Relative Bradycardia in Scrub Typhus

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Abstract. To investigate the relationship between heart rate and temperature, we examined 493 febrile patients with documented disease. These patients were diagnosed serologically and analyzed retrospectively: 337 (68.4%) responded to fever with increased heart rate < 10 beats/minute/°C (relative bradycardia [RB]), and 156 patients had a heart rate response ≥ 10 beats/minute/°C (general heart rate increase [GHRI]). The RB group had a higher median resting heart rate and lower heart rate at maximum temperature than the GHRI group. Despite differences in heart rate response, no significant differences were seen in clinical outcomes (acute kidney injury, systemic inflammatory response syndrome [SIRS], and death). We concluded that most patients with scrub typhus presented with RB. In scrub typhus infection, RB can be included as one of the clinical features for differential diagnosis from other infectious diseases.

Scrub typhus is a mite-borne infectious disease caused by *Orientia tsutsugamushi*. The disease occurs 7–10 days after the bite of an infected mite.¹ Variable clinical manifestations and complications related to scrub typhus have been reported. Because the pathogenesis of scrub typhus is increased vascular permeability and perivasculitis of small blood vessels, variable cardiac complications can be caused by damage to cardiac tissue.² Arrhythmia is one of the reported cardiac complications and includes nonsymptomatic electrocardiographic changes and serious arrhythmias such as ventricular tachycardia and Torsades de pointes, as well.^{3–5}

Relative bradycardia (RB) is an inappropriately low heart rate response to every 1-degree rise in body temperature that occurs in scrub typhus cases.⁶ Cases of sinus node dysfunction and conduction disorder with atrioventricular block have been reported.^{3,7} RB in patients with scrub typhus has been mentioned in the literature. Deshmukh et al.⁸ reported that pulse rate in patients with scrub typhus tends to be low in the early stages of disease. In a study from 1946, pulse rate was reported as labile, sometimes varying as low-to-normal pulse increases.⁹ In a previous report, RB was found in up to 40% of cases without a specific definition, and no details were given.¹⁰ To investigate the relationship between heart rate and temperature in patients with scrub typhus, we examined 493 febrile patients with documented scrub typhus.

We conducted a retrospective electric medical records' review of 493 patients, serologically diagnosed with scrub typhus from September 2000 to February 2010 in a tertiary care referral hospital. Excluded were patients treated with any kinds of heart rate lowering agents or having febrile illnesses other than scrub typhus. The study protocol was reviewed and approved by the institutional review board (IRB) of Chonbuk National University Hospital (IRB Number; CUH 2016-08-002).

Body temperature and heart rate were collected on presentation, during treatment, and after symptom resolution. Fever was defined as temperature greater than 37.8°C. Febrile heart rate and temperature were reviewed on initial patient evaluation, before application of antibiotic treatment. Baseline

temperature and heart rate were assessed when patients had become afebrile after treatment. Although no uniform definition of RB exists, we defined it a priori as an increase in the heart rate from a baseline of less than 10 beats/minute/°C increase in temperature.⁶ Patients exhibiting a pulse increase greater than 10 beats/minute/°C were classified as without having RB (GHRI).

A positive diagnosis of scrub typhus was defined as a passive hemagglutination assay (PHA) titer against *O. tsutsugamushi* of 1:80 in a single serum sample or a 4-fold or greater increase in titer at follow-up.¹¹ PHA was performed at the NeoDIN Medical Institute in Seoul, Korea, using Genedia Tsutsu PHA II test kits for qualitative and quantitative detection of antibodies against *O. tsutsugamushi* in human serum. Sheep erythrocytes sensitized to Karp and Gilliam strains of *O. tsutsugamushi*, including the Boryong strain found in Korea, were used with the test kits.¹²

For continuous variables, comparisons between two groups were made using Student's *t* test. Fischer's exact test was used to evaluate categorical variables. All continuous variables are described as means ± SD. Significant differences between two estimated correlation coefficients were tested based on *z* scores using Fisher's *z* transformation. All analyses were two tailed, with clinical significance defined as *P* < 0.05. All statistical processing was calculated using SPSS-PC 18.0 (Statistical Package for the Social Sciences, SPSS-PC, Inc., Chicago, IL).

The general relationship between heart rate and increased temperature was assessed in 493 patients with scrub typhus: 337 (68.4%) responded to fever with a heart rate increase < 10 beats/minute/°C (RB) and 156 patients had a heart rate response ≥ 10 beats/minute/°C (GHRI). Baseline characteristics of the two groups are in Table 1. No significant differences were seen in baseline characteristics, clinical manifestations, and laboratory findings between the two groups. The average heart rate response for the entire febrile scrub typhus patients was 6.31 ± 11.35 beats/minute/°C.

Basal temperatures were not significantly different between the two groups. Maximum temperature was significantly higher in the RB group than the GHRI group (Table 2). The RB group had a higher median resting heart rate than the GHRI group (RB group versus GHRI group, 80.2 ± 11.5 versus 77.2 ± 10.7 beats/minute; *P* = 0.006). The RB group had a significantly lower heart rate than the GHRI group at maximum

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TABLE 1
Characteristics of 493 patients with scrub typhus

	RB (N = 337)	GHRI (N = 156)	P value
Age (years)	64.9 ± 12.3	64.4 ± 12.8	0.658
Gender (male)	138 (41.1%)	63 (40.4%)	0.922
Underlying diseases			
Diabetes	63 (18.8%)	30 (19.4%)	0.606
Hypertension	91 (27.0%)	52 (33.3%)	0.121
Chronic kidney disease	3 (0.9%)	6 (3.8%)	0.066
Chronic lung disease	21 (6.3%)	12 (7.8%)	0.561
Clinical manifestations			
Fever	307 (91.1%)	135 (86.5%)	0.122
Chills	307 (91.1%)	136 (87.2%)	0.180
Headache	148 (43.9%)	73 (46.8%)	0.550
Myalgia	230 (68.2%)	110 (70.5%)	0.613
Arthritis	12 (3.6%)	9 (5.8%)	0.259
Cough	111 (32.9%)	51 (32.7%)	0.957
Dyspnea	86 (25.5%)	52 (33.3%)	0.072
Nausea/Vomiting	114 (33.8%)	46 (29.5%)	0.338
Abdominal pain	96 (28.5%)	42 (26.9%)	0.719
Skin rash	207 (61.4%)	89 (57.1%)	0.357
Eschar	210 (62.3%)	94 (60.3%)	0.662
Lymphadenopathy	25 (7.4%)	9 (5.8%)	0.502
Conjunctivitis	17 (5.0%)	15 (9.6%)	0.055
Laboratory findings			
WBC	9,484.9 ± 5,122.2	9,552.0 ± 4,542.6	0.889
Hemoglobin	11.9 ± 1.9	12.0 ± 1.8	0.502
Hematocrit	34.6 ± 6.4	34.6 ± 5.1	0.981
Platelet	151.9 ± 93.9 K	147.8 ± 86.0 K	0.642
AST	138.5 ± 354.7	104.4 ± 77.2	0.242
ALT	104.1 ± 182.9	87.9 ± 87.2	0.298
Total bilirubin	1.3 ± 3.7	1.1 ± 1.0	0.525
Albumin	3.3 ± 0.5	3.4 ± 1.8	0.382
PT (sec)	13.3 ± 7.6	13.7 ± 8.5	0.666
Outcomes			
Acute kidney injury	62 (18.4%)	32 (20.5%)	0.564
Death	20 (6.1%)	8 (5.2%)	0.136

ALT = alanine aminotransferase; AST = aspartate aminotransferase; GHRI = general heart rate increase; PT = prothrombin time; RB = relative bradycardia; SIRS = systemic inflammatory response syndrome; WBC = white blood cell. No significant differences were seen in baseline clinical characteristics and clinical outcomes between the two groups.

temperature (RB group versus GHRI group, 84.6 ± 12.5 versus 100.1 ± 17.3 beats/minute, $P < 0.001$). Δ Heart rate/ Δ temperature (Heart rate on maximal temperature – heart rate on baseline / maximal temperature – baseline temperature) showed the opposite effect between the two groups during fever (RB group versus GHRI group, 1.17 ± 8.15 versus 17.89 ± 8.65 , $P < 0.001$) (Figure 1). Despite differences in the heart rate response between RB and GHRI patients, no significant differences were seen in clinical outcomes (acute kidney injury $P = 0.564$, SIRS $P = 0.523$, death $P = 0.136$) between the two groups (Table 1).

This study showed the prevalence of RB in patients with scrub typhus was 68.4%. This rate was higher than previous reports. Aronoff et al.⁶ reported the prevalence of 53% and Fang et al.¹⁰ of 40%. This large study determined the

prevalence of and the implications for the disease course in scrub typhus.

RB is a poorly defined clinical term that is often used in the literature and in daily practice as a clinical sign for an individual patient or a characteristic feature of some diseases. The term has been defined in several studies.^{13–15}

RB is an important diagnostic finding for variety of infectious diseases including typhoid fever, Legionnaires' disease, psittacosis, typhus, leptospirosis, malaria, and babesiosis.¹⁵ RB may be used to differentiate among infectious diseases in specific clinical situations. Because the prevalence of RB in patients with scrub typhus was up to 70% in our study, it could also be used as a diagnostic feature to differentiate among conditions.

In our study, basal heart rate was higher in the RB group than the GHRI group. However, the maximal heart rate was

TABLE 2
Alternation of body temperature and heart rate

	RB (N = 337)	GHRI (N = 156)	P value
Basal temperature (°C)	36.4 ± 0.3	36.4 ± 0.3	0.522
Maximal temperature (°C)	38.1 ± 0.9	37.8 ± 0.8	< 0.001
Basal heart rate	80.2 ± 11.5	77.2 ± 10.7	0.006
Heart rate at maximal temperature	84.6 ± 12.5	100.1 ± 17.3	< 0.001
Δ Heart rate/ Δ temperature*	1.17 ± 8.15	17.89 ± 8.65	< 0.001

GHRI = general heart rate increase; RB = relative bradycardia. Basal temperatures were not significantly different between the two groups. The RB group had a higher median resting heart rate and lower heart rate at maximal temperature than the NRB group.

* Δ Heart rate/ Δ temperature: heart rate on maximal temperature – heart rate on baseline/maximal temperature – baseline temperature.

FIGURE 1. Distribution of $\Delta\text{heart rate}/\Delta\text{temperature}$ by group. $\Delta\text{Heart rate}/\Delta\text{temperature}$ showed the opposite effect between the two groups during fever.

higher in the GHRI group than the RB group. In other words, the $\Delta\text{heart rate}/\Delta\text{temperature}$ was higher in the GHRI group than the RB group (Figure 1). These were unusual findings for patients with scrub typhus compared with other RB-presenting diseases. This finding was consistent with previous reports for RB in scrub typhus.⁶

The RB did not seem to affect clinical outcomes in this study. This result might suggest that RB caused by *O. tsutsugamushi* does not mean critical heart involvement. The pathogenesis of RB in patients with scrub typhus has not been proven. Future works could determine the pathogenesis.

In conclusion, most patients with scrub typhus are associated with RB, not related to clinical outcome. RB in scrub typhus can be considered as one of the clinical features for differential diagnosis from other infectious diseases.

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