

Prevalence of Coronary Artery Lesions on the Initial Echocardiogram in Kawasaki Syndrome

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Objectives: To determine whether coronary artery lesions (ectasia and aneurysm) are commonly observed on the initial echocardiogram of patients with acute Kawasaki syndrome, whether coronary artery ectasia and/or aneurysms occur more frequently in patients with incomplete Kawasaki syndrome than in those patients with complete findings, and whether earlier diagnosis and treatment of Kawasaki syndrome are associated with less frequent occurrence of coronary artery ectasia and/or aneurysm.

Design: A retrospective medical record review.

Setting: A tertiary care pediatric hospital.

Participants: One hundred patients treated for Kawasaki syndrome between July 1, 1998, and June 30, 2003, who were identified by a medical record search.

Main Outcome Measure: Prevalence of coronary artery lesions (ectasia and aneurysm) on the initial and subsequent echocardiograms.

Results: Forty-four percent of patients had a coronary artery lesion (31% with ectasia, 13% with aneurysm) on the initial echocardiogram. Patients with incomplete Kawasaki syndrome were treated significantly later (median, 10 days) and had a significantly higher occurrence of coronary artery aneurysms over the course of their illness (37%) than those with complete Kawasaki syndrome, who were treated at a median of 7 days ($P < .001$) and had a 12% aneurysm occurrence ($P = .009$). Patients treated by day 7 of illness had a less frequent occurrence of aneurysm (6%) compared with those patients treated between days 8 and 10 of illness (27%) ($P = .03$).

Conclusions: Coronary artery lesions are frequently detected on the initial echocardiogram of children with Kawasaki syndrome. If future studies show ectasia to have a relatively high degree of specificity for Kawasaki syndrome, the initial echocardiography may be a useful adjunctive diagnostic test.

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KAWASAKI SYNDROME (KS) IS a systemic vasculitis with a predilection for the coronary arteries. It is currently the leading cause of acquired heart disease in children in the United States.¹ The etiology is unknown and there are no pathognomonic laboratory features. Diagnosis is therefore based on clinical criteria, the presence of fever for at least 5 days plus at least 4 of 5 typical physical findings, as well as supportive but nonspecific laboratory values. However, KS may be difficult to distinguish from common bacterial or viral infections. In addition, patients with KS may have fewer than 4 of the 5 criteria. These incomplete cases are more difficult to recognize and may have a higher incidence of coronary artery lesions (CALs).^{2,3} Treatment with intravenous immunoglobulin (IVIG) and aspirin markedly reduces the development of coronary artery aneurysms.^{4,5} Furthermore, there is evidence that earlier treatment leads

to a lower incidence of aneurysm formation.^{1,2,6,7} Timely diagnosis and treatment are therefore important.

Echocardiograms are often obtained at the time of diagnosis to serve as a baseline study of the coronary arteries and to screen for cardiac findings occasionally seen in acute KS, such as pericardial effusions, myocarditis, or valvular dysfunction. Echocardiography is repeated in the subacute phase of illness to detect development of CALs.¹ Until very recently, however, echocardiography has not been recommended as an adjunctive test to establish a diagnosis of KS.¹ Although earlier studies^{4,5,8} reported low rates of CALs on the initial echocardiogram, more recent studies^{9,10} suggest that previously applied definitions of aneurysm and ectasia may have significantly underestimated the true prevalence of CALs. If CALs are commonly detected on the initial echocardiogram, then echocardiography may be a useful adjunct in diagnosing KS. In this study, we evaluated the preva-

lence of CALs on the initial echocardiogram of patients with acute KS. In addition, we evaluated whether patients with incomplete KS were treated later in the course of their illness than patients with complete findings and whether CALs or the 2 subsets of CAL, ectasia and aneurysm, were observed more frequently in the patients with incomplete KS during the course of their illness than in patients with complete findings. To assess the potential impact of earlier diagnosis of KS, we also evaluated the relationship between the timing of the treatment for KS and the frequency of occurrences of CALs and the CAL subsets of ectasia and aneurysm.

METHODS

We conducted a retrospective medical record review of all of the patients treated with IVIG and aspirin for KS at Schneider Children's Hospital, New Hyde Park, NY, between July 1, 1998, and June 30, 2003. Patients were identified by a search of medical records and a database of patients who underwent echocardiography in the Division of Cardiology. Inpatient and outpatient medical records and echocardiogram reports were reviewed for all of the patients. Patients were excluded if they had an alternate diagnosis that reasonably accounted for their illness. We recorded the following data for each patient: age, sex, duration of fever, presence or absence of each clinical criterion for KS, duration of illness to time of treatment, occurrence of periungual peeling in the subacute stage, and timing and findings of initial and subsequent echocardiograms. In addition, for each patient, we determined whether the initial echocardiogram influenced the diagnosis of KS. Patients in whom there was no documentation of a commitment to treat with IVIG prior to a report of abnormality on the echocardiogram were considered to have a diagnosis that was influenced by echocardiographic findings.

The fever criterion and the 5 other clinical criteria of KS were applied as previously described¹ with the following exceptions: (1) patients who defervesced following treatment with IVIG were considered to have fulfilled the fever criterion even if they were febrile for fewer than 5 days, and (2) periungual desquamation qualified as fulfilling the criterion for extremity changes only if present at the time of diagnosis.

An episode of KS was classified as complete if the patient fulfilled the fever criterion plus at least 4 of the 5 other clinical criteria. Episodes were classified as incomplete if either the fever criterion or presence of at least 4 of the other criteria were not fulfilled.

Echocardiograms were obtained with Sequoia echocardiographic imagers (Siemens Medical Solutions USA, Inc, Malvern, Pa). Performed projections included subxyphoid, parasternal long and short axis, and apical views. M-mode, 2-dimensional, Doppler flow, and color flow mapping studies were routinely performed. All of the studies were reviewed and reported by a pediatric cardiology attending (97% of the studies were interpreted by Y.S., A.R., or F.Z.B.). The echocardiographers distinguished between 2 subsets of CAL: ectasia and aneurysm. The echocardiographer found coronary artery ectasia if the vessel either was qualitatively dilated or tapered abnormally such that it did not taper as it progressed distally (distal ectasia) or such that it tapered precipitously from its origin (proximal ectasia). The echocardiographer found aneurysm if there was an isolated and distinct outpouching of a coronary artery segment. Based on the echocardiogram reports, results were classified as normal, ectasia, or aneurysm; a study with both ectasia and aneurysm was classified as aneurysm.

All of the echocardiogram reports were reviewed. The initial echocardiography was the first study performed at the time of diagnosis. For patients with more than 1 subsequent echo-

cardiogram, the result of the study with the most marked abnormality was recorded. The final echocardiogram was the study most recently performed at the time of data collection and was included only if performed long enough into the course of the illness to be considered indicative of final coronary status, ie, at least 6 weeks from the onset of illness if the study results were normal and at least 90 days from the onset of illness if the study results were abnormal.

Proportions were compared using the Fisher exact test. Continuous variables (time to treatment and age at presentation) were analyzed using the nonparametric Mann-Whitney test. The institutional review board of Long Island Jewish Medical Center, New Hyde Park, approved the study protocol.

RESULTS

One hundred three patients were treated for KS. Three were excluded because alternate diagnoses were established: 1 patient had systemic lupus erythematosus, 1 had Behçet syndrome, and 1 had enteroviral infection. All of the 3 patients had CALs. Of the remaining 100 patients, 7 had diagnoses of infectious diseases (4 patients with group A β -hemolytic streptococcal infection, 1 with parvovirus infection, 1 with adenovirus infection, and 1 with enterotoxin B-producing *Staphylococcus aureus* infection) but were still considered by the infectious diseases attending physician to have KS.

Sixty patients (60%) were male. The median age at diagnosis was 2.5 years. At the time of diagnosis, 73 patients (73%) fulfilled complete criteria (**Table 1**). A higher percentage of patients with incomplete KS (8 [30%] of 27 patients) were aged 12 months or younger compared with those with complete KS (10 [14%] of 73 patients), but this difference was not significant ($P=.08$). The median day of illness at the time of treatment was 8 days. Patients with complete KS were treated significantly earlier (median, 7 days; range, 3-19 days) than patients with incomplete KS (median, 10 days; range, 6-26 days; $P<.001$). In all but 5 patients, the initial echocardiogram was obtained within 24 hours of treatment; 4 of the 5 patients had an initial echocardiogram obtained within 48 hours of treatment and 1 within 72 hours of treatment. At some time during their course of illness, 75% of patients had documentation of aneurysm and/or periungual desquamation, findings highly characteristic of KS (Table 1).

Forty-four percent of patients had CALs on the initial echocardiogram; 31 (31%) had ectasia and 13 (13%) had aneurysms (**Table 2**). There was no significant difference in the prevalence of CALs ($P=.18$) or the CAL subset of ectasia ($P=.63$) on the initial echocardiogram between patients with complete and incomplete KS. However, the prevalence of the CAL subset of aneurysm on the initial echocardiogram in patients with incomplete KS (30%) was significantly higher than in patients with complete KS (7%) ($P=.006$). Findings on the initial echocardiogram influenced the diagnosis of KS or the timing of the diagnosis of KS in 14 patients. Of these patients, 6 had aneurysms, 7 had ectasia, and in 1 patient, the preliminary reading was ectasia but the official interpretation was normal coronary arteries.

To assess the prevalence of CALs on the initial echocardiogram in patients diagnosed early in the course of

Table 1. Clinical Findings of Patients With Complete and Incomplete Kawasaki Syndrome

Clinical Finding	All Patients, No. (%) (N = 100)	Patients With Complete KS, No. (%) (n = 73)	Patients With Incomplete KS, No. (%) (n = 27)	Patients With Diagnosis by Echocardiogram, No. (%) (n = 14)*
Criteria fulfilled				
Fever criterion	98 (98)	73 (100)	25 (93)	13 (93)
0 of 5 clinical criteria	1 (1)	NA	1 (3)	1 (7)
1 of 5 clinical criteria	3 (3)	NA	3 (11)	3 (21)
2 of 5 clinical criteria	4 (4)	NA	4 (15)	2 (14)
3 of 5 clinical criteria	19 (19)	NA	19 (70)	3 (21)
4 of 5 clinical criteria	52 (52)	52 (71)	NA	5 (36)
5 of 5 clinical criteria	21 (21)	21 (29)	NA	0
Periungual peeling†	67 (67)	57 (78)	10 (37)	5 (36)
Presence of aneurysm†	19 (19)	9 (12)	10 (37)	8 (57)
Peeling or aneurysm†	75 (75)	57 (78)	18 (67)	11 (79)

Abbreviations: KS, Kawasaki syndrome; NA, not applicable.

*Echocardiogram influenced either the diagnosis or the timing of the diagnosis of KS.

†Documented at any time during the patient's course of illness.

Table 2. Comparison of Echocardiographic Findings in Patients With Complete and Incomplete Kawasaki Syndrome

Echocardiogram Finding	All Patients, No. (%) (N = 100)	Patients With Complete KS, No. (%) (n = 73)	Patients With Incomplete KS, No. (%) (n = 27)	P Value*
Initial echocardiogram				
CAL†	44 (44)	29 (40)	15 (56)	.18
Ectasia	31 (31)	24 (33)	7 (26)	.63
Aneurysm‡	13 (13)	5 (7)	8 (30)	.006
Presence of lesion on any echocardiogram				
CAL†	64 (64)	45 (62)	19 (70)	.49
Ectasia§	45 (45)	36 (49)	9 (33)	.18
Aneurysm‡	19 (19)	9 (12)	10 (37)	.009

Abbreviations: CAL, coronary artery lesion; KS, Kawasaki syndrome.

*P values compare complete KS with incomplete KS.

†The number of patients with CAL is the sum of the patients with ectasia and aneurysm.

‡Some patients with aneurysm also had ectasia in another vessel.

§Ectasia was the most marked lesion at any point.

||Finding includes 4 patients with initial ectasia who subsequently developed aneurysm (3 patients with complete KS, 1 with incomplete KS) and 1 patient with aneurysm that regressed to ectasia on a subsequent echocardiogram (incomplete KS).

their illness, we reanalyzed the data for patients presenting on or before the seventh day of illness and for those presenting between days 8 and 10 of illness. Considering only the 49 patients treated on or before day 7 of illness, 21 (43%) had a CAL (all of which were ectasia) on the initial echocardiogram. Similarly, of 26 patients treated on days 8 to 10 of illness, 11 (42%) had a CAL; 6 patients (23%) had ectasia and 5 (19%) had an aneurysm on the initial echocardiogram. Thus, CALs were commonly observed on the initial echocardiogram of patients diagnosed by the 7th and 10th days of illness.

The relationship between the findings on the initial and subsequent echocardiograms was examined (Figure). Coronary artery lesions were found on the subsequent echocardiogram in significantly higher percentages of patients who had an initial echocardiogram showing ectasia (77%) or aneurysm (85%) compared with those with normal initial echocardiographic results (36%). Sixty-four patients (64%) had a CAL at some point during their course of illness; however, only 11 patients (11%) had a CAL (6% of which were ectasia and 5% were aneurysm) on the final echocardiogram. Eighty-seven patients (87%)

had normal coronary arteries on the final echocardiogram. In 2 patients, a CAL was detected on a final echocardiogram obtained before 90 days of illness; hence, their final coronary status could not be evaluated.

The frequency of occurrence of CALs over the course of illness was compared in patients with complete and incomplete KS (Table 2). Coronary artery lesions overall as well as the CAL subset of ectasia were observed in similar percentages of patients with complete and incomplete KS. In contrast, the CAL subset of aneurysm was observed in a significantly higher percentage of those with incomplete KS (10 [37%] of 27 patients) compared with those with complete KS (9 [12%] of 73 patients) ($P = .009$).

The relationship between the duration of illness before treatment and the frequency of occurrence of CALs was examined. Thirty-five (71%) of 49 patients treated on or before day 7 of illness had a CAL during their course compared with 14 (54%) of 26 patients treated on days 8 to 10 of illness and 15 (60%) of 25 patients treated after day 10 of illness. These differences were not statistically significant ($P = .29$ comparing patients treated on or before day 7 of illness, between days 8 and 10 of illness,

and after day 10 of illness). In contrast, the CAL subset of aneurysm was observed significantly more often with a longer time to treatment. Three (6%) of 49 patients treated on or before day 7 of illness had an aneurysm during their course compared with 7 (27%) of 26 patients treated on days 8 to 10 of illness ($P=.03$). Similarly, a higher percentage of patients treated after 10 days of illness (9 [36%] of 25 patients) developed an aneurysm during their course compared with patients treated on or before day 10 of illness (10 [13%] of 75 patients) ($P=.02$).

Eighty-three percent of the initial echocardiograms were interpreted by 1 of 2 cardiologists (Y.S. and A.R.). The 2 cardiologists detected the presence of CALs at similar rates, with one finding CALs on 25 (51%) of 49 echocardiograms and the other finding CALs on 15 (44%) of 34 echocardiograms ($P=.66$).

Sixteen patients (10 with complete KS) were given more than 1 dose of IVIG for refractory KS. One patient received a third dose of IVIG, and 4 received steroids after 2 doses of IVIG. Twelve of the patients who received multiple doses of IVIG, including 4 patients with aneurysm, developed CALs during the course of their illness.

COMMENT

Recently, the American Heart Association¹ (AHA) published guidelines on the diagnosis and treatment of KS that recommended the use of echocardiography as a diagnostic tool for patients with suspected incomplete KS. Of note, this recommendation is based on expert opinion, and the sensitivity and specificity of findings on the initial echocardiogram have not been clinically validated. In our study, we found a 44% prevalence of CALs on the initial echocardiogram. Other recent series^{7,10,11} of patients with KS have found a similarly high prevalence of CALs on the initial echocardiogram. These findings suggest that echocardiography may be a useful adjunctive test for the diagnosis of KS. Diagnostic use of the echocardiogram may be particularly useful in those patients with incomplete KS in whom the diagnosis is more difficult and, as a consequence, often delayed.

Consistent with other reported series of patients with KS,^{2,3,12} a substantial percentage of our patients had incomplete criteria for KS. In our study, these patients were treated significantly later and had a significantly higher rate of coronary artery aneurysms than those patients with complete KS. Benefit of treatment by day 10 of illness has been previously demonstrated.^{1,2,4,5,13} Furthermore, some evidence suggests that treatment as early as day 6 to 7 confers a better coronary artery prognosis than later treatment.^{6,7} The AHA guidelines recommend that treatment be initiated before the 10th day of illness and preferably before the 7th day of illness.¹ Considering treatment before and after these time points, we found that the percentage of patients with aneurysm increased significantly with a longer time to treatment. Based on the findings of our study, use of the echocardiogram as suggested by the AHA guidelines early in the course of illness in a patient with suspected incomplete KS may lead to earlier treatment and an improved coronary artery outcome.

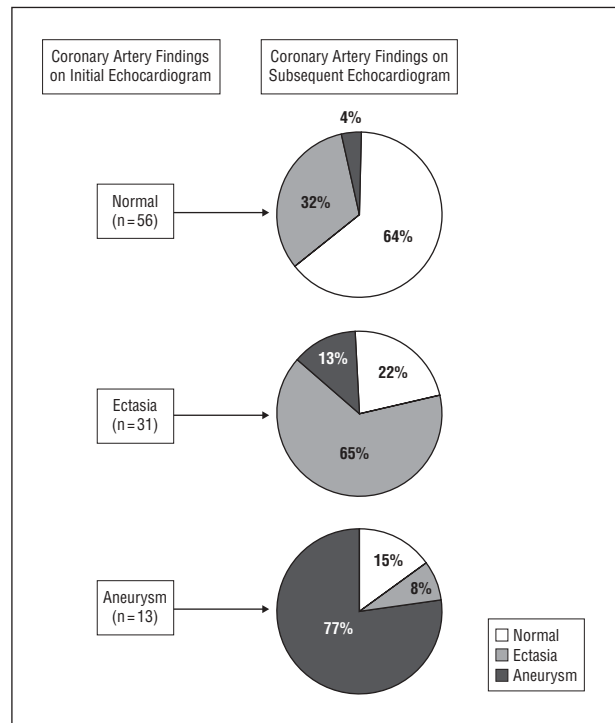


Figure. Coronary artery lesions (ectasia or aneurysm) were observed on subsequent echocardiograms in significantly more patients with ectasia ($P<.001$) or aneurysm ($P=.002$) on the initial echocardiograms than in patients with normal coronary arteries on the initial echocardiograms.

The prevalence of CALs on the initial echocardiogram of patients with acute KS that we report is much higher than that which had been reported in the literature during the 1980s and through much of the 1990s. In each of the 2 IVIG treatment studies by Newburger et al^{4,5} in which only patients with complete KS treated in the first 10 days of illness were included, less than 4% of patients with KS had CALs on the initial echocardiogram. Similarly, Barron et al⁸ found CALs on the initial echocardiogram in only 1 (2%) of 51 patients with complete KS treated by day 7 of illness. In comparison, of our patients with complete KS treated within 7 days of illness, CALs were present on the initial echocardiogram in 39%. Newer imaging technology that allows for a more accurate evaluation of the coronary arteries may partially explain the discrepancy. However, the evolution of the criteria used to define CALs is likely to be a more important factor. In earlier studies,^{4-6,8} CAL was defined by a coronary artery diameter that exceeded an absolute measurement (ie, a 3- or 4-mm internal diameter). Two recent studies^{9,10} suggest that these criteria may miss a significant proportion of abnormalities, and instead, they recommend the use of a CAL definition based on comparisons to body surface area (BSA)-adjusted norms of coronary artery internal diameters. Defining a CAL as a vessel with an internal diameter that is 2 or more SDs higher than the BSA-adjusted norm, 2 studies of patients with KS published in 2002 found prevalences of CALs on the initial echocardiogram of 34%⁷ and 47%¹⁰ of patients. The 2004 AHA guidelines also use BSA-adjusted criteria to define a CAL when the finding is used to diagnose a patient with incomplete KS. Using these guidelines, the results of echocardiography are consid-

ered supportive of a diagnosis of KS if a coronary artery has an internal diameter greater than 2.5 SDs over the BSA-adjusted norm or if an artery has a diameter greater than 2 SDs over the age-adjusted norm in conjunction with 2 other echocardiographic findings compatible with acute KS (pericardial effusion, mitral regurgitation, decreased systolic function, perivascular brightness, and lack of tapering of a vessel).

A limitation of this study is that a finding of ectasia was a subjective interpretation of the echocardiographer. As coronary artery diameters were not routinely recorded on the echocardiogram reports, we could not retrospectively apply BSA-adjusted criteria or the full AHA algorithm to most of our patients. Although it is possible that our definition of ectasia was less specific than ectasia defined by other methods, rates of CAL in our study were similar to those found in the recent literature on KS.^{7,10,11} In addition, the 2 cardiologists who accounted for 83% of initial echocardiographic study evaluations recorded findings of CALs at similar rates. As this study was a retrospective record review of echocardiographic findings at the time of diagnosis and consequently only 1 cardiologist interpreted each echocardiogram, we were unable to evaluate the internal validity of these findings.

We also found that occurrence of a CAL on the initial echocardiogram was predictive of CAL occurrence on a subsequent echocardiogram in a given patient. Given that the echocardiographers for the subsequent echocardiograms were not blinded to the results of the initial echocardiogram, observer bias may have influenced this finding. However, our finding that the vast majority of patients with ectasia had normal coronary arteries on the final echocardiogram supports the validity of the diagnosis of ectasia rather than a misdiagnosed variant of a normal coronary artery.

As noted earlier, echocardiographic findings described in the AHA guidelines for diagnosis of KS are based on expert opinion, and the positive and negative predictive values of particular echocardiographic findings have not been validated in clinical trials. The specificity of a finding of ectasia must be ascertained before echocardiography can be validated as a diagnostic adjunct for KS. Although previously published studies have measured the dimensions of coronary arteries in healthy children, we are unaware of studies that compare artery dimensions of children with KS with those of similarly aged children with other acute febrile illnesses. Indeed, in our study, 3 children with CALs did not have KS, indicating that the specificity of a CAL was less than 100% for diagnosis of KS. In addition, a recent study¹⁴ notes that patients with newly diagnosed juvenile rheumatoid arthritis may have coronary artery dilatation. If CALs may be found in other inflammatory diseases, the specificity of a finding of a CAL in KS may be limited.

A further limitation of this study is the retrospective design. As this study was a retrospective review of clinical data, the cardiologists were not blinded to the diagnosis of suspected KS. A reader-blinded case-control study comparing the coronary arteries of children with KS with the coronary arteries of age-matched febrile children would help to evaluate the positive and negative predic-

tive values of the initial echocardiogram as an adjunctive test for diagnosing KS.

Our findings demonstrate that CALs are common on the initial echocardiogram of patients with acute KS. If these lesions are found to have a relatively high degree of specificity for KS, the initial echocardiogram may be a valuable tool in diagnosing the illness early in its course. Further studies are needed to help determine the utility of the initial echocardiogram in diagnosing KS and to determine echocardiographic findings that are most sensitive and specific for a diagnosis of KS.

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