Left Ventricular Contractility and Function in Kawasaki Syndrome

Effect of Intravenous γ-Globulin

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To investigate the effect of Kawasaki syndrome on myocardial function, as well as the influence of high-dose intravenous γ-globulin therapy on resolution of functional abnormalities, we studied 98 patients with Kawasaki syndrome during five time intervals from onset of illness: 1) 10 days or less, 2) 11–31 days, 3) 1–3 months, 4) 3–12 months, and 5) 1–3 years. Normal controls included 48 children under age 8 years, without known cardiovascular disease. Using two-dimensional directed M-mode echocardiograms, we obtained chamber dimensions, fractional shortening, rate-corrected velocity of shortening (Vcfc) adjusted for end-systolic wall stress, and early diastolic function parameters that included adjusted peak rates of left ventricular dimension change, wall thinning, and their respective timing. Left ventricular systolic and diastolic dimensions were larger (both \( p < 0.01 \)) in patients than in normal subjects in period 1. Stress-adjusted Vcfc was much lower in patients in the 3 months after disease onset; by period 5, contractility was comparable in patients and normal subjects. Adjusted indexes of early diastolic function did not differ significantly between patients and normal subjects. To investigate the effect of γ-globulin, we analyzed data on 47 patients prospectively randomized to therapy with aspirin alone (\( n = 19, 40\% \)) or to aspirin plus γ-globulin, 400 mg/kg/day for 4 consecutive days (\( n = 28, 60\% \)). In period 1, before treatment, the two groups had mean fractional shortening and stress-adjusted Vcfc comparable to each other but much lower than those of normal subjects (\( p \leq 0.001 \)). Patients treated with aspirin alone continued to have diminished fractional shortening and Vcfc compared with normal subjects in periods 2, 3, and 4 (all \( p \leq 0.05 \)). In contrast, fractional shortening and Vcfc in γ-globulin–treated patients in these periods were comparable to those of normal subjects. By period 5, no difference was detected in systolic function or contractility between either treatment group and normal subjects. We conclude that early abnormalities of left ventricular contractility and myocardial function, as assessed by echocardiography, generally resolve by 1–3 years after disease onset and that recovery is accelerated by administration of IVGG in the acute phase. (Circulation 1989;79:1237–1246)

Kawasaki syndrome is a febrile illness of unknown etiology that occurs primarily in infants and young children. First described in Japan in 1967, Kawasaki syndrome is now recognized worldwide in children of all racial groups. Coronary artery aneurysms or ectasia develop in approximately 15–25% of children with the disease and may lead to myocardial infarction, sudden death, or angina pectoris.\(^5\)–\(^8\) Recently, therapy with intravenous γ-globulin in the acute phase of Kawasaki syndrome has been shown to decrease the frequency of occurrence of coronary artery abnormalities.\(^9\)–\(^13\)

Although depressed left ventricular function is a well-known feature of acute Kawasaki syndrome, investigations of long-term myocardial function with differing methodologies have produced conflicting results.\(^14\)–\(^20\) To our knowledge, no reports have been published on the effect of intravenous γ-globulin therapy on myocardial function.

The purpose of the present study was to investigate the natural history of Kawasaki syndrome with
respect to myocardial contractility by the use of newer noninvasive methods that are independent of loading conditions and to examine the late effects of Kawasaki syndrome on diastolic function. In addition, we report the effect of intravenous γ-globulin therapy for Kawasaki syndrome on myocardial systolic and diastolic function.

Methods

Subjects

Patients included 98 children with a history of Kawasaki syndrome who were prospectively evaluated at The Children’s Hospital, Boston, between February 1984 and July 1987. All children met the criteria for Kawasaki syndrome as defined by the Centers for Disease Control.3 Echocardiograms for analysis of myocardial function were obtained from patients with Kawasaki syndrome during five time intervals from onset of the illness: 1) 10 days or less (36 patients), 2) 11–31 days (43 patients), 3) 1–3 months (56 patients), 4) 3 months to 1 year (17 patients), and 5) 1–3 years (27 patients). When a child was studied more than once within an interval, we chose the earliest study for analysis. Forty-one patients had an echocardiogram performed in only one time period; 33 patients in two periods; 12 patients in three periods; and 12 patients in four periods. No children received cardioactive medications. No patients had aortic or mitral regurgitation. Normal subjects were 48 children under 8 years of age who were free of known cardiovascular disease, were taking no cardioactive medications, and had normal results from physical examinations, electrocardiograms, and intracardiac anatomy by two-dimensional echocardiography.

Data Recordings

Data were collected by previously reported methods.21 Children younger than age 2.5 years usually received sedation with chloral hydrate. We obtained echocardiograms with a Hewlett-Packard 77020A 2-dimensional ultrasound system with two-dimensional directed M-mode capabilities (Palo Alto, California). High speed (100 mm/sec) hard copy M-mode echocardiograms were obtained of the left ventricular minor axis with simultaneous phonocardiogram, electrocardiogram, and indirect axillary or carotid pulse tracing. The phonocardiogram was recorded with simultaneous M-mode recording of aortic valve closure to permit positive identification of A2. Peak systolic and diastolic blood pressures were measured with a Dinamap 845 Vital Signs Monitor (Critikon, Tampa, Florida).

Data Analysis

The indirect axillary or carotid pulse tracing, and the left ventricular echocardiogram including the endocardial border of the septum and the endocardial and epicardial borders of the left ventricular posterior wall, were hand-digitized with a Franklin Quantic 1200 echocardiographic analysis system (Bruce Franklin, Seattle, Washington). This instrument is equipped with a digitizing pad with a sampling rate of 80/cm, giving a maximum net digitizing rate of 800/sec. After data input, the device is programmed to correct the carotid pulse tracing for pulse transmission delay by aligning the dicrotic notch with the first high-frequency component of A2. From the digitized data, the following instantaneous measurements are derived by averaging 3–6 cardiac cycles: 1) pressure during left ventricular ejection determined by linear interpolation with a calibrated carotid pulse tracing as described previously22; 2) left ventricular internal diameter; 3) first derivative of dimension with respect to time, the peak value of this first derivative, and the time from the Q wave to the occurrence of this maximum; 4) left ventricular posterior wall thickness; 5) first derivative of wall thickness with respect to time, the peak value of this first derivative, and the time from the Q wave to the occurrence of this maximum; and 6) the left ventricular wall stress throughout ejection, which was calculated as

\[
WS = \frac{(P)(D)}{(h)\left(1 + (h/D)\right)^n}
\]

where WS is the wall stress (g/cm²), P is the pressure (mm Hg), D is the dimension, h is the wall thickness (cm), and 1.35 is the conversion factor from mm Hg to g/cm².

End-diastolic left ventricular dimension and wall thickness were measured at the time of maximum left ventricular dimension, whereas the end-systolic dimension and wall thickness were measured at the time of the first high-frequency component of the second heart sound. Left ventricular ejection time was measured from the simultaneous pulse tracing and adjusted for heart rate by dividing by the square root of the RR interval. The left ventricular percent fractional shortening was calculated as the difference between the dimensions at end diastole and end systole divided by end-diastolic dimension. The rate-adjusted mean velocity of shortening was calculated by dividing fractional shortening by the rate-adjusted ejection time. The left ventricular percent fractional wall thickening was calculated as the difference between the wall thicknesses at end systole and end diastole divided by the end-diastolic wall thickness.

Coronary artery abnormalities were defined in accordance with the criteria outlined by the Japanese Ministry of Health.24

Statistical Analysis

We used t tests and analysis of variance to compare groups with respect to unadjusted measured variables. When variables required adjustment for confounders, we used analysis of covari-
TABLE 1. Adjusted Means of Echocardiographic Variables in a Subset of Patients With Kawasaki Syndrome in Therapeutic Trial

<table>
<thead>
<tr>
<th>Variable (Covariate)</th>
<th>Period 1</th>
<th>Period 2</th>
<th>Period 3</th>
<th>Period 4</th>
<th>Period 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (n)</td>
<td>16</td>
<td>5</td>
<td>14</td>
<td>8</td>
<td>16</td>
</tr>
<tr>
<td>Vcfc (ESWS)</td>
<td>0.97*</td>
<td>0.93†</td>
<td>-</td>
<td>-</td>
<td>1.00‡</td>
</tr>
<tr>
<td>FS (ESWS)</td>
<td>31.95*</td>
<td>31.39‡</td>
<td>37.41</td>
<td>-</td>
<td>33.23‡</td>
</tr>
<tr>
<td>EDD (BSA)</td>
<td>3.20</td>
<td>4.46†</td>
<td>3.26</td>
<td>3.03‡</td>
<td>3.08</td>
</tr>
<tr>
<td>ESD (BSA)</td>
<td>2.19‡</td>
<td>2.37*</td>
<td>2.04</td>
<td>2.03</td>
<td>2.01</td>
</tr>
<tr>
<td>PFR (EDD)</td>
<td>8.69</td>
<td>8.18</td>
<td>9.85</td>
<td>9.06</td>
<td>9.04</td>
</tr>
<tr>
<td>TPTR (RR)</td>
<td>0.37</td>
<td>0.38</td>
<td>0.38</td>
<td>0.37</td>
<td>0.40</td>
</tr>
<tr>
<td>TPFR (RR)</td>
<td>0.39</td>
<td>0.40</td>
<td>0.38</td>
<td>0.36‡</td>
<td>0.40</td>
</tr>
</tbody>
</table>

Vcfc, rate-adjusted mean velocity of shortening; ESWS, end-systolic wall stress; FS, fractional shortening; EDD, end-diastolic dimension; BSA, body surface area; ESD, end-systolic dimension; PTR, peak thinning rate; ESH, end-systolic wall thickness; EDH, end-diastolic wall thickness; PFR, peak filling rate; TPFR, time to peak filling rate.

*\( p \leq 0.001 \) compared with normal subjects; †\( p \leq 0.01 \) compared with normal subjects; ‡\( p \leq 0.05 \) compared with normal subjects; §\( p \leq 0.01 \) γ-globulin compared with aspirin group; ¶\( p \leq 0.05 \) γ-globulin compared with aspirin group;

\( p \leq 0.001 \) γ-globulin compared with aspirin group.

ance to test for group differences.\(^{25}\) Covariates were selected by prior modeling on normal subjects. The specific covariates for which function variables were adjusted are given in Table 1.

Using analysis of covariance with a three-level group factor,\(^{25}\) we investigated the effect of treatment with intravenous γ-globulin on contractility and function; groups included patients treated with intravenous γ-globulin plus aspirin, patients treated with aspirin alone, and normal subjects. To ensure comparability of treatment groups, we analyzed only data on patients from our hospital enrolled in a multicenter, prospective, randomized trial to assess the efficacy of γ-globulin (Immuno AG, Vienna, Austria) in reduction of prevalence of coronary artery abnormalities.\(^{9}\) Multiple regression techniques were used to explore the relations between measures of myocardial mechanics and laboratory parameters of systemic inflammation. Statistical analyses were performed with Statistical Analysis Systems (Cary, North Carolina).\(^{26}\)

Results

Natural History of Kawasaki Syndrome

Among the 98 children with Kawasaki syndrome, 66 (67%) were male, 16 (16%) had coronary artery abnormalities on at least one echocardiogram, and 57 (58%) received intravenous γ-globulin therapy within the first 10 days of the illness. We have summarized in Table 2 the mean ages, body surface areas, and echocardiographic measurements of patients studied within each of five time intervals from onset of the disease as well as those of the 48 normal subjects in whom we obtained two-dimensional echocardiographic evaluation of left ventricular function with the same data recording and analytic techniques.

Left ventricular end-diastolic and systolic dimensions, adjusted (with analysis of covariance) for the cubed root of body surface area,\(^{27}\) were significantly higher (both \( p < 0.01 \)) in patients with Kawasaki syndrome within the first 10 days of illness (period 1) than in normal subjects. Both adjusted dimensions tended to be higher in patients during the subsequent four time periods than in normal subjects, but the differences were not significant. Fractional shortening was significantly lower \( (p < 0.01) \) in patients during periods 1 and 3 than in normal subjects, but fractional shortening between the two groups was comparable in subsequent periods (later than 3 months after illness onset). Heart rate in patients was higher during period 1 \( (p < 0.01) \), which is consistent with the fever and anemia characteristic of the acute phase of the illness. During period 5, patients had a lower mean heart rate than did normal subjects, which may be attributed to their older age. Significant differences were not found between groups in wall thickness, peak or end-systolic wall stress, blood pressure, or fractional wall thickening.

We compared the groups with respect to rate-adjusted velocity of shortening (Vcfc), adjusted for end-systolic wall stress,\(^{21}\) as a measure of left ventricular contractility. Contractility was significantly diminished in period 1 \( (p < 0.001) \) and period 3 \( (p = 0.0021) \), which is consistent with known occurrence of myocarditis and clinical congestive heart failure in Kawasaki syndrome. In the period between 3 months and 1 year (period 4), stress-adjusted Vcfc tended to be lower in patients with Kawasaki syndrome than in normal subjects, but the difference was not significant. Subsequent to 1 year after disease onset (period 5), the two groups had comparable load-independent indexes of left ventricular contractility.
To assess the effect of Kawasaki syndrome on the early diastolic function, we examined the peak rates of left ventricular dimension increase and of posterior wall thinning as well as the time to these peak velocities. Using analysis of covariance, we adjusted peak filling rate for fractional shortening and for end-diastolic dimension, factors that have been previously shown to contribute to their variance in normal subjects.\textsuperscript{28} Peak thinning rate was controlled for fractional wall thinning and for wall thickness difference (end-systolic minus end-diastolic wall thickness). Time to peak filling and peak thinning rates were controlled for the RR interval, based on previous studies.\textsuperscript{28} We detected no significant differences between patients with Kawasaki syndrome and normal subjects in adjusted peak filling rate, peak thinning rate, time to peak thinning rate, or time to peak filling rate during any period of comparison.

**Effect of γ-Globulin**

We investigated the effect of treatment of acute Kawasaki syndrome with intravenous γ-globulin on left ventricular contractility as well as on systolic and early diastolic function. Of 47 children enrolled from our center in a prospective, therapeutic trial, 28 (60\%) had been randomized to receive a regimen of intravenous γ-globulin (400 mg/kg/day for 4 consecutive days) plus aspirin, and 19 (40\%) were randomized to receive aspirin alone. The mean age, body surface area, and measured echocardiographic variables of children treated with γ-globulin plus aspirin and of those treated with aspirin alone

<table>
<thead>
<tr>
<th>Variable</th>
<th>Normal group</th>
<th>Kawasaki Syndrome Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects (n)</td>
<td>48</td>
<td>36</td>
</tr>
<tr>
<td>BSA</td>
<td>0.60 (0.27)</td>
<td>0.59 (0.18)</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>2.47 (2.47)</td>
<td>2.50 (1.95)</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>104.41 (25.77)</td>
<td>122.13† (20.94)</td>
</tr>
<tr>
<td>EDD</td>
<td>3.04 (0.66)</td>
<td>3.29*‡ (0.47)</td>
</tr>
<tr>
<td>ESD</td>
<td>1.94 (0.49)</td>
<td>2.26‡§ (0.57)</td>
</tr>
<tr>
<td>EDH</td>
<td>0.53 (0.11)</td>
<td>0.56 (0.12)</td>
</tr>
<tr>
<td>ESH</td>
<td>0.87 (0.17)</td>
<td>0.89 (0.16)</td>
</tr>
<tr>
<td>PFR</td>
<td>9.53 (2.23)</td>
<td>9.40 (2.56)</td>
</tr>
<tr>
<td>PTR</td>
<td>−5.15 (1.84)</td>
<td>−4.85 (1.34)</td>
</tr>
<tr>
<td>ESWS</td>
<td>41.44 (12.52)</td>
<td>45.25 (12.55)</td>
</tr>
<tr>
<td>Vcfc</td>
<td>1.10 (0.12)</td>
<td>0.97†§ (0.17)</td>
</tr>
<tr>
<td>FS</td>
<td>36.49 (4.15)</td>
<td>31.53† (5.34)</td>
</tr>
<tr>
<td>TFTR (msec)</td>
<td>0.39 (0.04)</td>
<td>0.36† (0.04)</td>
</tr>
<tr>
<td>TPFR (msec)</td>
<td>0.40 (0.05)</td>
<td>0.37† (0.05)</td>
</tr>
<tr>
<td>FWT</td>
<td>38.70 (8.09)</td>
<td>36.48 (10.52)</td>
</tr>
</tbody>
</table>

Values are mean±SD.

BSA, body surface area; HR, heart rate; EDD, end-diastolic dimension; ESD, end-systolic dimension; EDH, end-diastolic wall thickness; ESH, end-systolic wall thickness; ESWS, end systolic wall stress; Vcfc, rate-adjusted mean velocity of stretching; FS, fractional shortening; TFTR and TPFR, time to peak thinning rate; TFTR and TPFR, time to peak filling rate; FWT, fractional wall thinning.

*\(p<0.05\) on unadjusted measure (t test); †\(p<0.01\) on unadjusted measure (t test); ‡\(p<0.01\) on adjusted variable (analysis of covariance); §\(p<0.001\) on adjusted variable (analysis of covariance).
are displayed in Table 3. Patients who received intravenous γ-globulin did not differ significantly from those treated with aspirin alone in their mean end-diastolic or end-systolic dimensions adjusted for the cubed root of body surface area in any time period. Using analysis of covariance to adjust for end-systolic wall stress, we found that fractional shortenings in the aspirin and γ-globulin groups were similar in period 1, before beginning treatment. In periods 2 and 4, γ-globulin–treated patients had significantly higher stress-controlled shortening fractions \((p=0.012\) and \(p=0.019\), respectively) than those treated with aspirin alone. By period 5, stress-controlled fractional shortening was similar in children in the two treatment groups. Compared with normal subjects, children treated with aspirin alone had lower stress-controlled fractional shortening in period 1 \((p=0.017)\), period 2 \((p=0.018)\), period 3 \((p=0.004)\), and period 4 \((p=0.043)\), but values were similar in period 5. In contrast, stress-controlled fractional shortening of the γ-globulin–treated children was significantly lower than that of normal subjects only in period 1 \((p=0.001)\), before treatment.

We also compared patients with Kawasaki syndrome in the two treatment groups to each other and to normal subjects with respect to stress-adjusted Vcfc as a load-independent measure of contractility. Using analysis of covariance to control for end-systolic wall stress, we found that patients in the two treatment groups had comparable values for mean Vcfc in period 1, before treatment. However, children treated with γ-globulin

<table>
<thead>
<tr>
<th>Variable</th>
<th>10 days</th>
<th>11–31 days</th>
<th>1–3 months</th>
<th>3–12 months</th>
<th>1–3 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>BSA</td>
<td>0.58</td>
<td>0.55</td>
<td>0.56</td>
<td>0.53</td>
<td>0.61</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>2.38</td>
<td>2.00</td>
<td>2.36</td>
<td>1.50</td>
<td>2.44</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>120.45</td>
<td>114.39</td>
<td>98.86</td>
<td>103.63</td>
<td>100.30</td>
</tr>
<tr>
<td>EDD</td>
<td>3.40</td>
<td>3.20</td>
<td>3.22</td>
<td>2.95</td>
<td>3.15</td>
</tr>
<tr>
<td>ESD</td>
<td>2.20</td>
<td>2.33</td>
<td>2.02</td>
<td>1.97</td>
<td>2.06</td>
</tr>
<tr>
<td>EDH</td>
<td>0.57</td>
<td>0.58</td>
<td>0.54</td>
<td>0.61</td>
<td>0.55</td>
</tr>
<tr>
<td>ESH</td>
<td>0.90</td>
<td>0.89</td>
<td>0.94</td>
<td>0.87</td>
<td>0.91</td>
</tr>
<tr>
<td>PFR*</td>
<td>8.91</td>
<td>8.79</td>
<td>10.18</td>
<td>8.81</td>
<td>9.25</td>
</tr>
<tr>
<td>PTR*</td>
<td>−4.74</td>
<td>−4.35</td>
<td>−5.58</td>
<td>−3.80</td>
<td>−5.18</td>
</tr>
<tr>
<td>ESWS</td>
<td>44.88</td>
<td>44.77</td>
<td>40.50</td>
<td>37.40</td>
<td>44.65</td>
</tr>
<tr>
<td>Vcfc*</td>
<td>0.96</td>
<td>0.92</td>
<td>1.14</td>
<td>1.02</td>
<td>1.05</td>
</tr>
<tr>
<td>FS*</td>
<td>31.60</td>
<td>31.05</td>
<td>37.46</td>
<td>33.81</td>
<td>34.53</td>
</tr>
<tr>
<td>TPFR*</td>
<td>0.36</td>
<td>0.38</td>
<td>0.40</td>
<td>0.36</td>
<td>0.41</td>
</tr>
<tr>
<td>TPFR*</td>
<td>0.38</td>
<td>0.40</td>
<td>0.40</td>
<td>0.35</td>
<td>0.41</td>
</tr>
<tr>
<td>FWT</td>
<td>35.37</td>
<td>34.75</td>
<td>42.79</td>
<td>29.23</td>
<td>39.35</td>
</tr>
</tbody>
</table>

Values are mean±SD.

BSA, body surface area; HR, heart rate; EDD, end-diastolic dimension; ESD, end-systolic dimension; EDH, end-diastolic wall thickness; ESH, end-systolic wall thickness; PFR, peak filling rate; PTR, peak thinning rate; ESWS, end-systolic wall stress; Vcfc, rate-adjusted mean velocity of shortening; FS, fractional shortening; TPFR, time to peak thinning rate; TPFR, time to peak filling rate; FWT, fractional wall thinning.

*Significance testing displayed for adjusted measure only (See Table 1); \(p<0.001\) by ANOVA, aspirin vs. γ-globulin–treated groups; \(p<0.05\) by ANOVA, aspirin-treated vs. control group.
had a higher mean stress-adjusted Vcfc in periods 2
\(p=0.007\) and 4 \(p=0.017\). Subsequent to 1 year
after disease onset, we could detect no difference in
contractility between children in the two treatment
groups. Compared with normal subjects, children
who received only aspirin therapy had lower con-
tractility in period 1 \(p=0.006\), period 2 \(p=0.016\),
period 3 \(p=0.002\), and period 4 \(p=0.005\). In
contrast, contractility for the \(\gamma\)-globulin–treated
children differed from that of normal subjects in period 1
\(p=0.001\) but not in any subsequent time periods.

Patients in the two treatment groups did not differ
significantly in adjusted indexes of early diastolic
function. Compared with normal subjects, patients
 treated with aspirin alone had higher adjusted time
to peak filling rates in periods 2 and 5 \(p=0.013\ and
0.015\), respectively. No differences were found
between normal subjects and \(\gamma\)-globulin–treated
patients with Kawasaki syndrome in any para-

eters of early diastolic function.

Relation of Indexes of Inflammation to Left
Ventricular Contractility

Laboratory indexes of acute inflammation were
prospectively obtained in the same subgroup of
children enrolled in the therapeutic trial. We
explored whether the intensity and duration of
elevation of these indexes could predict left ventric-
ular contractility. White blood cell count, absolute
band count, and serum concentration of \(\alpha_1\)-
antitrypsin (reflecting the acute phase response)
were measured at the time of enrollment (within 10
days of fever onset) and then 4–6 days, 2 weeks,
and 7 weeks after enrollment. When controlling for
treatment group, we found that none of the labora-
tory indexes was significantly associated with con-
tractility in the same period.

Similarly, we could detect no significant relation
between systolic contractility or diastolic function
parameters and the presence of coronary artery
abnormalities. However, the relatively small num-
ber of patients with such abnormalities precludes
sufficient power to exclude their association with
indexes of left ventricular function.

Discussion

We found that Kawasaki syndrome causes abnor-
malities of left ventricular systolic function that
may persist after resolution of clinical and labora-
tory indexes of systemic inflammation. In addition,
these function abnormalities improved more rapidly
in children treated in the acute phase with high-dose
intravenous \(\gamma\)-globulin with aspirin than in those
who received aspirin alone. Subsequent to 1 year
after onset of Kawasaki syndrome, we could detect
no differences in indexes of left ventricular systolic
and diastolic function in patients with Kawasaki
syndrome in the two treatment groups compared
with each other or compared with control subjects.

Abnormalities of myocardial function on echo-
cardiographic assessment are consistent with patho-
logic features of the myocardium in Kawasaki
syndrome.29 In an autopsy series, Fujiwara and
Hamashima30 found that interstitial myocarditis was
prominent in the last month after disease onset but
that massive fibrosis of the myocardium and endocar-
dial fibroelastosis were observed in patients dying
in the late phase of the disease (range, 40 days to 4
years). Most deaths resulted from complications of
coronary artery lesions. In another autopsy series,
Tanaka et al31 reported hypertrophy and myocardial

![Figure 1. Plots of relation of the rate-adjusted velocity of shortening (Vcfc, above) and percent fractional shortening (%FS, below) to afterload (end-systolic wall stress) in normal subjects less than 8 years of age. Each plot depicts the mean population regression line and 95% confidence intervals for these normal subjects.](http://circ.ahajournals.org/Downloaded from)
degeneration but could not ascertain from their data whether this was secondary to ischemia or myocarditis. Of greater relevance is a study by Yutani et al in which 201 patients with Kawasaki syndrome underwent biopsy of the right ventricular myocardium to assess the evolution and course of myocardial changes. Aneurysms of the coronary arteries were present in 12.9% of patients. The time interval between onset of disease and myocardial biopsy ranged from 2 months to 11 years. Myocardial abnormalities, including fibrosis and disarrangement, abnormal branching, and hypertrophy of myocytes, could be detected in all time periods after disease onset; their severity was unrelated to the presence of coronary artery abnormalities. Histologic sequelae of myocarditis thus appeared to persist.

Patients included in these autopsy and biopsy series did not receive intravenous $\gamma$-globulin therapy. In view of the echocardiographic evidence that administration of intravenous $\gamma$-globulin promotes more rapid recovery of myocardial contractility, it may be speculated that such therapy decreases the long-term histologic abnormalities of the myocardial contractility.
of myocardial dysfunction resulting from Kawasaki syndrome. The use of high-dose intravenous γ-globulin in the acute phase of Kawasaki syndrome was reported previously to decrease the prevalence of coronary artery abnormalities and the severity of systemic inflammation. The effect on myocardial mechanics is especially interesting because few therapeutic agents have been shown to rapidly reverse the ventricular dysfunction associated with myocarditis due to other causes. The mechanism by which γ-globulin ameliorates the myocarditis of Kawasaki syndrome is unknown. Previous work suggests that its mode of action is likely to involve, in part, modulation of the immune system. The beneficial effect of intravenous γ-globulin on myocardial contractility constitutes an additional benefit of its use in this disease.

Previously published reports on left ventricular mechanics after Kawasaki syndrome have produced conflicting results concerning the relation of coronary artery lesions to persistence of left ventricular dysfunction. Some investigators have reported resolution of decreased left ventricular function in the convalescent phase of the illness except in children with aneurysms. One report related persistence of dysfunction to the severity of coronary artery involvement. Anderson et al were unable to detect a relation between coronary artery lesions and either early or late myocardial dysfunction, findings similar to those of the present
FIGURE 3. Plots of relation of the rate-adjusted velocity of shortening (Vcfc) to afterload (end-systolic wall stress, ESS) in patients treated in the acute phase of Kawasaki syndrome (KS) with high-dose intravenous \( \gamma \)-globulin plus aspirin (IVGG, above) compared with aspirin alone (ASA, below) during five time periods. The mean population regression lines and 95% confidence intervals for normal subjects in our laboratory are shown in each plot as in Figure 1. Panel A: In period 1 (\( \leq 10 \) days after onset of Kawasaki syndrome), no significant difference was found between patients in the two treatment groups. Panel B: In period 2 (11–31 days after disease onset), children treated with \( \gamma \)-globulin had significantly increased contractility (i.e., higher ESS-Vcfc relation) compared with those receiving aspirin alone \( (p=0.007) \). Panel C: In period 3 (1–3 months after disease onset), patients treated with \( \gamma \)-globulin tended to have increased contractility compared with those receiving aspirin alone, but the increase was not significant. Panel D: In period 4 (3–12 months after disease onset), patients treated with \( \gamma \)-globulin had significantly increased contractility (i.e., higher ESS-Vcfc relation) compared with those receiving aspirin alone \( (p=0.017) \). Panel E: In period 5 (1–3 years after disease onset), patients in the two treatment groups had similar contractility.

study and consistent with the histologic studies noted above. The differences in conclusion reached by these investigators may be attributable, in part, to variation in the severity of coronary lesions among the patient populations studied (e.g., presence of children with myocardial infarction).

The occurrence of late abnormalities of left ventricular function among children without coronary artery lesions also has been controversial. Several studies\(^{14,20} \) noted resolution of left ventricular dysfunction within 2 months of disease onset, whereas Anderson et al\(^{15} \) described long-term abnormalities of both left ventricular size and of systolic and early diastolic function. Prior studies did not include children treated with intravenous \( \gamma \)-globulin and differed from each other and from the present study in methods of evaluation of myocardial function. These studies have relied on load-dependent indexes of ventricular function such as fractional shortening. We noted a wide range of afterload (end-systolic stress) with rapid changes over time, rendering such indexes incapable of accurately detecting abnormal contractility in these patients. The stress-adjusted Vcfc has previously been shown\(^{21} \) to provide a load-independent index of contractility, enabling us to recognize changes in contractility over time and differences between groups.

The optimal methods for normalizing diastolic function parameters remains controversial. In previous studies, we have found such parameters to be dependent on both left ventricular dimensions and on systolic function.\(^{28} \) Adjusting for covariates related to dimension and systolic function, we did not find important differences in early diastolic function between either Kawasaki syndrome patients and control subjects or between patients treated with \( \gamma \)-globulin plus aspirin compared with aspirin alone.

In comparing left ventricular contractility among children treated with intravenous \( \gamma \)-globulin plus aspirin with that of children treated with aspirin alone, we did not study all patients sequentially in all time periods. Such differential follow-up makes it impossible to exclude selection bias, although the timing of echocardiographic evaluations was determined largely by the patient’s ability to cooperate with protocol-specified time windows and was determined by the feasibility of obtaining a stress-velocity analysis related to patient cooperation or sedation. Relatively few children were treated with aspirin alone in period 1 (within 10 days of onset) or with either treatment regimen in period 4 (3–12 months). For these reasons, it would be desirable for the results reported here on the differential effects of the treatment regimens to be confirmed in a larger study. Such a study probably could not be prospectively performed in North America at the present time because high-dose intravenous \( \gamma \)-globulin is almost universally administered for acute Kawasaki syndrome to decrease the prevalence of coronary artery abnormalities.

We conclude that early abnormalities of left ventricular contractility and myocardial performance, as assessed by two-dimensional echocardiography, have generally resolved by 1–3 years after Kawasaki syndrome onset and that recovery is accelerated by administration of high-dose intravenous \( \gamma \)-globulin in the acute phase. These data suggest an encouraging long-term outlook for myocardial function in this disease, despite previous reports of persistent late myocardial histologic abnormalities. Assessment of the full impact of Kawasaki syndrome on heart function must await the follow-up of these children into adulthood.
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References


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