Analysis of Exercise Capacity of Children with Kawasaki Disease by a Coronary Artery z Score Model (ZSP Version 4) Derived by the Lambda-Mu-Sigma Method

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Objective To compare exercise capacity measured by direct cardiopulmonary exercise testing (CPET) of children with Kawasaki disease with different coronary artery diameter z scores (CA z score).

Study design This was a retrospective study that recruited children with Kawasaki disease after the acute stage receiving CPETs determined by CPET with treadmill. CA z score was based on a model using the Lambda-Mu-Sigma method. Max-Z was defined as the maximum z score of the proximal left anterior descending CA (LCA) or right CA (RCA). Children with Kawasaki disease with a Max z <2.0 and ≥2.0 were defined as Kawasaki disease group 1 and Kawasaki disease group 2, respectively.

Results We recruited 32 boys and 17 girls with a mean age of 12.39 ± 3.61 years. Kawasaki disease group 1 (n = 36) had significantly higher peak metabolic equivalent (peak-MET) and peak rate pressure product (PRPP) than Kawasaki disease group 2 (n-13) ($P = .046$, $P < .001$). Max-Z correlated with peak-MET moderately and negatively ($P < .001$, Spearman rho= - .506). Max-Z correlated with PRPP modestly and negatively ($P = .011$, Spearman rho= - .360).

Conclusions Children after Kawasaki disease with a coronary artery Max-Z ≥ 2.0 had significantly lower peak exercise capacity than those with a Max-Z < 2.0. Max-Z might be used as an indicator of CA reserve and exercise capacity during peak exercise after the acute stage of Kawasaki disease. *(J Pediatr 2018;■■:■■-■■).*

Children with Kawasaki disease may develop coronary artery (CA) aneurysms (CAAs) or CA ectasia.[1] The z score describes how many SDs above or below the mean size or age-specific population mean a given measurement lies.[2] Most CA z scores define the CAA to be small if the CA z score is ≥2.5 to <5.0, large if the CA z score is ≥5.0 to <10.0, and giant if the CA z score is ≥10.0.[3,4] Lin et al evaluated 412 healthy children across Taiwan and established reference ranges for CA diameter in Taiwanese children younger than 6 years of age.[2] However, there is no available norm of CA for children older than 6 years of age among the Chinese population. Kobayashi et al established a novel Lambda-Mu-Sigma model with which to estimate the sex-specific z score of each internal CA diameter (measured by ZSP v 4 calculator, Tohru Kobayashi, Tokyo, Japan) after collecting data in 3851 healthy Japanese children aged from 0 months to 18.9 years old.[5]

Rate-pressure product is defined by heart rate multiplied by systolic blood pressure. It is a reliable indicator of myocardial oxygen demand. Peak rate-pressure product (PRPP) reflects the myocardial oxygen demand and myocardial workload during exercise.[6] A low PRPP suggests compromise of coronary perfusion and decreased left ventricular function.[7,8]

Previous studies proved that even though there was no evidence of a CA lesion, children with Kawasaki disease had lower myocardial flow reserve and higher total coronary resistance compared with their normal peers.[9-11] In this study, we evaluated

AT	Anaerobic threshold
AT MET	Metabolic equivalent at anaerobic threshold
CA	Coronary artery
CAA	Coronary artery aneurysm
CPET	Cardiopulmonary exercise testing
FEV1	Forced expiratory volume in 1 second
FVC	Forced vital capacity
LCA	Left anterior descending CA
Max-Z	Largest coronary artery z score of proximal LCA or RCA
METs	Metabolic equivalents
MVV	Maximal voluntary ventilation
PRPP	Peak rate-pressure product
RCA	Right CA
RER	Respiratory exchange ratio
VE	Minute ventilation
VCO_2	Carbon dioxide production
VO_2	Oxygen consumption

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if children with Kawasaki disease with a largest CA z score of proximal left anterior descending artery (LCA) or right coronary artery (RCA) (Max-Z) ≥2.0, measured by the ZSP v 4 calculator, have lower cardiopulmonary performance than those with a Max-Z <2.0. We also evaluated if the CA z score measured by the ZSP v 4 calculator could be representative of myocardial perfusion of children with Kawasaki disease during exercise.

Methods

This was a retrospective cohort study. The data were collected at 1 medical center in southern Taiwan. We recruited children aged 5-18 years referred to the pediatric cardiology outpatient clinic from October 2012 to October 2017 for regular follow-up of Kawasaki disease, with the following additional inclusion criteria: subjects who underwent a complete transthoracic echocardiographic examination, standard 12-lead electrocardiogram, and symptom-limited treadmill exercise test. Exclusion criteria were patients after Kawasaki disease with the presence of significant structural heart disease, moderate to severe cardiac valvular disease, significant arrhythmia ventricular hypertrophy, and concurrent known pulmonary disease. Basic patient characteristics including sex, age, body weight, height, and body fat were recorded. This study was approved by the institutional review board of Kaohsiung Veterans General Hospital (number: VGHKS17-CT11-11).

Before treadmill exercise testing, each subject was familiarized with both the procedures and equipment used in exercise testing. The purpose of the testing was explained to subjects and their families before informed consent was obtained (verbal consent from subjects and written consent from families). We used symptom-limited exercise testing, which was composed of a treadmill, a flow module, a gas analyzer, and an electrocardiographic monitor (Metamax 3B; Cortex Biophysik GmbH Co, Leipzig, Germany), to measure exercise capacity. All children with Kawasaki disease underwent exercise testing according to the ramped Bruce protocol suggested by the American College of Sports Medicine. We terminated the test when children demonstrated subjective symptoms, when they could no longer continue, or when they attained maximal effort as indicated by the American College of Sports Medicine.[12] The oxygen consumption (VO_2) and carbon dioxide production (VCO_2) were measured by the breath-by-breath method during the testing. In addition, minute ventilation (VE), blood pressure, heart rate, and respiratory exchange ratio (RER) were measured throughout the exercise test. The measured VO_2 was divided by a constant 3.5 $mL \cdot kg^{-1} \cdot min^{-1}$ to derive metabolic equivalents (METs). The anaerobic threshold (AT) was determined by the VE/VO_2 and VE/VCO_2 methods.[13]

A pulmonary function test was performed by spirometry at rest. Forced vital capacity (FVC), forced expiratory volume in 1 second (FEV1), and maximal voluntary ventilation (MVV) were measured. We divided the measured FVC into predicted FVC, measured FEV1 by predicted FEV1, and measured MVV by predicted MVV. The predicted value of each spirometry measure was calculated based on spirometric reference equations for healthy children in Taiwan.[14]

All patients with Kawasaki disease were examined in the supine or right decubitus position using a sector probe with more than a 5-MHz frequency and underwent complete 2-dimensional echocardiographic studies with both color flow and spectral Doppler examinations. Echocardiographic studies were performed using standard measurement methods for pediatric CA recommended by the Japanese Society of Kawasaki Disease. The focus depth was set to the CA being measured, and the frame rate was increased to raise the time resolution. The intraluminal diameters of CA segments were measured from inner edge to inner edge. The RCA and LCA were measured 3-5 mm distal to their origins in the parasternal short-axis view.[15] Routinely examined cardiac structures such as valves, left atrial diameter, left ventricular diameter, aortic root diameter, end-diastolic and end-systolic left ventricular internal diameter were also measured according to the guidelines and standards for performing pediatric echocardiograms by the American Society of Echocardiography.[16]

The CA z score was computed by the ZSP v 4 calculator after entering sex-specific data on age, body height, body weight, body surface area using the Haycock formula,[17] and diameter of CA measured by echocardiography.[5] The largest CA z score of the proximal LCA or RCA was defined as Max-Z. Children with Kawasaki disease with a Max-Z < 2.0 and ≥ 2.0 were defined as Kawasaki disease group 1 and Kawasaki disease group 2, respectively.

We used SPSS for Windows v 19.0 released 2010 (IBM Corp Armonk, New York) for all analyses. Data were expressed as the mean ± SD. A Mann-Whitney U test (for continuous variables) or χ^2 test (for categorical variables) was used to compare demographic characteristics, exercise capacity, pulmonary function, and echocardiographic findings between Kawasaki disease group 1 and Kawasaki disease group 2. Spearman correlation analysis was used to determine the associations between exercise capacity and measurable echocardiographic variables (including the CA z score). A P value of ≤.05 was considered statistically significant.

Results

Of the 53 patients who met the inclusion criteria, 2 patients had moderate valvular disease, 1 patient had significant cardiac structural problems, and 1 patient had significant arrhythmia. Therefore, 49 children with Kawasaki disease were entered into the study. Among all the final recruited subjects, there were 36 (73.47%) patients in Kawasaki disease group 1 and 13 (26.53%) patients in Kawasaki disease group 2.

The mean ages of all patients with Kawasaki disease, patients in Kawasaki disease group 1, and patients in Kawasaki disease group 2 were 12.39 ± 3.61, 11.97 ± 3.42, and 13.54 ± 4.01 years old, respectively (**Table I**). There were no statistically significant differences in sex, age, weight, height, body mass index, body fat, systolic blood pressure and diastolic blood pressure, resting heart rate, and routine spirometry measures (in-

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