# 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 $\chi^2$ 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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**Table I. Demographic characteristics of patients with Kawasaki disease**

| | Kawasaki disease total (n = 49) | Kawasaki disease group 1 (n = 36) | Kawasaki disease group 2 (n = 13) | *P* value* |
|---|---|---|---|---|
| Sex (male female) | 32:17 | 25:11 | 7:6 | .31 |
| Age (y) | 12.39 ± 3.61 | 11.97 ± 3.42 | 13.54 ± 4.01 | .18 |
| Height (cm) | 151.17 ± 18.20 | 150.72 ± 17.97 | 152.45 ± 19.52 | .77 |
| Weight (kg) | 46.62 ± 16.87 | 46.04 ± 14.86 | 48.25 ± 22.16 | .69 |
| BMI (kg/m$^2$) | 19.44 ± 4.07 | 19.09 ± 3.60 | 19.33 ± 8.58 | .32 |
| Body fat (%) | 17.48 ± 7.40 | 16.75 ± 6.89 | 20.42 ± 5.20 | .29 |
| Resting SBP (mm Hg) | 113.47 ± 13.47 | 115.53 ± 11.80 | 107.77 ± 16.47 | .08 |
| Resting DBP (mm Hg) | 68.12 ± 9.06 | 67.75 ± 8.12 | 69.15 ± 11.61 | .64 |
| Resting heart rate (bpm) | 82.10 ± 13.66 | 81.36 ± 13.58 | 84.15 ± 14.21 | .53 |
| FVC (L) | 2.57 ± 1.02 | 2.36 ± .84 | 3.09 ± 1.25 | .11 |
| Predicted FVC (%) | 96.20 ± 19.96 | 95.06 ± 20.23 | 98.73 ± 20.17 | .64 |
| FEV1 (L) | 2.34 ± .97 | 2.12 ± 0.78 | 2.87 ± 1.21 | .10 |
| Predicted FEV1 (%) | 100.36 ± 25.04 | 98.16 ± 25.31 | 105.19 ± 25.04 | .47 |
| FEV1/FVC (%) | 90.44 ± 7.24 | 89.86 ± 7.26 | 91.84 ± 7.39 | .48 |
| MVV (L) | 64.26 ± 29.38 | 58.77 ± 24.98 | 77.45 ± 36.02 | .09 |
| Predicted MVV (%) | 91.69 ± 40.64 | 92.17 ± 42.20 | 90.10 ± 38.10 | .91 |

*BMI*, body mass index; *DBP*, diastolic blood pressure; *SBP*, systolic blood pressure.
Data are the mean ± SD.
*Refers to the *P* value of a Mann-Whitney U test (continuous variables) or $\chi^2$ test (categorical variables) between Kawasaki disease group 1 and Kawasaki disease group 2.

cluding FVC, predicted FVC, FEV1, predicted FEV1, MVV, and predicted MVV) between Kawasaki disease group 1 and Kawasaki disease group 2.

**Table II** presents the echocardiographic findings of all recruited patients with Kawasaki disease, Kawasaki disease group 1, and Kawasaki disease group 2. The proximal RCA z score, proximal LCA z score, and Max-Z of all recruited subjects were 1.18 ± 1.13, 1.45 ± .79, and 1.67 ± .90, respectively. In Kawasaki disease group 1, the proximal RCA z score, proximal LCA z score, and Max-Z were .75 ± .72, 1.16 ± .49, and 1.30 ± .44, respectively. Patients in Kawasaki disease group 2 had a proximal RCA z score of 2.39 ± 1.21 of, a proximal LCA z score of 2.24 ± .92, and a Max-Z of 2.69 ± 1.05. Other echocardiographic findings, including end-diastolic left ventricular internal diameter, end-systolic left ventricular internal diameter, left ventricular shortening fraction, diameter of left atrial, and diameter of the aortic root showed no statistically significant differences between Kawasaki disease group 1 and Kawasaki disease group 2.

**Table III** shows the performance of the exercise test of all recruited patients with Kawasaki disease, Kawasaki disease group 1, and Kawasaki disease group 2, respectively. The peak RER of all patients was 1.17 ± .09 and 6 children (12.24%) had a peak RER less than 1.1. When compared with Kawasaki disease group 2, Kawasaki disease group 1 had a significantly higher peak MET (10.67 ± 1.55 vs 9.55 ± 2.08, $P = .046$), peak RER (1.19 ± .09 vs 1.11 ± .07, $P = .005$), peak systolic blood pressure (170.83 ± 31.37 mm Hg vs 140.38 ± 17.16, $P < .001$), and PRPP (30687.81 ± 5746.33 vs 24439.38 ± 3502.05, $P < .001$). Other measures, including MET at the point of AT (AT MET), heart rate at the point of AT, peak diastolic blood pressure, and heart rate reserve at 1 minute after termination of the test, showed no statistically significant differences between Kawasaki disease group 1 and Kawasaki disease group 2.

**Table IV** demonstrates the correlations between variables of exercise capacity (PRPP, AT MET, and peak MET) and echocardiographic variables (diameter of proximal RCA and LCA, and Max-Z by the ZSP v 4 calculator). There was a

**Table II. Echocardiographic findings of children with Kawasaki disease**

| | Kawasaki disease total (n = 49) | Kawasaki disease group 1 (n = 36) | Kawasaki disease group 2 (n = 13) | *P* value* |
|---|---|---|---|---|
| LVIDd (cm) | 4.00 ± .77 | 4.03 ± .69 | 3.92 ± .97 | .69 |
| LVIDs (cm) | 2.33 ± .45 | 2.36 ± .41 | 2.24 ± .54 | .44 |
| LV shortening fraction (%)† | 41.53 ± 6.13 | 41.22 ± 6.23 | 42.36 ± 6.02 | .58 |
| LA (cm) | 2.01 ± .36 | 1.99 ± .32 | 2.07 ± .47 | .49 |
| AO (cm) | 1.79 ± .37 | 1.76 ± .30 | 1.87 ± .52 | .50 |
| RCA diameter (cm) | .29 ± .11 | .26 ± .05 | .38 ± .17 | .019* |
| LCA diameter (cm) | .33 ± .12 | .29 ± .05 | .43 ± .18 | .021* |
| RCA z score‡ | 1.18 ± 1.13 | .75 ± .72 | 2.39 ± 1.21 | < .001* |
| LCA z score‡ | 1.45 ± .79 | 1.16 ± .49 | 2.24 ± .92 | < .001* |
| Max-Z† | 1.67 ± .90 | 1.30 ± .44 | 2.69 ± 1.05 | < .001* |

*AO*, diameter of aortic root; *LA*, diameter of left atrium; *LV*, left ventricular; *LVIDd*, end-diastolic LV internal diameter; *LVIDs*, end-systolic LV internal diameter.
Data are the mean ± SD.
*Refers to the *P* value of a Mann-Whitney U test between Kawasaki disease group 1 and Kawasaki disease group 2.
†LVIDd-LVIDs/ LVIDd,
‡Measured by ZSP v 4 calculator.


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**Table III. Performance of exercise test in all patients with Kawasaki disease, Kawasaki disease group 1, and Kawasaki disease group 2**

| | Kawasaki disease Total (n = 49) | Kawasaki disease group 1 (n = 36) | Kawasaki disease group 2 (n = 13) | *P* value* |
|---|---|---|---|---|
| AT MET | 7.24 ± 1.26 | 7.39 ± 1.21 | 6.82 ± 1.33 | .17 |
| AT heart rate (bpm) | 144.35 ± 12.60 | 144.86 ± 11.73 | 142.92 ± 15.22 | .64 |
| peak MET | 10.37 ± 1.75 | 10.67 ± 1.55 | 9.55 ± 2.08 | .046† |
| peak heart rate (bpm) | 178.27 ± 10.30 | 179.72 ± 8.53 | 174.23 ± 13.70 | .10 |
| peak VE (L) | 45.30 ± 15.42 | 46.78 ± 15.36 | 41.21 ± 15.45 | .27 |
| peak RER | 1.17 ± .09 | 1.19 ± .09 | 1.11 ± .07 | .005† |
| Numbers (%) of peak RER < 1.1 | 6 (12.24%) | 3 (8.34%) | 3 (23.08%) | .17 |
| peak SBP (mmHg) | 162.76 ± 31.22 | 170.83 ± 31.37 | 140.38 ± 17.16 | <.001† |
| peak DBP (mmHg) | 87.14 ± 19.03 | 89.50 ± 19.36 | 80.62 ± 17.12 | .15 |
| PRPP | 29 030.06 ± 5908.65 | 30 687.81 ± 5746.33 | 24 439.38 ± 3502.05 | <.001† |
| Heart rate reserve at 1 min | 26.51 ± 9.24 | 26.62 ± 9.88 | 26.23 ± 7.66 | .90 |

*peak MET*, largest MET during entire exercise testing; *peak PD*, percentage of predicted peak MET; *peak RER*, largest respiratory exchange ratio during entire exercise testing.
Data are the mean ± SD.
*Refers to the *P* value of a Mann-Whitney U test between Kawasaki disease group 1 and Kawasaki disease group 2.
†*P* < .05.

modest-negative association between PRPP and Max-Z significantly (Spearman rho = −.360, *P* = .011). AT MET correlated with the diameter of proximal RCA (Spearman rho = −.410, *P* = .003), the diameter of proximal LCA (Spearman rho = −.494, *P* < .001), and with Max-Z (Spearman rho = −.404, *P* = .004) modest-moderate negatively. Peak MET correlated with the diameter of proximal RCA (Spearman rho = −.345, *P* = .015), the diameter of proximal LCA (Spearman rho = −.563, *P* < .001), and Max-Z (Spearman rho = −.506, *P* < .001) modest-moderate negatively.

## Discussion

Few studies have evaluated exercise performance of patients with Kawasaki disease with different Max-Z. Allen et al found that work rate, heart rate reserve, and $VO_2$ max of patients with Kawasaki disease were within the normal range for healthy children.[18] Rhodes et al showed that patients with Kawasaki disease did not differ significantly from healthy subjects with regard to $VO_2$ max, peak workload, and AT.[19] Our previous study showed similar findings as the previous studies except that the PRPP of patients with Kawasaki disease was significantly lower than that of healthy age- and sex-matched peers.[11]

**Table IV. Correlation between performance of exercise test and echocardiographic findings in children with Kawasaki disease**

| | PRPP | AT MET | Peak MET |
|---|---|---|---|
| Proximal RCA | −.156 | −.410 | −.345 |
| | .286 | .003† | .015* |
| Proximal LCA | −.054 | −.494 | −.563 |
| | .715 | < .001† | < .001† |
| Max-Z ‡ | −.360 | −.404 | −.506 |
| | .011* | .004† | < .001† |

Upper row: Spearman rho, Lower row: *P* value.
*P < .05.
†P < .01.
‡Measured by ZSP v 4 calculator.

Paridon et al evaluated exercise capacity in 3 groups (group 1 with no objective evidence of CAA, group 2 with resolved CAA, and group 3 with persistent CAAs) of children and adolescents after Kawasaki disease by cycle ergometer. They concluded that maximal $VO_2$ is normal after Kawasaki disease regardless of CA status.[20] However, because of to the relatively smaller sample size, no subgroup analysis was done between patients with different CA z scores and healthy controls.

The RER is defined as the ratio of carbon dioxide production and oxygen consumption measured via respiratory gas analysis. If the RER value at the end of the test (peak RER) exceeds 1.0, additional energy is supplied anaerobically to increase $VCO_2$.[21] It is considered the minimal condition to perform sufficient effort during cardiopulmonary exercise testing (CPET) when the peak RER is ≥1.10.[12,22] Most patients in our study had RER ≥1.10. There was no significant difference in numbers of subjects with RER < 1.1 between Kawasaki disease group 1 and Kawasaki disease group 2. This means that most children in our study, in both Kawasaki disease group 1 and Kawasaki disease group 2, could reach the peak exercise testing value. Therefore, it was reasonable to use peak MET and PRPP to analyze the peak exercise capacity of children with Kawasaki disease during CPET.

Children after Kawasaki disease tend to exercise less than their healthy peers. Banks et al determined functional health status and physical activity of Kawasaki disease children by accelerometry and The Physical Activity Questionnaire with the observation that children after Kawasaki disease (11 ± 3 years old) performed less moderate-to-vigorous physical activity than healthy children.[23] Most children after Kawasaki disease could meet maximal effort during exercise (indicated by RER ≥1.10) as observed in this study. Our previous study observed that after the acute stage of Kawasaki disease, children could maintain normal cardiorespiratory fitness except for PRPP.[11] Therefore, we believe it is important to provide health promotion in children after Kawasaki disease and it is reasonable to provide physical activity counseling with no restrictions or precautions in children after Kawasaki disease as suggested by the



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American Heart Association in their guideline for Kawasaki disease management in 2017.[24]

It has been well established that the risk for CA stenosis is intimately associated with both the size and location of CAA.[25] Although the CAA might modify to normal lumen diameter (especially those that are not large), this regression in the size of aneurysms may be accompanied by abnormalities of both vessel wall reactivity and intimal thickness as well as cardiovascular events later in life.[26,27]

Our study found that both the PRPP and peak RER of Kawasaki disease group 1 were significantly higher than those of Kawasaki disease group 2. Because PRPP is an indicator of coronary flow reserve and peak RER is an objective measure to assess the degree of effort during CPET, we could assume that performance might be weaker and coronary perfusion might be compromised during peak exercise in children after Kawasaki disease with Max-Z ≥ 2.0.

The association between Max-Z and exercise capacity in children with Kawasaki disease was similar, regardless of whether the CA z score was defined by the ZSP v 4 calculator, Dallaire equation, or Fuse calculator, suggesting that Max-Z could be consistent in different CA z score models. The database of the Dallaire equation included 841-996 of each proximal CA and did not generate sex-specific models to avoid a decrease in statistical power.[28] On the other hand, the database of the ZSP v 4 calculator included the largest number to date (more than 1700 patients of each sex) and could generate a sex-specific model without loss of statistical power. The ZSP v 4 calculator presented novel z score curves for internal CA diameter by sex using the Lambda-Mu-Sigma method and showed a better fit to the theoretical distribution of z score models compared with the Fuse calculator[4] (which is the predecessor of the ZSP v 4 calculator). Therefore, we still suggest using the ZSP v 4 calculator for the CA z score.

This study must be viewed in light of the following limitations. First, our study was a retrospective analysis. Even though we recruited all 49 subjects and they received treadmill exercise testing within days after completing the transthoracic echocardiographic examination, there was still variation in the timing of the follow-up. Second, no patients with Kawasaki disease in this study received exercise testing in the acute stage. To appreciate the full extent of CA diameter variation (eg, regression of CA dilatation after the acute stage for other reasons such as discrepancies between coronary arterial growth and somatic growth) along with time,[10] our results might not apply to children with Kawasaki disease in the acute stage. Third, the relatively small numbers limited our ability to perform multivariate analyses or to test the discrimination of z scores reliably. In addition, we only recruited subjects in 1 medical center in southern Taiwan. A larger cross-national study is needed for further evaluation. Fourth, there might be some variations when measuring CA diameter. Last, even though normally distributed reference ranges for CA diameters in Taiwanese children younger than 6 years of age have been established, we still lack a well-accepted equation for the CA z score for Taiwanese children older than 6 years of age. The ZSP v 4 calculator we chose is based on data from multiple centers across Japan. The Max-Z by the ZSP v 4 calculator cannot fully reflect the true CA condition of Chinese children with Kawasaki disease.

Because children after Kawasaki disease with Max-Z ≥ 2.0 could maintain sufficient but lower exercise fitness than those with Max-Z < 2 after the acute stage, we believe that it is important to promote cardiovascular health. However, because they might still have compromised coronary perfusion during peak exercise, it remains crucial to both assess and monitor the cardiovascular risk of children after Kawasaki disease with Max-Z ≥ 2.0. ■

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