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Research Article

Diastolic Dysfunction is Present by Tissue Doppler in Acute Kawasaki Disease but is Not Predictive of IVIG Responsiveness

Alexander Raskin[1]*, Rohit S Loomba[2] and Edward Kirkpatrick[1]

[1]*Department of Cardiology, Children's Hospital of Wisconsin/Medical College of Wisconsin, Milwaukee, Wisconsin, USA*

[2]*Department of Cardiology, Advocate Children's Hospital, Oak Lawn, Illinois, USA*

***Corresponding Author:** Alexander Raskin, Department of Cardiology, Children's Hospital of Wisconsin/Medical College of Wisconsin, Milwaukee, Wisconsin, USA.

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Abstract

Early recognition of Kawasaki disease and treatment with intravenous immunoglobulin (IVIG) is necessary to help reduce the risk of coronary artery abnormalities, such as coronary artery aneurysms. However, some patients do not respond to an initial dose of IVIG and require additional doses. Prediction of these IVIG non-responders may be of assistance in altering initial therapy to make it more effective. Scoring systems have been developed for the Japanese population to predict patients who may require more than a single administration of IVIG, but they have not been validated in a more heterogeneous U.S. population. This study evaluates echo markers for diastolic function in acute Kawasaki disease, and if these echo parameters can be used to predict IVIG response. A total of 63 patients with acute complete Kawasaki disease were compared to 63 controls. Those with Kawasaki disease demonstrated significantly decreased mitral lateral and septal e' and a' ratios. When IVIG responders and non-responders were compared there were no significant differences identified.

Keywords: *Diastolic Dysfunction; Tissue Doppler; Acute Kawasaki Disease; IVIG Responsiveness*

Introduction

Kawasaki disease the leading cause of acquired pediatric heart disease and one of the most common childhood vasculitides [1,2]. There is limited understanding of the mechanisms and underlying pathophysiology. The characteristics of Kawasaki disease including fever, bilateral nonexudative conjunctivitis, erythema of the oral mucosa and lips, rash, cervical lymphadenopathy, and changes in the extremities have been previously well described and are the basis for the clinical diagnosis [3]. Kawasaki is generally self-limited, but failure to diagnose and treat may lead to long term sequelae. In those who are untreated, coronary artery aneurysms or coronary ectasia develop in 15 to 25% of children, which may lead myocardial infarction or sudden death [4,5]. The current treatment approach includes aspirin and IVIG infusion within the first few days of illness. This has been shown to reduce the risk of developing coronary artery aneurysms [6]. Unfortunately, not all children respond to IVIG treatment as manifest by persistence of fever after completion of IVIG infusion. These children will undergo a second IVIG infusion. Failure to respond to the second round of IVIG poses a management dilemma [7-9].

Previous studies in the Japanese population have focused on clinical scoring systems to predict response to IVIG [10-12]. Those that were predicted to be non-responders were shown to benefit from initial treatment with IVIG and pulse steroids when comparing the development of coronary artery lesions [13]. Unfortunately, these scoring systems failed to be validated in a more heterogeneous U.S. population [14-17].

Aside from laboratory abnormalities and coronary artery changes, acute Kawasaki disease is associated with valvular regurgitation and myocarditis. Studies have previously demonstrated diastolic dysfunction during acute KD by echocardiographic parameters [18,19]. Small scale studies assessing IVIG responsiveness by echocardiographic diastolic function parameters have had mixed results [20,21].

Aim of the Study

The aim of this study was to assess echocardiographic parameters of diastolic function in acute Kawasaki disease in a heterogeneous U.S Midwestern population, and to determine whether these can be used to predict IVIG response.

Methods

We identified patients with typical Kawasaki disease who were cared for at our institution between January 2000 to December 2011. Patients were included in the final analyses if they had diastolic function data obtained via mitral valve tissue Doppler at the time of initial echocardiographic evaluation. Those without tissue Doppler data were not included in the analysis. Age and gender matched control with diastolic function data were also identified and included in the final analysis.

Demographic data collected included age, gender, and race while clinical data included number of days of symptoms and IVIG response. Diastolic function data included mitral valve inflow data regarding the e and a waves as well as tissue Doppler data (e', a', and s' wave) for the lateral and septal mitral valve leaflets.

Results

A total of 182 patients were identified with Kawasaki disease. Patients with incomplete/atypical Kawasaki disease were excluded. A total of 63 patients with complete Kawasaki disease were ultimately included for analysis. Echocardiographic data was obtained for 63 age and gender matched control patients as well. Of those with Kawasaki disease, 17 (27%) were IVIG responders while 46 (73%) were not.

Baseline characteristics were compared between responders and non-responders. There was no significant difference in age, days of illness at diagnosis, race, or coronary artery aneurysms. There was a significantly higher proportion of males in the non-responder group (69% versus 52%, $p = 0.019$).

When compared to controls, those with complete Kawasaki disease demonstrated significantly decreased mitral lateral (2.35 ± 1.21 vs. 3.59 ± 1.30, $p < 0.001$) and septal e' to a' ratios (1.70 ± 0.68 vs. 2.80 ± 0.89, $p < 0.001$). Mitral lateral e' wave was significantly decreased (0.17 ± 0.05 vs. 0.23 ± 0.05 $p < 0.001$). Additionally, mitral inflow A wave was significantly increased (0.59 ± 0.19 vs. 0.50 ± 0.15 $p < 0.027$).

When IVIG responders and non-responders were compared the only significant difference was increased septal e' in IVIG non-responders (0.17 ± 0.02 vs. 0.11 ± 0.02 $p < 0.001$). The remaining values failed to show statistical significance when comparing responders vs. non-responders (Table 1).

	Typical Kawasaki Disease	Control	P-value
Mitral inflow e wave	0.99 ± 0.17	1.02 ± 0.26	0.510
Mitral inflow a wave	0.59 ± 0.19	0.50 ± 0.15	0.027*
Mitral inflow e to a ratio	1.86 ± 0.73	2.06 ± 0.55	0.174
Mitral lateral e' wave	0.17 ± 0.05	0.23 ± 0.05	< 0.001*
Mitral lateral a' wave	0.08 ± 0.03	0.07 ± 0.03	0.102
Mitral lateral s' wave	0.09 ± 0.03	0.11 ± 0.03	0.046*
Mitral lateral e' to a' wave ratio	2.35 ± 1.210	3.59 ± 1.30	< 0.001*
Septal e' wave	0.13 ± 0.04	0.15 ± 0.03	0.114
Septal a' wave	0.11 ± 0.13	0.06 ± 0.02	0.120
Septal s' wave	0.09 ± 0.02	0.08 ± 0.02	0.643
Septal e' to a' wave ratio	1.70 ± 0.68	2.80 ± 0.89	< 0.001*

	Responder	Non-responder	P-value
Mitral inflow e wave	1.00 ± 0.18	0.95 ± 0.16	0.449
Mitral inflow a wave	0.57 ± 0.19	0.65 ± 0.19	0.270
Mitral inflow e to a ratio	1.95 ± 0.77	1.60 ± 0.05	0.186
Mitral lateral e' wave	0.17 ± 0.06	0.17 ± 0.05	0.884
Mitral lateral a' wave	0.08 ± 0.03	0.08 ± 0.02	0.996
Mitral lateral s' wave	0.09 ± 0.04	0.10 ± 0.03	0.771
Mitral lateral e' to a' wave ratio	2.44 ± 1.37	2.11 ± 0.56	0.449
Septal e' wave	0.11 ± 0.02	0.17 ± 0.02	< 0.001
Septal a' wave	0.07 ± 0.02	0.18 ± 0.21	0.282
Septal s' wave	0.08 ± 0.03	0.09 ± 0.02	0.590
Septal e' to a' wave ratio	1.65 ± 0.45	1.81 ± 1.02	0.666

Table 1: *Comparison of diastolic function characteristics between controls and those with Kawasaki disease as well as responders versus non-responders.*

Discussion

This study demonstrated that patients with acute Kawasaki disease have significantly greater diastolic dysfunction when compared to controls. This is consistent with previous findings and postulated to be secondary to diffuse myocardial inflammation [18-21]. However, this study did not identify any significant diastolic dysfunction when comparing IVIG responders and non-responders. The septal e' was significantly higher in the non-responder group, which is the opposite pattern expected with diastolic dysfunction. Takeuchi., *et al*. had similar findings where diastolic parameters were not predictive of IVIG responsiveness [21]. This differs from the findings of Phadke., *et al*. who described significant differences in the septal and mitral lateral e' of IVIG responders and non-responders. However, the ROC analysis demonstrated respective AUC's of 0.66 and 0.70, which represents poor to fair accuracy [20].

Effectively predicting IVIG response can have an important impact in management of Kawasaki disease. Non-responders have been shown to have higher rates of coronary artery changes [17,20]. Various Japanese studies have used clinical scores to predict IVIG response with fairly high sensitivity and specificity [10-12]. Effective risk stratification and early treatment with IVIG and steroids was then shown to have reduced the incidence of coronary artery abnormalities in this population [13]. Unfortunately, when applied to a more heterogeneous U.S. population these clinical predictive models failed to be validated [14-17]. Outside of Japan, a reliable clinical tool has yet to be developed that predicts IVIG responsiveness. It seems that echocardiographic markers of diastolic function do not accomplish this task, as demonstrated in this study.

This study was limited by several factors. This was a retrospective study and therefore is susceptible to selection bias. Additionally, the relatively low sample size limits the power of this study. It is possible that with a larger sample size more significant differences may have been noted between the IVIG response groups. Additionally, the proportion of non-responders was quite high in this cohort of patients. This does not represent the true proportion of Kawasaki disease patients at our institution who are non-responders. This is the result of selection bias due to not all patients having gotten tissue Doppler assessment as part of their echocardiograph.

Conclusion

This study showed that patients with acute Kawasaki disease have higher rates of diastolic dysfunction. However, markers of diastolic function were not predictive of IVIG responsiveness. Further studies are needed to create an effective system of assessing IVIG responsiveness in the U.S. population.

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