ORIGINAL ARTICLES

Heart Rate, Responsiveness to Intravenous Immunoglobulin, and Coronary Artery Aneurysms in Kawasaki Disease

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Objective To evaluate whether heart rate (HR) was associated with intravenous immunoglobulin (IVIG) responsiveness or development of coronary artery lesions (CALs) in patients with Kawasaki disease.

Study design We conducted a retrospective cohort study using data from in patients with Kawasaki disease who were hospitalized in our institution from 2006 to 2016. The patients were divided into 5 groups according to the age- and temperature-adjusted HR z score ($HRZ_{age/temp}$) just before IVIG administration. The ORs of outcomes were estimated by using logistic regression models, with the middle group set as the reference.

Results Of the 322 patients, a total of 98 patients (30%) were refractory to initial IVIG treatment. The patients whose $HRZ_{age/temp}$ belonged to the lowest group were at the highest risk of being refractory to the initial IVIG treatment (OR 2.10 [95% CI 1.01-4.37]). Multivariable analyses showed the same trend, though this was not statistically significant. The patients with the highest $HRZ_{age/temp}$ were most likely to develop CALs (OR 2.61 [95%CI 0.86-7.92]).

Conclusions In patients with Kawasaki disease , HRs has a different relationship with IVIG responsiveness and CALs. Low $HRZ_{age/temp}$ might be associated with high risk of being refractory to the initial IVIG treatment, while the risk of developing CALs increased among those whose HRs were high. Further studies are necessary to investigate the mechanisms regarding HR and these outcomes in Kawasaki disease . *(J Pediatr 2018;■■:■■-■■).*

Kawasaki disease is an acute febrile illness in childhood characterized by bilateral conjunctivitis, redness of the lips and oral mucosa, cervical lymphadenopathy, rash, and change in the extremities. High-dose intravenous immunoglobulin (IVIG) has been established as the first-line treatment for patients with Kawasaki disease in the acute phase for its effectiveness in reducing the inflammation and the occurrence of coronary artery lesions (CALs).[1-3] However, 10%-20% of patients are refractory to the initial IVIG treatment.[4-6] These patients tend to have fever for longer periods and are considered to be at high risk of presenting with CALs.[4-6] Therefore, the prediction of unresponsiveness to the initial IVIG and treatment stratification has emerged as an important issue in this era.

Several studies on clinical prediction rules for IVIG responsiveness have been published; Kobayashi et al developed a prediction rule for responsiveness to the initial IVIG treatment, which was validated and showed high discriminative ability.[7] Egami et al reported a good discrimination of nonresponders among patients with Kawasaki disease treated with IVIG using this model.[8] Other studies described the potential for stratifying patients with Kawasaki disease to provide more aggressive treatments to those who are likely to be resistant to IVIG treatment.[9,10] The published prediction models are based on patients' age, the clinical day of IVIG treatment, and laboratory findings, such as platelet count, C-reactive protein, or liver enzymes.

Heart rate (HR) is a simple approach to assessing the status of pediatric patients. HR is a principal component of various diagnostic criteria such as systemic inflammatory response syndrome,[11] clinical tools such as triage systems in emergency department,[12,13] or early warning systems for hospitalized patients.[14,15] Although HR has been widely shown to be a useful predictor in pediatric care, its utility in patients with Kawasaki disease has not been clarified so far. The principal aim of this study was to elucidate the association between HR and responsiveness to the initial IVIG treatment in Kawasaki disease. We also investigated its association with the development of CALs.

AST	Aspartate aminotransferase
CRP	C-reactive protein
PLT	Platelet
CALs	Coronary artery lesions
HR	Heart rate
$HRZ_{age/temp}$	Age- and temperature-adjusted HR z score
IVIG	Intravenous immunoglobulin
% Neutrophil	Percentage of neutrophils

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Methods

This study was a retrospective cohort study that used the clinical records of patients with Kawasaki disease who were hospitalized in Kobe City Medical Center General Hospital from April 2006 to March 2016. Patients who were diagnosed with Kawasaki disease in the acute phase and treated with IVIG (2g/kg) were included in this study.

According to the *Diagnostic Guidelines for Kawasaki Disease (5th revision)*,[16] patients are diagnosed with typical Kawasaki disease if they have a fever and at least 4 of the 5 principal features (change in extremities, polymorphous exanthema, conjunctival injection, changes in lips and oral cavity, cervical lymphadenopathy), or if they have a fever and 3 principal features with coronary artery abnormalities detected. In this study, we also included patients with Kawasaki disease who had a fever and 3 principal features without coronary artery abnormalities ("incomplete Kawasaki disease") unless other diseases mimicking Kawasaki disease were verified by laboratory findings because inclusion of incomplete Kawasaki disease was considered clinically relevant. Patients were excluded if the initial IVIG treatment had already started before admission to our hospital, if treatments except for aspirin or other antiplatelet drugs were given together with the initial IVIG treatment, or if data pertaining to vital signs were missing. For recurrent patients with Kawasaki disease, only the data for the first hospitalization were included.

The study protocol was approved by the Ethics Committee of Kyoto University, Graduate School and Faculty of Medicine (R0538) and Kobe City Medical Center General Hospital (no.160604).

Because the number of sampling points for vital signs varied from patient to patient, we used the data before IVIG was started. HRs were extracted from electrocardiogram for monitoring, and axillary temperatures were recorded. Using the formula that Daymont et al reported (the calculation table was obtained from the author through personal communication),[17] Heart rate was adjusted for age and body temperature, and given as a z core (age- and temperature-adjusted HR z score [$HRZ_{age/temp}$]).

The primary outcome of this study was responsiveness to the initial IVIG treatment. Patients were defined as being responsive to the IVIG treatment or "responders" if the temperature dropped and stayed below 38.0°C within 24 hours after IVIG had ended. The secondary outcome was the presence of CALs including transient dilatation of coronary arteries. Coronary arteries were considered abnormal when examinations by 2-dimensional echocardiography showed that internal lumen diameters were ≥3 mm in patients <5 years old, ≥4 mm in patients ≥5 years old, or >+2.5 SD for patients' body surface area.

The following data were collected just before initial IVIG was started: white blood cell count, percentage of neutrophils (% neutrophil), hematocrit, platelet count (PLT), serum concentrations of C-reactive protein (CRP), serum sodium, aspartate aminotransferase (AST), alanine aminotransferase, total bilirubin, and serum albumin.

Statistical Analyses

Patient characteristics were described by numbers and percentages for the categorical variables, and medians and IQRs for the continuous variables. The distribution of variables was compared by the Welch *t* test or Fisher exact test between patients who showed response to the initial IVIG treatment and those who did not.

According to $HRZ_{age/temp}$, the patients were divided into 5 groups at the quintile points, labeled as group 1 (those with the lowest $HRZ_{age/temp}$) to group 5 (those with the highest $HRZ_{age/temp}$). ORs for the outcomes were calculated using multiple logistic regression models using group 3 as the reference group. We constructed 4 models including different variables from the following candidates: sex, clinical day of the initial IVIG treatment, white blood cell count, % neutrophil, hematocrit, PLT, CRP, sodium, AST, total bilirubin, and albumin. Model 1 contained only $HRZ_{age/temp}$ as the explanatory variable (crude model); model 2 further included clinical day of the initial IVIG treatment, % neutrophil, PLT, CRP, sodium, and AST (these variables were all included in the Kobayashi score[7]); model 3 contained the same variables as model 2 plus total bilirubin (included in another prediction rule[18]), hematocrit and albumin (these variables might affect intravascular volume status); and model 4 included all the candidate variables above (full model). Because the data for several variables were considerably lacking, we conducted multiple imputations by chained equations for these data.

For sensitivity analyses, we conducted multivariable analyses using the models that included the patients' age as the explanatory variable so that the adjusting method could not remove the dependencies of HR on age. We also performed sensitivity analyses using only the data of typical patients with Kawasaki disease, or the data from those without any missing data.

Wald tests were used to obtain *P* values. All reported *P* values were 2-tailed, and *P* values of less than .05 were considered statistically significant. R (v 3.4.2, R Development Core Team, Vienna, Austria) was used for all analyses.[19]

Results

During the study period, a total of 501 patients with Kawasaki disease were hospitalized. Of the 501 patients, 107 patients were excluded; 48 patients were likely to have other diseases mimicking Kawasaki disease; 21 patients were not in the acute phase; 16 patients repeatedly suffered from Kawasaki disease on 2 occasions or more (only the first hospitalization was included in these patients); in 14 patients, essential data were missing; and in 8 patients, the initial IVIG treatments had already started in other institutions. Of the 394 eligible patients, 322 were given IVIG treatment and included in the analyses (**Figure 1**).

Of the 322 patients given the initial IVIG treatment at our institution, 224 patients were defined as responsive to the initial IVIG treatment, and the remaining 98 patients were regarded as nonresponders. **Table I** shows the baseline characteristics of IVIG responders and nonresponders. The median