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The incidence of arrhythmias during exercise stress tests among children with Kawasaki disease: A single-center case series

Varun Aggarwal MD[1,2] | Kristen Sexson-Tejtal MD[1] | Wilson Lam MD[1] | Santiago O. Valdes MD[1] | Caridad M. de la Uz MD[1] | Jeffrey J. Kim MD[1] | Christina Y. Miyake MD, MS[1]

[1]The Lillie Frank Abercrombie Section of Cardiology, Department of Pediatric Cardiology, Texas Children's Hospital and Baylor College of Medicine, Houston, Texas

[2]Department of Pediatrics, Division of Pediatric Cardiology, Masonic Children's Hospital, University of Minnesota, Minneapolis, Minnesota

Correspondence
Christina Y. Miyake, The Lillie Frank Abercrombie Section of Cardiology, Department of Pediatric Cardiology, Texas Children's Hospital, 6651 Main St, Legacy Tower, Suite# E1960.22, Houston, TX 77030, USA.
Email: cymiyake@bcm.edu

Abstract

Objective: Based on 2017 guidelines, participation in competitive sports with prior history of Kawasaki Disease (KD) requires those with coronary artery aneurysms (CAA) z score ≥ 5 to undergo evaluation for evidence of inducible ischemia or arrhythmias. The use of exercise stress testing (EST) to evaluate arrhythmias among KD patients has never been reported. This retrospective single-center case series study sought to describe the presence of inducible arrhythmias during EST in KD patients with or without CAA.

Methods: Single-center retrospective review of medical records of patients diagnosed with KD between 1989-2015 at Texas Children's Hospital, Houston, Texas who underwent EST were included.

Results: Among 1007 patients diagnosed with KD, 95 (9%) underwent 165 ESTs at a median time of 9.6 years (IQR 5.8-11.3 years) from diagnosis. Of these 95 patients, 37 had normal coronaries, 21 dilated (z score 2 to <2.5), 10 small (5 >z ≥2.5), 12 medium (10>z ≥ 5 absolute dimension <8 mm), 10 large (z ≥10 or absolute dimension ≥8 mm), 5 severe (myocardial infarct or bypass graft). Supraventricular tachycardia was not seen. Ventricular arrhythmias during EST were uncommon and seen only among patients with CAA z ≥5. Ventricular tachycardia occurred in a single patient with a large CAA, known VT and ICD. High-grade ventricular ectopy was seen in one patient who had severe CAA and underwent bypass grafting.

Conclusions: Arrhythmias on EST were noted only among patients with CAA z ≥5. The current guidelines are a reasonable approach to increasing healthy activity among KD patients. Clarification regarding which inducible arrhythmias meet criteria for activity restriction may be helpful to guide sport participation.

KEYWORDS
aneurysm, arrhythmia, coronary artery, exercise stress test, Kawasaki disease, sports participation

1 | INTRODUCTION

Kawaski Disease (KD) is a systemic vasculitis of unclear etiology that can result in development of CAA and long-term complications.[1] While ischemic heart disease is the major cause of death in KD, patients can develop arrhythmias[2] ,and sudden death has been reported in 0.8% within 4.4 ± 1.6 years[3] after the onset of KD. The impact of CAA and coronary artery disease on the development of arrhythmias in KD is unknown. Encouraging exercise could have significant benefit among KD patients, reducing the burden of obesity, lipid imbalance, and further worsening of coronary artery disease in these children.[4] However, the risk of arrhythmias during competitive or high-intensity sports has not been evaluated.

Based on recently published 2017 guidelines[5], competitive or high-intensity sports participation in KD is now guided by evaluation for inducible ischemia or arrhythmias among patients who develop CAA with a z score ≥5 during their course. Those whose aneurysm remained less than a z score of 5 are allowed to participate without restriction. The modality to evaluate inducible arrhythmias is not clarified; however, use of EST to evaluate arrhythmia inducibility among susceptible patients is not uncommon prior to competitive sports participation. The incidence of inducible arrhythmias during EST among KD patients with and without coronary artery involvement has not been previously reported. The purpose of this study was to describe the presence of arrhythmias during EST among KD patients who underwent EST at our institution and the potential impact of these results on sports participation based on recently published guidelines[5].

2 | METHODS

We performed a retrospective review of all children seen and followed with a diagnosis of KD at Texas Children's Hospital, Houston, Texas between February 1989 and December 2015. All patients who underwent EST with or without stress perfusion imaging (PI) were included. Exclusion criteria included: presence of significant structural heart disease, known cardiomyopathy or heritable arrhythmia disorder, moderate-severe cardiac valvular disease or any concurrent pulmonary or neurological disease. Medical records of these patients were reviewed from the electronic medical record. Baseline characteristics including age, sex, body weight, height, date of KD onset, initial presentation, and treatment received for acute KD was noted.

All KD patients undergo complete 2-dimensional echocardiographic studies with color flow and spectral Doppler examination using a standard institutional protocol. The intraluminal diameter of coronary artery segments is measured from inner edge to inner edge. The right coronary artery and left anterior descending coronary artery are measured 3-5 mm distal to their origins in the parasternal short-axis view.[6] The coronary artery z scores are computed in our laboratory using the Dallaire equation[7] and Fuse Z-scoring calculator.[8] Maximum z score of a coronary artery was defined as the maximal z score of the proximal left or right coronary artery measured by echocardiography. The echocardiographic reports, computed tomography (CT) scan, and magnetic resonance imaging (MRI) data (when available) was reviewed to evaluate the extent of coronary involvement in these patients. Patients were sub-classified according to their maximum coronary artery involvement prior to the EST as normal coronaries (no coronary involvement) , coronary artery dilation only (z score 2 to <2.5), small aneurysms (z score ≥2.5 to <5), medium aneurysms (z score ≥5 to <10 and absolute dimension <8 mm), large aneurysms (z score ≥10 or absolute dimension ≥8 mm)[5]. In addition, patients with history of myocardial infarct or bypass graft prior to the EST were classified as severe coronary artery disease.

All electrocardiograms (ECG) and 24-hour Holter monitoring data was reviewed from the electronic record stored in MUSE. They were reviewed independently blinded to other clinical information for any supraventricular tachycardia (≥3 beats) and ventricular arrhythmias including premature ventricular contractions (PVC), ventricular couplets, and ventricular tachycardia (VT). High-grade ventricular ectopy was defined as frequent isolated PVCs (>10/hr on Holter monitor), multiform PVCs, or any ventricular couplets. Ventricular tachycardia was defined as three or more consecutive rapid ventricular beats defined as a minimum rate 20% greater than baseline heart rate (HR).

Exercise stress testing is not deemed mandatory for clinical management in all patients with KD and is ordered at the discretion of the clinician. In addition, EST is not performed if the child cannot run safely while on a treadmill and is rarely performed in our instituation among children under the age of 5 years. Thus, not all patients diagnosed with KD underwent EST at our instituation. Patients who did undergo EST underwent testing on a treadmill using the Bruce protocol. The test was terminated when the children demonstrated subjective unbearable symptoms.[9] The oxygen consumption (VO2) was measured by the breath-by-breath method during the testing. In addition, minute ventilation (VE), BP, HR, and all arrhythmias were measured and recorded throughout the exercise test. All stress testing data is stored in electronic record in MUSE. The data were independently reviewed by a pediatric (CYM) and an adult electrophysiologist (WL) who were blinded to patient clinical history and coronary artery z scores. All ESTs were evaluated for supraventricular tachycardia, high-grade ventricular ectopy or VT.

Stress PI was performed using a treadmill stress with Bruce protocol followed by Single-photon emission computed tomography (SPECT). For SPECT, 14 mCi Tc-99 Cardiolite is administered at peak stress and gated SPECT images were obtained.

Statistical analysis was performed using SPSS for Windows version 19.0 (Released 2010; Armonk, NY: IBM Corp) to provide descriptive statistics including mean, median, and standard deviation. Due to the small numbers in this study and likely confounders regarding which KD patients underwent EST, comparative statistical analysis was not performed. The study was approved by the institutional review board.

3 | RESULTS

A total of 1007 patients were diagnosed and evaluated for KD during the study period. Among these, 95 patients (64 males, 31 females) underwent a total of 165 EST and met the inclusion criteria. Median age at diagnosis of KD was 3.8 (IQR 1.1, 6.4) years. Among these 95 patients, 37 had normal coronaries, 21 dilated (z score 2 to <2.5), 10 small (5 >z ≥2.5), 12 medium (10>z ≥ 5 absolute dimension <8 mm), 10 large (z ≥10 or absolute dimension ≥8 mm), 5 severe (myocardial infarct or bypass graft) (Table 1, Figure 1). Seventy six (80%) were treated with IVIG, 7 with IVIG and steroids, and 2 received no IVIG. In 10 patients, initial treatment regimen after initial diagnosis could not be determined by record review. In the 2 patients who did not receive IVIG, 1 did not have any coronary artery disease on follow-up and the other developed severe CAA ultimately requiring coronary artery bypass grafting.

In addition to echocardiography, additional imaging included CT scans in 7, cardiac MRI in 17, diagnostic cardiac catheterization in 19. Three patients underwent coronary bypass grafts, one patient underwent coronary artery stenting, and one patient underwent placement of an internal cardioverter defibrillator for VT. The median (IQR) time from diagnosis to last follow-up was 5.9 (1.9, 9.6) years. There were no mortalities in this cohort.

There were 54 Holters performed in 18 patients. On these 24-hour Holter evaluations, supraventricular tachycardia was not seen. Two patients (1 severe and 1 large CAA) had frequent premature uniform ventricular complexes (>10/hr), one patient with severe CAA had ventricular couplets, and one patient with severe CAA (and ICD) had nonsustained VT.

The median (IQR) age at first EST was 11.9 (9.4, 14.9) years (Table 1) and occurred at a median (IQR) time of 9.6 (5.8, 11.3) years from diagnosis. Figure 2 depicts the distribution of age at KD diagnosis and age at first EST performed. The EST was limited by fatigue in a majority of the patients. Despite the limitation, adequate HR (>85% maximum predicted) was achieved in 70 (73.7%) patients, including 74% of patients with at least medium CAA. Oxygen consumption (VO2) at peak exercise was measured in 84 patients and IQR was 47.3 (41.5, 59.0) mL/kg/min.

During EST, SVT was not seen (Figure 1). Two patients had ventricular arrhythmias/high grade ventricular ectopy. One patient with large CAA, known history of VT and ICD, demonstrated ventricular couplets and a 3 beat run of polymorphic VT at 150 bpm during recovery. He was the only patient with both regional wall motion abnormalities and ventricular dysfunction on his initial presenting echocardiogram at diagnosis. High-grade ventricular ectopy consistent of increasing ventricular couplets at peak exercise was seen in one patient. This patient had severe coronary disease and was status post bypass graft. Both patients were noted on Holter testing to have these same arrhythmia findings on their EST and Holter monitor. Six patients were noted to have isolated PVCs during mid to peak exercise or in immediate recovery. PVCs were not seen in any of the patients without coronary artery involvement.

SPECT imaging was done in 26 of the 95 patients using Technetium Tc99m sestamibi injection during peak exercise. Four patients had no coronary artery involvement, 4 had dilated coronaries, 5 small aneurysm, 7 moderate aneurysms, 2 large aneurysm, and 4 severe coronary artery disease. Two patients with known infarcts and one patient with past history of large aneurysm had fixed perfusion defects on perfusion imaging. There were no patients with inducible reversible ischemia on EST with PI in our cohort.

TABLE 1 Demographic and clinical characteristics

Characteristic	N = 95
Age at diagnosis (years)	3.8 (1.1, 6.4)
Coronary Artery Aneurysm	
Normal (z score ≤2)	37
Dilated (z score 2 to <2.5)	21
Small (5 >z ≥2.5)	10
Medium (10>z ≥ 5; <8 mm)*	12
Large (z ≥10 or ≥8 mm)*	10
Severe (myocardial infarct or bypass graft)	5
Age at EST (years)	11.9 (9.4, 14.9)
Time since diagnosis at time of EST (years)	9.6 (5.9, 11.3)
EST Arrhythmias (number patients)	
SVT	0
High grade ventricular ectopy	1
VT	1
Holter monitor (number patients)	18
SVT	0
High grade ventricular ectopy	2
VT	1
Males (n, %)	64 (67.4%)
Height (cm)	120.8 (98.8, 142.5)
Weight (kg)	28.8 (15.2, 37.9)
LVEF at time of EST (%)	62 (57.5, 64.5)
Follow up since diagnosis (years)	5.9 (1.9, 9.6)

Note: Data is median (IQR).

Abbreviations: IQR, interquartile range; EST, exercise stress test; cm, centimeters; kg, kilograms; LVEF, left ventricle ejection fraction; VO_2, maximal oxygen consumption.

*Absolute dimension.

4 | DISCUSSION

There is movement toward increasing sports participation for children afflicted with heart conditions.[10] In KD , vasculitis leading to coronary artery involvement can result in both ischemia and arrhythmias.[11] However, restricting KD patients without any clear evidence of risk may have serious negative psychological and physical implications.[12] Recently published 2017 guidelines[5] recommend KD patients with CAA (z-score≥5) undergo surveillance with stress imaging for presence of inducible ischemia or

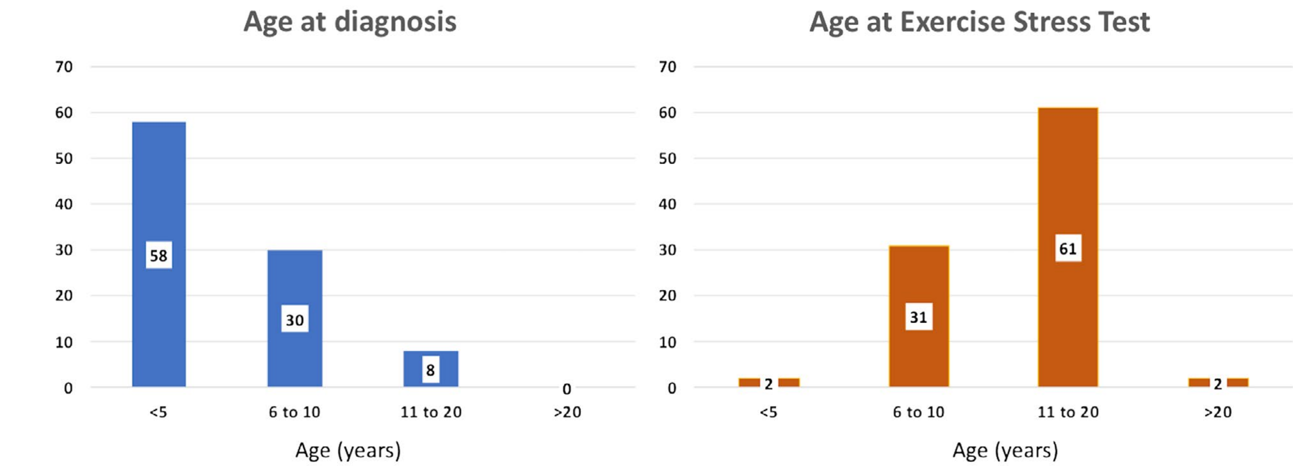

FIGURE 1 Age at diagnosis of KD and the age at first exercise stress test

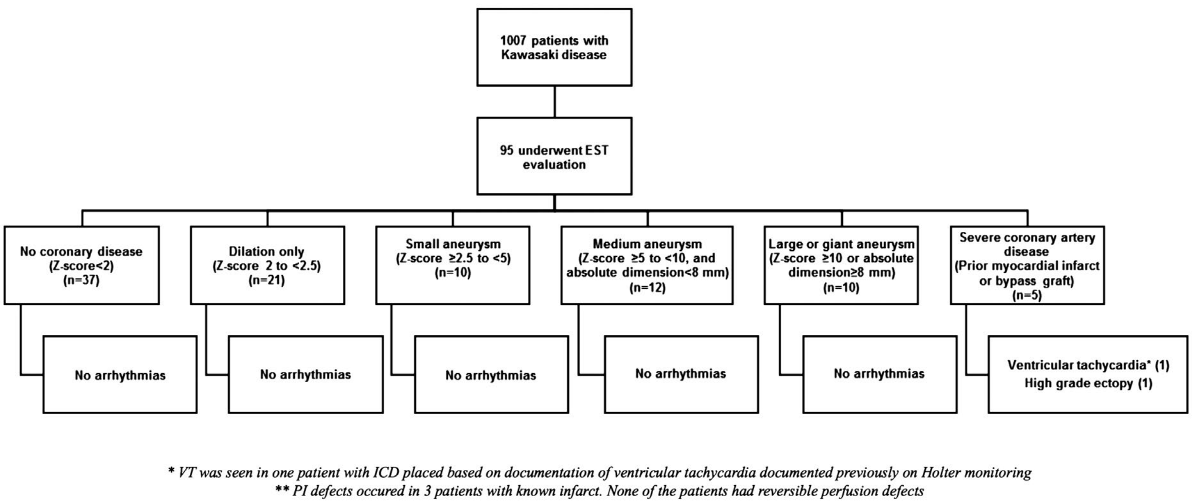

FIGURE 2 Size of coronary artery involvement and arrhythmias during exercise stress testing

evaluation of exercise induced arrhythmias. There has been no data to date regarding inducible arrhythmias during EST in this cohort. We present the largest case series describing the presence of inducible arrhythmias during EST in children with KD who underwent EST.

We also sought to describe how EST results would have affected sports participation in this group of patients based on their EST and the current 2017 guidelines. In our cohort, supraventricular arrhythmias were not seen. Ventricular arrhythmias were seen only among patients with large aneurysms or severe disease necessitating bypass grafting. VT was identified in a single patient with a prior history of VT who had undergone ICD implantation prior to EST who was already sports restricted. All other patients would have been cleared from an arrhythmia standpoint (ie, disregarding anticoagulation status). In this cohort, there was one patient with worsening ventricular couplets at peak exercise without VT. This patient had a prior bypass graft and was already restricted from sports. Therefore, the results from the EST would not have affected sports participation status in any of these patients. In fact, the Holter monitors on both patients with ventricular arrhythmias revealed the same ventricular arrhythmias. In the case of 2 patients (1 severe and 1 large CAA), Holter monitoring revealed frequent isolated PVCs while their EST did not reveal any higher grade ectopy or VT. This raises an important point. What constitutes "inducible arrhythmias" is not clearly defined in the 2017 guidelines[5]. While one might consider inducible SVT or VT as sports limiting, a patient such as ours with worsening ventricular couplets with increasing exertion raises at least some concern about potential risks. Each patient will likely need to be assessed individually; however, further information about potential risk factors based on arrhythmia burden, if any, and guided by larger studies may be useful for evaluating and making final decisions. The guidelines[5] also appear to state that either ischemia or arrhythmia can be assessed, suggesting that both are not required. In a young patient unable to run on a treadmill or bicycle, nonphysiological stress imaging with pharmacological agents may help with that evaluation. However, among older children, pharmacological stress imaging may limit true assessment for physiological stress induced arrhythmias.

Although our cohort did not demonstrate any new arrhythmias with exercise stress testing, clearance of a child who is capable of exercising, and with a history of moderate aneurysms to play competitive sports should warrant consideration of an EST to evaluate exercise induced arrhythmias. Based on an estimated 5523 hospitalizations associated with KD in the United States in 2006 among children <5 years of age,[13] there continues to be a growing population of KD patients being followed over lifetime; thus, these guidelines will have some impact on these children's lives.

The current study has several limitations. This is a retrospective study with potential for the selection bias as only about 10% of the patients with KD followed at our institute underwent EST during the study period. The low numbers are in part due to the fact that EST is not prescribed for young patients who cannot safely run on a treadmill. In addition, EST is not a mandatory part of clinical management. The decision to undergo EST was solely at the discretion of the treating physician. EST at our institution is pursued predominantly among higher risk patients or due to exercise related symptoms including chest pain or palpitations. The limited number of patients tested does not provide a thorough evaluation of our entire KD population. The highest risk patients may not have been evaluated. Among those that did undergo EST, 26% did not reach predicted HR and thus the EST may have underestimated inducible arrhythmias. The median age at EST was 11.9 years at a median time of 9.6 years from diagnosis. The median follow-up of the study population was 5.9 years and it remains to be determined if these patients will have increased cardiovascular events as they age especially as the risk factors for coronary artery disease increase.

In this retrospective cohort of KD patients, incidence of inducible arrhythmias during EST was low. Ventricular arrhythmias were seen only among patients with at least moderate aneurysms. Our data and findings are in agreement with the current published guidelines, however larger studies are warranted and clarification regarding specific arrhythmia criteria for sports restrictions may be helpful.

CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest with the contents of this article.

AUTHOR CONTRIBUTIONS

VA, KST, and CYM were involved with conceptualizing the idea. VA, CYM, and WL performed data acquisition. VA, CYM performed data analysis drafted the manuscript. CYM, KST, WL, SOV, CMU, and JJK helped in drafting and revising the manuscript critically. All authors approve the submitted and final version of the manuscript.

ORCID

Varun Aggarwal https://orcid.org/0000-0002-3699-126X

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