Original Contribution

Relative tachycardia is associated with poor outcomes in post-cardiac arrest patients regardless of therapeutic hypothermia

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Abstract

Article history:
Received 18 March 2018
Received in revised form 15 May 2018
Accepted 13 June 2018

Background: To investigate whether the relationship between heart rate and neurological outcome is independent of therapeutic hypothermia (TH) and whether heart rate is related to hemodynamic instability post-cardiac arrest.

Methods: Retrospective review of an out-of-hospital cardiac arrest registry was performed. The primary exposure was heart rate quartiles at 24 h post-cardiac arrest. The primary outcome was a poor neurological outcome, which was defined as having a cerebral performance category (CPC) of 3–5 at 28 days. Secondary outcomes were mean blood pressure and serum lactate at 24 h and Sequential Organ Failure Assessment (SOFA) scores at admission.

Results: In total, 155 patients were enrolled. The proportion of patients with a poor CPC was significantly greater in higher heart rate quartiles; similar results were observed in patients who did and did not undergo TH. Serum lactate levels at 24 h were significantly higher in the 3rd and 4th quartile groups than in the 1st quartile group. Additionally, SOFA scores were significantly higher in the 4th quartile group than in the 1st and 3rd quartile groups.

Conclusions: Relative tachycardia is associated with poor neurological outcomes in post-cardiac arrest patients, independent of TH, and with higher serum lactate levels and admission SOFA scores.

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1. Introduction

The overall survival to discharge rate for out-of-hospital cardiac arrest (OHCA) is approximately 10% [1, 2]. However, over half of patients who are successfully resuscitated and survive to hospital admission eventually die during subsequent post-resuscitation care [2]. Cerebral ischemic injury is the most common cause of death during this period. In addition, the hemodynamic instability caused by myocardial dysfunction and systemic ischemia-reperfusion injury may exacerbate neurological damage or even cause death [3, 4]. Despite ongoing debate regarding the optimal target temperature, therapeutic hypothermia (TH) is the only proven treatment for mitigating this injury [5].

Recent studies have reported that bradycardia observed during TH is associated with good neurological outcomes in comatose survivors of OHCA [6–8]. As sinus bradycardia is a normal physiological response to hypothermia, its occurrence during TH may reflect preserved autonomic regulation of the heart in patients with less severe ischemic injury [9]. Tachycardia can also be accompanied by an increase in sympathetic tone during post-cardiac arrest care. The most common cause of sympathetic stimulation is an excess of circulating catecholamine due to both endogenous catecholamine release by acute stressful conditions, such as a shock state, and exogenous catecholamine use, such as vasopressors and inotropics.

We hypothesized that bradycardia during post-cardiac arrest care may not represent intact autonomic regulation of the heart in response to TH but that it may represent the absence of serious stressful conditions, such as hemodynamic instability and shock, requiring vasopressors. To test this hypothesis, we investigated whether the relationship between heart rate and neurological outcome is independent of TH and whether heart rate is related to hemodynamic instability during the post-cardiac arrest period.

2. Methods

2.1. Study design and patients

This was a retrospective analysis of a prospectively collected multicenter cohort registry performed in three hospital emergency
The three institutions were urban teaching hospitals, with annual ED censuses of over 50,000, 70,000 and 80,000 patients. The records of patients who survived OHCA were prospectively collected under approval of the institutional review board (IRB Nos: H-1408-012-599, J-1408-012-599, and B-1401/234-402), and written informed consent was waived. The IRB also approved this retrospective analysis (IRB No. H-1610-035-797). Because the time of initiation for registration differed among the hospitals, patients were enrolled from December 2013 to April 2016, August 2014 to April 2016, and April 2015 to April 2016.

Patients who fulfilled the following criteria were eligible for enrollment: age ≥18 years, OHCA without traumatic causes of arrest, and restoration of spontaneous circulation (ROSC) in the prehospital setting or ED. To evaluate the association between heart rate during post-cardiac arrest care and neurological outcomes, the following exclusion criteria were applied: baseline cerebral performance category (CPC) of 3 or 4, post-ROSC Glasgow Coma Scale (GCS) of 14 or 15, transfer from the ED to another hospital after ROSC, or death within 24 h.

2.2. Study setting

Basic life support was provided by fire station-based emergency medical technicians, and advanced life support was administered after transport to the ED. If the patients were successfully resuscitated, the subsequent post-cardiac arrest care was performed in the intensive care unit. TH was performed at the discretion of the attending physician. If TH was performed, the target temperature of 33 °C was maintained for 24 h, and rewarming at a rate of 0.25 °C per h was applied. Surface cooling devices including Arctic Sun (Bard Medical, Covingon, GA) or Blanketrol (CSZ Medical, Cincinnati, OH) were used for TH induction, maintenance, and rewarming. If TH was not performed, temperature control only to avoid hyperthermia was applied. Other post-cardiac arrest care included hemodynamic optimization and selective emergent coronary angiography for patients with ST-elevation myocardial infarction or highly suspected acute myocardial infarction. Withdrawal of active life-sustaining therapy was allowed only for brain-dead patients for the purpose of organ donation.

2.3. Data collection

The following data were obtained from the post-cardiac arrest registry: age, gender, baseline CPC, witnessed arrest, bystander cardiopulmonary resuscitation (CPR), initial cardiac rhythm, GCS at ROSC, TH use, Sequential Organ Failure Assessment (SOFA) score at admission, survival at 28 days, and CPC at 28 days. Vital signs including mean blood pressure (BP), heart rate and body temperature at admission (0 h), 24 h, and 72 h were recorded. Serum lactate levels were measured at admission and at 24 h.

2.4. Exposure variables

The primary exposure was heart rate at 24 h post-cardiac arrest. Patients were categorized into heart rate quartiles at 24 h for all patients and in those with and without TH (Q1–Q4). All patients were categorized into the TH or non-TH group.

2.5. Outcome measures

The primary outcome was a poor neurological outcome defined as having a CPC of 3–5 at 28 days. The CPC scores were determined by the attending neurologist. In each site, a research nurse who was blinded to the research design defined the CPC score using electronic medical record system and telephone contact. For the validity of data, CPC score was re-evaluated by an independent neurologist and the agreement between the two CPC results was 99.7% in the previous study [10].

A brief description of the CPC score is as follows: Score 1, Complete recovery or mild disability; Score 2, Moderate disability but independent in activities of daily living; Score 3, Severe disability and dependent in activities of daily living; Score 4, Persistent vegetative state; Score 5, Dead. Secondary outcomes representing hemodynamic status included mean BP at 24 h, serum lactate level at 24 h, and SOFA score at admission.

2.6. Statistical analysis

Continuous variables are presented as means with 95% confidence intervals (CIs), and categorical variables are presented as percent frequencies of occurrence. The Wilcoxon rank-sum test was used to compare continuous variables, and the chi-square test or Fisher's exact test was used to compare categorical variables, as appropriate.

For primary outcome analysis, a positive or negative trend of proportions by heart rate quartiles in all patients and in those who did and did not undergo TH was determined. Multivariate logistic regression analysis was used to analyze the independent association between heart rate and neurological outcomes. Unadjusted odds ratios (ORs) of the 24-h heart rate quartiles for a poor CPC were calculated using univariate logistic regression analysis. The multivariate logistic regression analysis model A included age, gender, witnessed arrest, bystander CPR, and whether the initial rhythm was shockable. Model B included age, gender, witnessed arrest, bystander CPR, whether the initial rhythm was shockable, mean BP at 24 h, serum lactate level at 24 h, and admission SOFA score.

The Kruskal-Wallis test was used to investigate differences in BP, lactate levels, and SOFA scores among heart rate quartile groups. If a significant difference was observed, the Wilcoxon rank-sum test for two groups was performed separately. Two-tailed p values < 0.0083 were considered significant according to Bonferroni correction. Otherwise, two-tailed p values < 0.05 were considered to indicate statistical significance. All analyses were performed using Stata version 13.1 (Stata Corp, College Station, TX).

3. Results

3.1. Demographics

During the study period, 310 patients were evaluated for inclusion. A total of 155 patients were excluded. Exclusion criteria were a baseline CPC of 3 or 4, a post-ROSC GCS of 14 or 15, transferred to another hospital, and died within 24 h. Thus, the analysis involved 155 patients (Fig. 1), 90 (58.1%) and 65 (41.9%) of whom died and did not undergo TH, respectively. One hundred twenty-one patients (78.1%) had poor neurological outcomes.

Patients with a poor CPC were older and less likely to have a witnessed arrest or undergone bystander CPR (Table 1). A shockable rhythm was less frequent, and the GCS at ROSC was lower in the poor CPC group. However, the baseline characteristics were not different among 24 h heart rate quartiles (Supplement Table 1). Heart rates at 24 and 72 h were significantly higher in the poor CPC group. Additionally, the mean BP at 24 h was significantly higher and the SOFA score was lower in the poor CPC group.

3.2. Primary outcome

The proportion of patients with a poor CPC was significantly higher (test for trend, p = 0.003) in the higher heart rate quartiles (Fig. 2). The same result was observed for both patients who received TH (p = 0.014) and those who did not receive TH (p = 0.004).

According to univariate logistic regression analysis, only the 4th quartile group was significantly associated with a poor CPC (Q4, OR = 2.28, p = 0.159; Q3, OR = 2.93, p = 0.062; Q2, OR = 6.50, p = 0.008) (Fig. 3). Moreover, the 4th quartile group was
significantly associated with a poor CPC in multivariate logistic regression analysis including age, gender, witnessed arrest, bystander CPR, and initial rhythm (Q1, reference; Q2, OR = 1.22, p = 0.537; Q3, OR = 0.97, p = 0.984; Q4, OR = 1.34, p = 0.844).

3.3. Secondary outcome

Mean BP were not significantly different among heart rate quartiles (Kruskal-Wallis test, p = 0.051) (Fig. 4). Lactate levels at 24 h were significantly higher in the 3rd and 4th quartile groups than in the 1st quartile group (Wilcoxon rank-sum test, p = 0.006 and p = 0.003, respectively). In addition, the SOFA score of the 4th quartile group was significantly higher than that of the 1st and 3rd quartile groups (Wilcoxon rank-sum test, p = 0.003, both).

4. Discussion

In this study, we found relative tachycardia at 24 h to be associated with poor neurological outcomes in post-cardiac arrest patients; this association was observed regardless of whether patients underwent TH. After adjusting for demographic and prehospital resuscitation variables, the highest heart rate quartile was independently associated with poor neurological outcomes. However, this association was not observed after adjusting for post-cardiac arrest factors such as mean BP, serum lactate level, and SOFA score.

Bradydycardia occurs when the core body temperature decreases [9]. As mentioned previously, several studies have reported that bradycardia during TH is related to good neurological outcomes [6-8]. For example, Sørr-Jensen et al. [6] reported a retrospective analysis of 111 OHCA patients treated with TH (32 – 34 °C), in which bradycardia (< 60 beats/min) at 8 h after cardiac arrest was associated with good neurological outcomes at hospital discharge. In addition, Thomsen et al. studied 234 comatose survivors of OHCA with presumed cardiac etiology and a shockable primary rhythm who completed a 24-h TH protocol (33 °C) [7]. Sinus bradycardia (< 50 beats/min) was observed in 115 (49%) patients during TH and was independently associated with a lower 180-day mortality rate. In addition, Thomsen et al. [8] reported bradycardia (< 50 beats/min) to be independently associated with...
lower 180-day mortality and concluded that bradycardia during targeted temperature management (TTM) at 33 °C may be a novel, early marker of favorable outcomes. This association has also been observed in patients treated by TTM at 36 °C, but to a lesser extent [8]. Although these observations are consistent, the causal relationship between bradycardia and favorable outcomes remains unclear. One possible explanation is that bradycardia during TH reflects intact autonomic regulation of the heart in patients with less severe anoxic brain injury. Another study reported that increased heart rate variability, which is another marker of autonomic heart regulation, is associated with favorable neurological outcomes following OHCA [11]. This result supports the association between good neurological outcomes and preserved parasympathetic regulation of the heart representing as bradycardia in post-cardiac arrest patients. Another explanation for the association is that patients with relative tachycardia have elevated sympathetic activity. Plasma catecholamine concentrations are high in patients who survive OHCA [12]. Moreover, hemodynamic instability is common in post-cardiac arrest patients, resulting in half of these patients requiring vasopressors [3]. In one study, patients who received vasopressors had a faster heart rate than did those without vasopressors [3].

Previous studies on the relationship between bradycardia and good neurological outcomes also reported similar findings. For instance, a non-bradycardia group more frequently received epinephrine during CPR and epinephrine and norepinephrine during post-cardiac arrest care [6]. Additionally, bradycardia was not independently associated with favorable outcomes after adjusting for epinephrine during CPR and norepinephrine during the first 24 h [6]. In another study, the cardiovascular SOFA score was associated with 180-day mortality, and sinus bradycardia was independently associated with 180-day mortality in a multivariable model that did not include lactate levels or cardiovascular SOFA scores [7]. Patients with a fast heart rate also had high lactate levels at admission and a high cardiovascular SOFA score [8].

In the present study, patients with a fast heart rate exhibited increased serum lactate levels and higher admission SOFA scores (Fig. 4). Also, more patients in higher HR quartiles received norepinephrine and any vasopressor (Supplement Table 2). These findings indicate that post-cardiac arrest patients with relative tachycardia are more
Fig. 4. Blood pressure (A) and lactate (B) levels at 24 h and SOFA score (C) at admission according to quartiles of heart rate. * p values < 0.05 vs. Q1, † p values < 0.05 vs. Q3. Abbreviations: BP, blood pressure; SOFA, Sequential Organ Failure Assessment.

likely to have circulatory shock and multiple organ failure. However, the association between heart rate quartile and poor neurological outcome disappeared after adjusting for hemodynamic variables (Fig. 3). Because SOFA score is dependent on mean BP, one may argue that there is some confounding in model B. However, the multivariate analysis using variables of model B excluding mean BP showed similar results (Q1, reference; Q2, OR = 1.61, p = 0.789; Q3, OR = 0.89, p = 0.934; Q4, OR = 1.55, p = 0.773).

Notably, the association between heart rate and neurological outcome was observed regardless of whether TH was performed. Although body temperature did not differ according to neurological outcome (Supplemental Fig. 1), patients with poor outcomes in both the TH (rank-sum test, p = 0.006) and non-TH (rank-sum test, p = 0.008) groups had significantly higher heart rates at 24 h (Supplemental Fig. 2).

We suggest that the association between bradycardia and good neurological outcomes in post-cardiac arrest patients is due to the absence of excessive sympathetic stimulation caused by intrinsic and extrinsic catecholamines associated with hemodynamic instability. Previous studies have reported that patients with poor outcomes following OHCA had higher mean heart rates and more frequently received nor-adrenaline [13].

Several points should be considered when interpreting the results of this study. First, the decision to administer TH was at the discretion of the attending physician, and thus a standard protocol to provide TH was not applied. We excluded patients with a post-ROSC GCS of 14 or 15 because they were not anticipated to have a poor outcome. As a result, post-ROSC GCS was not different between the TH and non-TH groups (p = 0.271). We also excluded patients who died within 24 h to avoid including those in an irreversible state. However, disparity between the TH and non-TH groups might exist in this observational study. Specific reasons for not applying TH are described in Supplemental Table 3. Second, because this study was also an observational study, the causal relationship between heart rate and neurological outcome cannot be determined. Third, HR may vary over a relatively short period and depends on numerous factors such as medications, pain, and patient care activities. Therefore, using minimum or maximum values within a specific period may help to minimize the effect of variation in HR.

5. Conclusion

Relative tachycardia is associated with poor neurological outcomes in post-cardiac arrest patients, and this association is independent of whether TH is performed. Relative tachycardia is associated with increased serum lactate levels and SOFA scores at admission. These results suggest that relative tachycardia might be the result of hemodynamic instability.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ajem.2018.06.032.

Declaration of interest

The authors declare that there are no conflicts of interest.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial or not-for-profit sectors.

Acknowledgments

None.

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