, 44.1% of patients (297/674) died within 72 hours. The characteristics of the patients in this study, stratified by the primary outcome, are outlined in Supplementary Table 1, http://links.lww.com/CM9/A785.

The primary cause of the OHCA was cardiac in nature. Reperfusion therapy and therapeutic hypothermia were equally distributed between the two groups. Compared with the non-survival group, the survival group had more male patients (64.3% *vs.* 58.0%, $\chi^2 = 3.723$, $P = 0.032$), younger patients (60 [18–78] *vs.* 65 [18–75] years, $Z = -5.505$, $P < 0.001$), and more shockable rhythm (38.7% *vs.* 26.0%, $\chi^2 = 25.274$, $P < 0.001$). The survival group required less duration of mechanical ventilation (6.5 ± 0.5 days *vs.* 10.3 ± 1.8 days, $t = 11.000$, $P < 0.001$) and less time to ROSC (10 [5.0, 20.0] min *vs.* 12.5 [5.0, 25.0] min, $Z = -2.566$, $P = 0.013$).

The survival group had higher MAP (73.8 [53.3–92.0] mmHg *vs.* 70.0 [47.0–88.0] mmHg, $Z = -2.194$, $P = 0.024$) on day 1 [Supplementary Table 2, http://links.lww.com/CM9/A785]. At 72 hours after ROSC, the survival group had lower HR (87.9 [78.0–102.5] beats per minute [bpm] *vs.* 99.0 [80.0–114.0] bpm, $Z = -5.194$, $P < 0.001$), higher MAP (86.0 [77.0–93.8] mmHg *vs.* 81.7 [70.7–92.2] mmHg, $Z = -3.967$, $P < 0.001$), and lower dose of vasopressors (noradrenaline: 0.50 ± 0.06 μg·kg^{-1}·min^{-1} *vs.* 1.31 ± 0.33 μg·kg^{-1}·min^{-1}, $t = -3.420$, $P < 0.001$; dopamine: 5.30 ± 0.20 μg·kg^{-1}·min^{-1} *vs.* 8.83 ± 0.43 μg·kg^{-1}·min^{-1}, $t = -5.236$, $P < 0.001$).

There were no significant differences in PaO_2 and $PaCO_2$ between the two groups on day one [Supplementary Table 3, http://links.lww.com/CM9/A785]. On day three, the survival group had a significantly higher pH (7.41 [7.35–7.46] *vs.* 7.34 [7.29–7.43], $Z = -4.638$, $P < 0.001$) and PaO_2 (96.0 [79.7–125.5] mmHg *vs.* 81.5 [65.0–105.0] mmHg, $Z = -5.277$, $P < 0.001$), but lower $PaCO_2$ (38.0 [32.7–44.0] mmHg *vs.* 40.0 [33.0–49.4] mmHg, $Z = -1.585$, $P < 0.001$).

Compared with the non-survival group, the survival group had significantly lower lactate levels at admission (3.50 [1.80–7.61] mmol/L *vs.* 5.3 [2.27–10.00] mmol/L, $Z = -4.722$, $P < 0.001$) and better lactate clearance (66.53% [7.85%–100.00%] *vs.* 60.00% [19.48%–84.35%], $Z = -1.958$, $P < 0.001$).

Good neurologic prognosis at 28 days in the survival group was 53.8% (256/476). Compared with the non-survival group, the survival group had favorable neurological outcomes on day 1 (17.44% *vs.* 4.75%, $P < 0.001$) and day 3 (35.08% *vs.* 8.75%, $P < 0.001$).

All factors were included in the Cox regression analysis [Supplementary Table 4, http://links.lww.com/CM9/A785]. The results showed that the greater the lactate clearance, the lower the risk of death at 28 days (HR = 0.789, 95% CI: 0.727–0.855, $P < 0.001$). Other variables found to be significant in the Cox regression analysis were the time to ROSC (HR = 1.010, 95% CI: 1.003–1.017, $P = 0.007$), non-shockable rhythm (HR = 1.524, 95% CI: 1.060–2.192, $P = 0.023$), 72-hour HR (HR = 1.018, 95% CI: 1.000–1.103, $P = 0.015$), and MAP (HR = 0.985, 95% CI: 0.968–0.991, $P = 0.043$). Lactate clearance was the sole predictor of good neurologic outcomes (HR = 0.996, 95% CI: 0.994–0.999, $P = 0.005$).

Although the CA-ROSC success rate has been improved in out-of-hospital resuscitation, the survival discharge rates and favorable neurological outcomes remain unsatisfactory. Post-cardiac arrest care focuses on improving the systemic process of ischemia-reperfusion injury and non-specific inflammation. However, a difference existed between PCAS and septic shock, involving the application of vasopressors in the early stage. Increasing oxygen metabolism and reducing blood lactate levels are major contributing factors affecting the survival of PCAS and neurological damage.[3]

The systemic organs in individuals with PCAS undergo a series of changes during ischemia–reperfusion: impaired cardiac function leading to hemodynamic instability, oxygen debt, and lactate accumulation due to insufficient tissue perfusion and ischemia.[4] Inadequate lactate clearance results in tissue acidosis, brain damage, and multiple organ dysfunction. The massive use of vasopressors exacerbates hypoxia to the microcirculation, leading to overproduction and underutilization of lactic acid, consequently creating a vicious circle that increases the mortality rate. Therefore, hemodynamics and lactate levels were monitored in the early stage of PCAS.

We used a large-scale retrospective study with 28-day survival and good neurological outcomes as the primary endpoints and analyzed the effect of hemodynamics, oxygen metabolism, and lactate dynamics on patients with PCAS. These clinical indicators can be easily measured in a short time. We found that the levels of noradrenaline administered within 72 hours after ROSC in the non-survival group were 2.6 times higher than those in the survival group; however, improvement in MAP, PaO2, and lactate levels remained poor. The administration of a reasonable dose of vasopressors for hypotension in the early stage of ROSC was suggested to maintain a steady and ideal MAP that could be beneficial for treating PCAS.[5] In contrast, with high doses of vasopressors, although hypotension can be corrected, oxygen metabolism and blood lactate levels do not improve, and the prognosis remains poor.

Our study had certain limitations. First, this was a single-center retrospective study which may have a bias in the results. Second, the cumulative levels of adrenaline used in pre-hospital CPR were not collected. Third, lactate and blood gas data were not available due to limited conditions during resuscitation. Fourth, invasive hemodynamics (cardiac output, systemic vascular resistance, and stroke volume) and lactate levels were not continuously monitored in the first 72 hours after ROSC, and the volume of resuscitation fluid was not calculated.

Within 72 hours after ROSC, close monitoring of oxygen metabolism, hemodynamics and lactate metabolism is

vital. The application of high doses of vasopressors, which may improve the patient's hemodynamics, does not improve the 28-day mortality or neurological outcomes.

Conflicts of interest

None.

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