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ORIGINAL ARTICLE
Critical Care

Heart Rate After Resuscitation From Out-of-Hospital Cardiac Arrest due to Acute Coronary Syndrome Is an Independent Predictor of Clinical Outcome

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Background: Heart rate (HR) is a useful predictor of cardiovascular disease, especially in acute coronary syndrome (ACS). However, it is unclear whether there is an association between HR and clinical outcomes after resuscitation from out-of-hospital cardiac arrest (OHCA) due to ACS. The aim of this study was to investigate the impact of HR on clinical outcome in individuals resuscitated from OHCA due to ACS.

Methods and Results: Data from 3,687 OHCA patients between October 2002 and October 2014 were retrospectively analyzed. We divided 154 patients diagnosed with ACS into 2 groups: those with tachycardia (HR >100 beats/min, n=71) and those without tachycardia (HR ≤100 beats/min, n=83) after resuscitation. The primary endpoint was 1-year mortality and the secondary endpoint was neurological injury at discharge according to cerebral performance category score. Overall, mean HR was 95.6 beats/min. There were several significant differences in patient characteristics, indicating poor general condition of patients with tachycardia. Mortality at 1-year was 41.6%, and neurological injury at discharge was observed in 44.1% of individuals. In the multivariate analysis, tachycardia after resuscitation was an independent predictor of both 1-year mortality (hazard ratio, 2.66; 95% CI: 1.20–5.85; P=0.03) and neurological injury at discharge (odds ratio, 2.65; 95% CI: 1.27–5.55; P=0.04).

Conclusions: In patients who recovered from OHCA due to ACS, tachycardia after resuscitation predicted poor clinical outcome.

Key Words: Cardiac arrest; Cardiopulmonary resuscitation; Myocardial infarction

Out-of-hospital cardiac arrest (OHCA) is a growing public health issue carrying an enormous global burden of morbidity and accounting for approximately 15% of the total mortality in industrialized countries.[1–4] Individuals with OHCA continue to have a lower survival rate, reaching only 24% at admission, and only 7.6% of OHCA patients are eventually discharged based on a recent meta-analysis.[5] Higher mortality has remained mostly static during the past 3 decades, and 60% of individuals with OHCA who are discharged, have an unfavorable neurological outcome.[6]

The most common cause of OHCA with return of spontaneous circulation (ROSC) is acute coronary syndrome (ACS),[3] particularly in patients who survive to 30 days with favorable neurological function.[6] According to recent guidelines for care after cardiac arrest,[7] emergency percutaneous coronary intervention (PCI) is required if acute coronary occlusion occurs, and may improve clinical outcomes in resuscitated patients with ACS. Scientific advances are needed to improve the survival rate after OHCA, and the accurate and early prognostication of poor clinical outcome in resuscitated patients after OHCA is of growing importance in avoiding ineffective treatment and in providing realistic expectations for relatives.

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Heart rate (HR) is a simple, easily accessible, and useful cardiovascular parameter. Additionally, a significant association has been reported between increased HR at hospital arrival and higher mortality in patients with cardiovascular disease (CVD), especially ACS.[8–11] Nevertheless, the impact of HR after resuscitation on clinical outcome is not well known in the case of OHCA with ACS.

Thus, the aim of the present study was to investigate whether the clinical importance of increased HR was also

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Table 1. Patient Characteristics

Characteristics	Non-tachycardia (n=83)	Tachycardia (n=71)	P-value
Male	72 (86.7)	59 (83.1)	0.65
Age (years)	61.4±10.8	67.5±11.5	0.002
Comorbidities			
Hypertension	42 (50.6)	37 (52.1)	0.87
Diabetes mellitus	20 (24.1)	19 (26.8)	0.99
Dyslipidemia	33 (39.8)	23 (32.4)	0.40
Hemodialysis	1 (1.2)	4 (5.6)	0.18
Prior PCI	16 (19.3)	15 (21.1)	0.84
Initial rhythm VT/VF	65 (78.3)	53 (74.6)	0.70
Witnessed OHCA	77 (92.8)	59 (83.1)	0.08
Bystander CPR	75 (90.4)	55 (77.5)	0.04
Time to ROSC (min)	22.3±24.3	31.8±20.1	0.02
EMS response time (min)	6.7±3.1	8.3±3.8	0.02
Hospital arrival time (min)	35.2±11.6	33.2±7.7	0.33
Prehospital ROSC	64 (77.1)	42 (59.2)	0.02
Epinephrine use	33 (39.8)	42 (59.2)	0.02
Epinephrine dose (mg)	2.39±4.44	2.89±3.92	0.51
Door-balloon time (h)	1.53±0.48	1.60±0.63	0.44
STEMI (≥2 mm)	48 (57.8)	42 (59.2)	0.99
NSTEMI	35 (42.2)	29 (40.8)	0.99
Physical examination			
Normal light reflex	48 (57.8)	18 (25.3)	<0.001
Spontaneous breathing	44 (53.0)	26 (36.6)	0.05
Body temperature (°C)	35.9±0.9	35.8±0.9	0.40
SBP (mmHg)	119.5±41.4	127.4±45.2	0.39

Data given as mean±SD or n (%). CPR, cardiopulmonary resuscitation; EMS, emergency medical services; NSTEMI, non-ST elevation myocardial infarction; OHCA, out-of-hospital cardiac arrest; PCI, percutaneous coronary intervention; ROSC, return of spontaneous circulation; SBP, systolic blood pressure; STEMI, ST-elevation myocardial infarction; VF, ventricular fibrillation; VT, ventricular tachycardia.

true for predicting worse outcome of resuscitation in patients with ACS.

Methods

Subjects

Of 3,687 OHCA patients transported to the tertiary emergency hospital (Toho University Omori Medical Center, Tokyo, Japan) between October 2002 and October 2014, we retrospectively analyzed 154 consecutive patients presenting with OHCA with ACS who were successfully resuscitated and underwent immediate successful PCI with stenting after arrival at hospital. Patients who were <18 years old or who had unsuccessful PCI were excluded.

According to the current guidelines, ST elevation myocardial infarction (STEMI) was defined as an ST elevation ≥0.1 mV in 2 contiguous standard leads or ≥0.2 mV in precordial leads on post-resuscitation electrocardiogram (ECG).[12,13] Patients without STEMI but with elevated cardiac enzymes, both creatine phosphokinase-MB and troponin-I, were diagnosed as having non-STEMI (NSTEMI).

Study Design

Patients were divided into the non-tachycardia group and the tachycardia group according to HR on 12-lead ECG after resuscitation in the emergency room. All ECG were recorded at hospital arrival before any drug treatment apart from epinephrine for resuscitation. Tachycardia was defined as >100 beats/min. When patients had arrhythmia such as atrial fibrillation or atrioventricular block, the mean of the HR during the ECG recording was taken as the HR. This study was approved by the ethics committee of Toho University Omori Medical Center (no. M19030).

Endpoints

In the present study, the primary endpoint was defined as 1-year all-cause mortality. We also analyzed neurological outcome as evaluated on cerebral performance category (CPC) score at discharge as the secondary endpoint. A good neurological outcome was defined as CPC score 1 (normal) or 2 (mild or moderate impairment). A poor neurological outcome was defined as CPC score 3 (severe neurological disability and dependency), 4 (coma or vegetative state), or 5 (death).[14]

Data Collection

The data before arrival at hospital were collected from the emergency medical technician reports. These included whether the cardiac arrest was witnessed, details of bystander-delivered cardiopulmonary resuscitation (CPR), the initial observed rhythm based on ECG monitoring, time to ROSC and whether pre-hospital ROSC occurred, and the dose of epinephrine given. All data after arrival at hospital were also collected from the hospital charts. These included the patient's history, characteristics, vital signs,

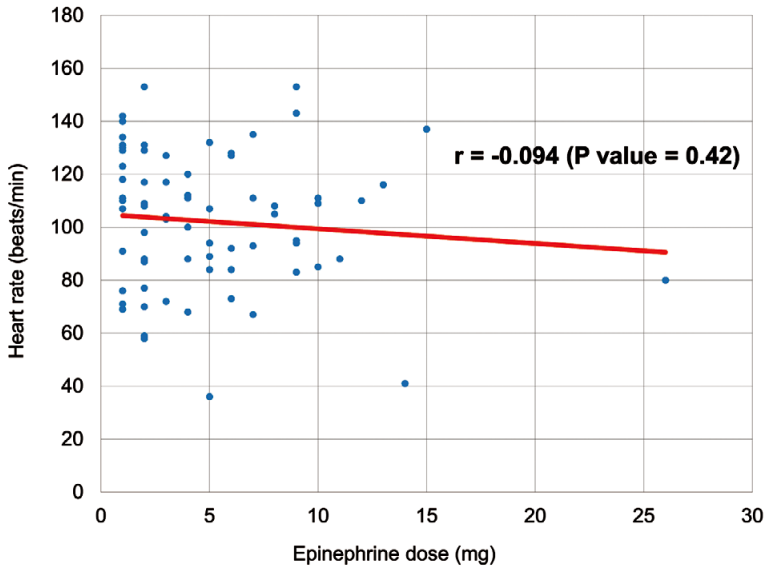

Figure 1. Correlation between heart rate and epinephrine dose in patients who received epinephrine before return of spontaneous circulation (n=75). r, correlation coefficient.

laboratory data, ECG, ultrasound cardiogram (UCG), invasive coronary angiography (ICA), treatment, and clinical outcome.

Statistical Analysis

The characteristics of the 2 groups (non-tachycardia and tachycardia) are described as n (%) for categorical variables, and as mean±SD for continuous variables. Variables were analyzed using Fisher's exact test, chi-squared test, or Mann-Whitney test. The association between HR after resuscitation and 1-year mortality was analyzed using Kaplan-Meier plots and log-rank test. In addition, to identify the independent predictors of endpoints (1-year mortality and neurological outcome at discharge), multivariate Cox proportional hazards and logistic regression analysis models were used after adjusting for demographics (age and gender) and HR >100 beats/min (model 1). Multivariate analysis models were also used to assess whether HR >100 beats/min in addition to demographics was associated with increased 1-year all-cause mortality and poor neurological outcomes after adjusting for other multiple factors found to be strong predictors in patients with OHCA, such as incident-related characteristics (bystander-delivered CPR, initial rhythm ventricular tachycardia/ventricular fibrillation [VT/VF] and time to ROSC; model 2) and epinephrine dose (model 3).[3,15,16] Furthermore, we analyzed additional models to evaluate statistical independency of HR from other important cardiovascular predictors in patients with ACS, such as left ventricular ejection fraction (model 4-1), systolic blood pressure at hospital arrival (model 4-2), maximum creatine kinase (model 4-3), and number of vessel disease (model 4-4).[17–19] In a subanalysis of epinephrine use during resuscitation, 1-year all-cause mortality was compared between the non-tachycardia and tachycardia groups on Kaplan-Meier analysis.

All statistical tests were 2-tailed, and the significance level was set at 5%. All analyses were performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria).

Results

Patient Characteristics

Mean HR for the non-tachycardia and tachycardia groups was 76.6 beats/min and 118.0 beats/min, respectively (P<0.001). Mean time to record HR on 12-lead ECG after ROSC was 19.5±11.3 min.

Table 1 lists the baseline patient characteristics between the non-tachycardia and tachycardia groups. Overall, mean age was 64.2 years, 85.1% of the patients were male, and 119 patients (77.3%) were resuscitated from a shockable rhythm, that is, VT or VF. Although the tachycardia group was older compared with the non-tachycardia group, clinical risk factors such as hypertension, diabetes mellitus, dyslipidemia, hemodialysis, and a history of PCI were not significantly different between the 2 groups. Compared with the non-tachycardia group, the tachycardia group had a longer time to ROSC and a higher frequency of epinephrine use. Nevertheless, the total dose of epinephrine prior to resuscitation was not significantly different between the 2 groups. In the analysis of patients with epinephrine use before ROSC, there was no correlation between HR after resuscitation and epinephrine dose (**Figure 1**; r=−0.094, P=0.42).

With regard to physical examination, patients without tachycardia had a 2-fold higher prevalence of normal light reflex at arrival compared with those presenting with tachycardia. Other characteristics were not significantly different between the 2 groups.

Examination Data

Examination findings and treatment information after hospital arrival are listed in **Table 2**. In each group, approximately three-quarters of the patients had sinus rhythm after resuscitation (P=0.99).

Patients in the tachycardia group had significantly higher lactate compared with the non-tachycardia group. Renal function, hemoglobin, and maximum creatinine kinase were not significantly different between the 2 groups. Other parameters including UCG and ICA also did not differ

Table 2. Examination Parameters and Treatment After Hospital Arrival

	Non-tachycardia (n=83)	Tachycardia (n=71)	P-value
ECG parameters			
HR (beats/min)	76.6±14.3	118.0±15.6	<0.001
Wide QRS (≥120 ms)	20 (24.1)	13 (18.3)	0.43
Arrhythmia			
Sinus rhythm	63 (75.9)	54 (76.1)	0.99
AF	15 (18.1)	16 (22.5)	0.55
CAVB	4 (4.8)	0 (0)	0.13
CLBBB	4 (4.8)	2 (2.8)	0.69
Laboratory parameters			
pH	7.21±0.19	7.29±0.19	0.46
Lactate (mmol/L)	8.64±5.29	10.97±4.60	0.02
Na (mEq/L)	138.6±4.2	138.3±4.0	0.69
K (mEq/L)	4.18±0.86	4.27±0.84	0.57
Ca (mEq/L)	9.15±0.58	9.01±0.65	0.20
BUN (mg/dL)	20.0±13.6	22.5±19.0	0.39
Cr (mg/dL)	1.34±1.75	1.69±2.12	0.32
eGFR (mL/min/1.73 m^2)	67.1±26.3	66.9±35.4	0.96
Hb (g/dL)	13.7±2.0	14.1±1.9	0.53
Max. CK (IU/L)	4,489±5,357	5,065±6,314	0.58
BNP (pg/mL)	227.7±346.8	365.6±541.8	0.11
UCG parameters			
LVEF (%)	47.1±18.7	41.6±16.8	0.09
LVDd (mm)	5.18±1.15	5.14±0.96	0.85
LVDs (mm)	3.79±1.19	3.87±1.01	0.73
ICA culprit lesion			
LMT	6 (7.2)	4 (5.6)	0.75
RCA	30 (36.1)	19 (26.8)	0.23
LAD	36 (43.4)	36 (50.7)	0.42
LCX	11 (13.3)	12 (16.9)	0.65
No. vessel disease			
1	34 (41.0)	31 (43.7)	0.75
2	26 (31.3)	17 (23.9)	0.37
3	23 (27.7)	23 (32.4)	0.60
Treatment			
Administration			
Dopamine	68 (81.9)	56 (78.9)	0.69
Dobutamine	33 (39.7)	29 (40.8)	0.99
Norepinephrine	58 (69.9)	59 (83.1)	0.06
PDE-3 inhibitor	1 (1.2)	2 (2.8)	0.60
Amiodarone	36 (40.9)	29 (40.8)	0.87
Nifekalant	2 (2.4)	1 (1.4)	0.99
Lidocaine	25 (30.1)	24 (33.8)	0.73
Nicorandil	56 (67.5)	45 (63.4)	0.61
Carperitide	9 (10.8)	2 (2.8)	0.07
Ventilator	82 (98.8)	66 (93.0)	0.10
IABP	58 (71.1)	52 (73.2)	0.72
PCPS	23 (27.7)	21 (29.6)	0.86
Hypothermia therapy	52 (62.6)	42 (59.2)	0.74

Data given as mean±SD or n (%). AF, atrial fibrillation; BNP, brain natriuretic peptide; BUN, blood urea nitrogen; CAVB, complete atrioventricular block; CK, creatinine kinase; CLBBB, complete left bundle branch block; Cr, creatinine; ECG, electrocardiogram; eGFR, estimated glomerular filtration rate; Hb, hemoglobin; HR, heart rate; IABP, intra-aortic balloon pumping; ICA, invasive coronary angiography; LAD, left anterior descending artery; LCX, left circumflex artery; LMT, left main trunk; LVDd, left ventricular end-diastolic diameter; LVDs, left ventricular end-systolic diameter; LVEF, left ventricular ejection fraction; PCPS, percutaneous cardiopulmonary support; PDE, phosphodiesterase; RCA, right coronary artery; UCG, ultrasound cardiography.

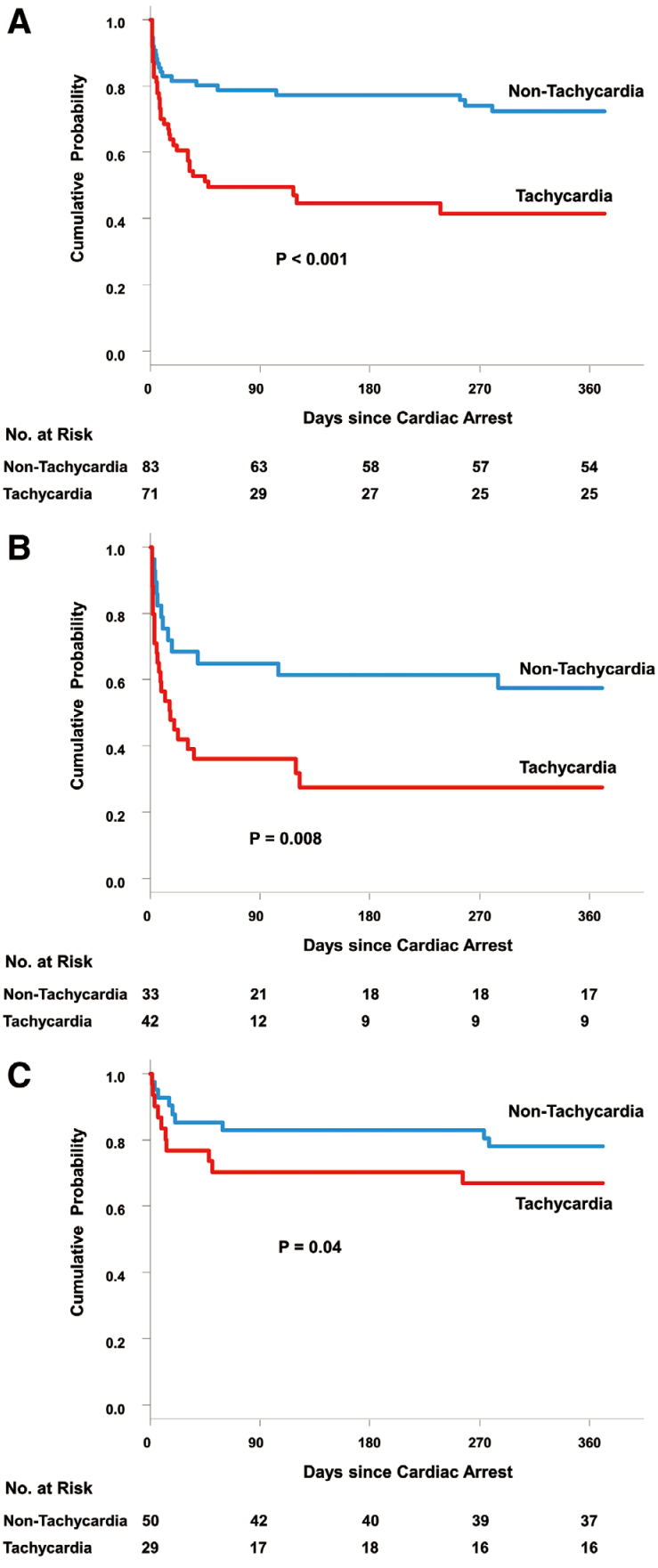

Figure 2. Kaplan-Meier survival curves for (**A**) out-of-hospital cardiac arrest due to acute coronary syndrome (including both in-hospital and after-discharge death), and (**B**) with (n=75) or (**C**) without epinephrine during resuscitation (n=79), according to tachycardia status.

Table 3. Multivariate Indicators of 1-Year All-Cause Mortality and Poor Neurological Outcome at Discharge

Model	All-cause mortality			Poor neurological outcome		
	Hazard ratio (95% CI)	P-value	C-statistics	Odds ratio (95% CI)	P-value	C-statistics
Model 1: HR >100 beats/min +demographics†	2.27 (1.30–3.95)	0.003	0.708	2.48 (1.45–4.18)	0.001	0.730
Model 2: model 1+incident††	2.41 (1.14–5.12)	0.009	0.799	2.09 (1.01–4.32)	0.02	0.815
Model 3: model 2+epinephrine dose	2.26 (1.22–4.19)	0.03	0.810	2.21 (1.19–4.11)	0.03	0.822
Model 4-1: model 3+LVEF	2.66 (1.20–5.85)	0.03	0.832	2.65 (1.27–5.55)	0.04	0.823
Model 4-2: model 3+SBP	2.64 (1.16–4.12)	0.03	0.822	2.12 (1.07–4.43)	0.02	0.831
Model 4-3: model 3+max. CK	2.28 (1.04–5.00)	0.04	0.830	2.44 (1.13–4.89)	0.03	0.832
Model 4-4: model 3+no. vessel disease†††	2.31 (1.23–4.35)	0.03	0.827	2.40 (1.36–4.66)	0.03	0.828

†Age, gender; ††incident-related characteristics (bystander-delivered CPR, initial rhythm VT/VF, time to ROSC); †††vessel disease: ≥75% stenosis on emergency coronary angiography. Abbreviations as in Tables 1,2.

between the 2 groups.

With regard to treatment after admission, all 154 patients were treated with catecholamine drugs, although there were no significant differences in individual catecholamine drugs between the 2 groups. The proportion of patients receiving additional treatment, such as other drugs, ventilator support, intra-aortic balloon pumping (IABP), percutaneous cardiopulmonary support (PCPS), and hypothermia therapy, was not significantly different between the groups.

Clinical Outcomes

The number of patients who had died at 1 year after OHCA was 41/71 (57.7%) in the tachycardia group and 23/83 (27.7%) in the non-tachycardia group (P<0.001). On Kaplan-Meier analysis the tachycardia group had a higher 1-year all-cause mortality than the non-tachycardia group (**Figure 2A**).

Of the 154 patients in this study, the number of patients with poor neurological outcome (CPC score 3–5) at discharge was 68 (44.1%): CPC score 3, 13 patients (8.4%); CPC score 4, 5 patients (3.2%); and CPC score 5, 50 patients (32.5%). The proportion of these patients with poor neurological outcome at discharge in the tachycardia and non-tachycardia groups was 44/71 (62.0%) and 24/83 (28.9%), respectively (P<0.001).

Absolute HR and HR >100 beats/min were the independent predictors of both endpoints (1-year all-cause mortality and poor neurological outcome). In adjusted multivariate Cox proportional and logistic regression models with regard to both endpoints, tachycardia was independently associated with a worse 1-year mortality, and with a poor neurological outcome at discharge (**Table 3**).

In terms of the utility of epinephrine during resuscitation, the 1-year all-cause mortality in the tachycardia group was increased compared with the non-tachycardia group, regardless of epinephrine use during resuscitation (73.8% vs. 42.4%, P=0.008 and 34.5% vs. 22.0%, P=0.04 in patients with and without epinephrine, respectively) (**Figure 2B**,**C**). Although a higher incidence of poor neurological outcome at discharge was observed in the tachycardia group compared with the non-tachycardia group regardless of epinephrine use during resuscitation, the difference was significant only for the patients treated with epinephrine (78.6% vs. 33.3%, P<0.001 and 37.9% vs. 26.0%, P=0.32 in patients with and without epinephrine, respectively).

Discussion

In the present study, we have shown that increased HR was strongly associated with both a higher 1-year mortality and a poor neurological outcome at discharge in patients resuscitated from OHCA due to ACS. Although associations between increased HR and poor clinical outcomes after ACS without cardiac arrest have been previously shown,[9,20–23] to our knowledge, this is the first study to suggest the importance of HR as an independent predictor of outcome in patients with ACS regardless of the antecedent cardiac arrest.

HR and the Impaired Autonomic Nervous System

The increase in HR after resuscitation is mainly caused by a stimulated (and not suppressed) sympathetic nervous system that results from hemodynamic instability and impaired vagal nerve function due to severe anoxic brain injury.[24–26] In the current study, the tachycardia group had higher lactate and a lower prevalence of normal light reflex, along with a lower incidence of bystander-delivered CPR and a longer time to ROSC. Furthermore, the early establishment of severe neurological injury that was noted in the tachycardia group might reflect the poor neurological outcomes at discharge, as suggested in the multivariate analysis models.

HR and Cardiac Function

Compared with non-cardiac causes, survivors of OHCA due to ACS frequently have severe cardiac injury and dysfunction, and thus cardiac reperfusion after resuscitation has a particular role in improving clinical outcomes.[7] Increased HR after resuscitation, however, leads to insufficient coronary blood flow due to a reduction in diastolic time and higher oxygen consumption because of excessive cardiac work.[27,28] Furthermore, inappropriate tachycardia leads to low cardiac output, despite high cardiac oxygen demand, which is directly associated with more myocardial damage and multiple organ failure.[27,28] Thus, increased HR might be directly associated with poor clinical outcome, as observed in the current study.

In spite of previous evidence from individuals with CVD, HR is conventionally judged to be less important than other physical or examination findings as a predictor or an intervention point in the setting of post-cardiac arrest syndrome (PCAS).[7,29] Given, however, that HR independently pre-

dicted clinical outcome even after resuscitation was taken into account, tachycardia may have particular importance as a marker or a therapeutic target for PCAS accompanied by ACS.

Increased HR and Epinephrine

Although a higher dose of epinephrine may cause increased HR after resuscitation because of its β-adrenergic effects, there is no clear evidence for a relationship between usage or dose of epinephrine and increased HR after ROSC. In the present study, the use of epinephrine was more commonly observed in the tachycardia group, but it is unknown whether epinephrine use affected HR because this group also had a longer time to CPR, which may have also affected HR. Increased HR after resuscitation is mainly caused by hemodynamic instability and cerebral injury, not by use or dose of epinephrine.[24–26] These earlier findings support our observation that tachycardia was an independent predictor of mortality and neurological outcome after adjusting for epinephrine dose. Furthermore, no correlation was shown between HR after resuscitation and epinephrine dose. On subanalysis, the effect of HR on clinical outcome was similar regardless of the status of epinephrine during resuscitation. Of interest, 1-year all-cause mortality was different between the tachycardia and non-tachycardia group but the difference was smaller in patients treated without epinephrine during resuscitation compared with those treated with epinephrine during resuscitation. This suggests that HR could be a more reliable and better prognostic marker in patients with poor general condition after ROSC such as those treated with epinephrine during resuscitation. Based on the present study, epinephrine usage or dose may have a lower impact on HR during or after resuscitation than the general or cerebral conditions after ROSC.

Study Limitations

There were several limitations in the present study. First, this was a retrospective observational study, and thus a causal relationship between tachycardia after resuscitation and increased mortality cannot be proven. Furthermore, this was a single-center study, and the number of enrolled patients was small. Additional studies are needed to confirm the present findings. Given the nature of the current study, >30% of the total patients had in-hospital death. In this regard, we were not able to investigate the impact of oral medication after PCI on clinical outcomes due to the limited number of patients who were successfully discharged but eventually died at 1 year (n=14). The relationship between oral medication and outcome in patients who are successfully discharged and rehabilitated needs to be investigated in the future. Although we collected the data by following a uniform procedure, we cannot exclude the possibility of other uncontrolled confounders. In particular, the time to ROSC was recorded based on the description of any witnesses. The actual onset time of OHCA for patients without a witness was not available. Furthermore, data on previous β-blocker therapy and Killip class at hospital arrival, which may affect HR and mortality after resuscitation, were not available for all patients. Finally, we analyzed HR after resuscitation based on that captured on ECG in the emergency room. Associations between HR during PCI or after patient admission were not evaluated.

Conclusions

HR after resuscitation was independently associated with 1-year all-cause mortality and neurological outcomes in patients with OHCA due to ACS. Despite successful resuscitation and PCI, increased HR after ROSC predicted poor clinical outcome.

Disclosures

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References

1. Zheng ZJ, Croft JB, Giles WH, Mensah GA. Sudden cardiac death in the United States, 1989 to 1998. *Circulation* 2001; **104:** 2158–2163.
2. Demirovic J, Myerburg RJ. Epidemiology of sudden coronary death: An overview. *Prog Cardiovasc Dis* 1994; **37:** 39–48.
3. Myat A, Song KJ, Rea T. Out-of-hospital cardiac arrest: Current concepts. *Lancet* 2018; **391:** 970–979.
4. Berdowski J, Berg RA, Tijssen JG, Koster RW. Global incidences of out-of-hospital cardiac arrest and survival rates: Systematic review of 67 prospective studies. *Resuscitation* 2010; **81:** 1479–1487.
5. Sasson C, Rogers MA, Dahl J, Kellermann AL. Predictors of survival from out-of-hospital cardiac arrest: A systematic review and meta-analysis. *Circ Cardiovasc Qual Outcomes* 2010; **3:** 63–81.
6. Nagao K, Nonogi H, Yonemoto N, Gaieski DF, Ito N, Takayama M, et al. Duration of prehospital resuscitation efforts after out-of-hospital cardiac arrest. *Circulation* 2016; **133:** 1386–1396.
7. Callaway CW, Donnino MW, Fink EL, Geocadin RG, Golan E, Kern KB, et al. Part 8: Post-cardiac arrest care: 2015 American Heart Association guidelines update for cardiopulmonary resuscitation and emergency cardiovascular care. *Circulation* 2015; **132:** S465–S482.
8. Fox K, Borer JS, Camm AJ, Danchin N, Ferrari R, Lopez Sendon JL, et al. Resting heart rate in cardiovascular disease. *J Am Coll Cardiol* 2007; **50:** 823–830.
9. Eagle KA, Lim MJ, Dabbous OH, Pieper KS, Goldberg RJ, Van de Werf F, et al. A validated prediction model for all forms of acute coronary syndrome: Estimating the risk of 6-month postdischarge death in an international registry. *JAMA* 2004; **291:** 2727–2733.
10. Addala S, Grines CL, Dixon SR, Stone GW, Boura JA, Ochoa AB, et al. Predicting mortality in patients with ST-elevation myocardial infarction treated with primary percutaneous coronary intervention (PAMI risk score). *Am J Cardiol* 2004; **93:** 629–632.
11. Morrow DA, Antman EM, Charlesworth A, Cairns R, Murphy SA, de Lemos JA, et al. TIMI risk score for ST-elevation myocardial infarction: A convenient, bedside, clinical score for risk assessment at presentation: An intravenous nPA for treatment of infarcting myocardium early II trial substudy. *Circulation* 2000; **102:** 2031–2037.
12. O'Gara PT, Kushner FG, Ascheim DD, Casey DE Jr, Chung MK, de Lemos JA, et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: Executive summary: A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines: Developed in collaboration with the American College of Emergency Physicians and Society for Cardiovascular Angiography and Interventions. *Catheter Cardiovasc Interv* 2013; **82:** E1–E27.
13. Task Force on the management of ST-segment elevation acute myocardial infarction of the European Society of Cardiology (ESC), Steg PG, James SK, Atar D, Badano LP, Blomstrom-Lundqvist C, Borger MA, et al. ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. *Eur Heart J* 2012; **33:** 2569–2619.
14. Jennett B, Bond M. Assessment of outcome after severe brain damage. *Lancet* 1975; **1:** 480–484.
15. Dumas F, Bougouin W, Geri G, Lamhaut L, Bougle A, Daviaud F, et al. Is epinephrine during cardiac arrest associated with

worse outcomes in resuscitated patients? *J Am Coll Cardiol* 2014; **64:** 2360–2367.
16. Kragholm K, Wissenberg M, Mortensen RN, Hansen SM, Malta Hansen C, Thorsteinsson K, et al. Bystander efforts and 1-year outcomes in out-of-hospital cardiac arrest. *N Engl J Med* 2017; **376:** 1737–1747.
17. Fox KA, Dabbous OH, Goldberg RJ, Pieper KS, Eagle KA, Van de Werf F, et al. Prediction of risk of death and myocardial infarction in the six months after presentation with acute coronary syndrome: Prospective multinational observational study (GRACE). *BMJ* 2006; **333:** 1091.
18. Burns RJ, Gibbons RJ, Yi Q, Roberts RS, Miller TD, Schaer GL, et al. The relationships of left ventricular ejection fraction, end-systolic volume index and infarct size to six-month mortality after hospital discharge following myocardial infarction treated by thrombolysis. *J Am Coll Cardiol* 2002; **39:** 30–36.
19. Sorajja P, Gersh BJ, Cox DA, McLaughlin MG, Zimetbaum P, Costantini C, et al. Impact of multivessel disease on reperfusion success and clinical outcomes in patients undergoing primary percutaneous coronary intervention for acute myocardial infarction. *Eur Heart J* 2007; **28:** 1709–1716.
20. Noman A, Balasubramaniam K, Das R, Ang D, Kunadian V, Ivanauskiene T, et al. Admission heart rate predicts mortality following primary percutaneous coronary intervention for ST-elevation myocardial infarction: An observational study. *Cardiovasc Ther* 2013; **31:** 363–369.
21. Kovar D, Cannon CP, Bentley JH, Charlesworth A, Rogers WJ. Does initial and delayed heart rate predict mortality in patients with acute coronary syndromes? *Clin Cardiol* 2004; **27:** 80–86.
22. Perne A, Schmidt FP, Hochadel M, Giannitsis E, Darius H, Maier LS, et al. Admission heart rate in relation to presentation and prognosis in patients with acute myocardial infarction: Treatment regimens in German chest pain units. *Herz* 2016; **41:** 233–240.
23. Wang SL, Wang CL, Wang PL, Xu H, Du JP, Zhang DW, et al. Resting heart rate associates with one-year risk of major adverse cardiovascular events in patients with acute coronary syndrome after percutaneous coronary intervention. *Exp Biol Med (Maywood)* 2016; **241:** 478–484.
24. Prengel AW, Lindner KH, Ensinger H, Grunert A. Plasma catecholamine concentrations after successful resuscitation in patients. *Crit Care Med* 1992; **20:** 609–614.
25. Lambert G, Naredi S, Eden E, Rydenhag B, Friberg P. Sympathetic nervous activation following subarachnoid hemorrhage: Influence of intravenous clonidine. *Acta Anaesthesiol Scand* 2002; **46:** 160–165.
26. Mendelowitz D. Advances in parasympathetic control of heart rate and cardiac function. *News Physiol Sci* 1999; **14:** 155–161.
27. Lang CC, Gupta S, Kalra P, Keavney B, Menown I, Morley C, et al. Elevated heart rate and cardiovascular outcomes in patients with coronary artery disease: Clinical evidence and pathophysiological mechanisms. *Atherosclerosis* 2010; **212:** 1–8.
28. Caetano J, Delgado Alves J. Heart rate and cardiovascular protection. *Eur J Intern Med* 2015; **26:** 217–222.
29. Hassager C, Nagao K, Hildick-Smith D. Out-of-hospital cardiac arrest: In-hospital intervention strategies. *Lancet* 2018; **391:** 989–998.