Evaluation of myocardial ischemia in Kawasaki disease by dobutamine stress signal-averaged ventricular late potentials

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Received 25 March 1997; accepted 8 July 1997

Abstract

Objective: To determine the possibility of diagnosing myocardial ischemia from signal-averaged electrocardiographic late potentials (LPs) in patients with Kawasaki disease. Methods: Dobutamine stress LPs were obtained in 85 children with a history of Kawasaki disease (48 without coronary artery lesions, 19 with coronary artery lesions without myocardial ischemia, and 18 with myocardial ischemia). The infusion of dobutamine was started at 5 μg/kg/min, increased to 30 μg/kg/min. The presence of LPs was determined by the filtered QRS duration, the root mean square voltage during the last 40 ms, and the duration of the signal under 40 mV. Results: Among the children without coronary lesions, LPs were detected in 4.2% at rest and in 2.1% with dobutamine stress. Among the group with coronary lesions but without ischemia, LPs were found in 5.3% at rest and in 5.3% with stress. In the group with ischemia, LPs were present in 44.4% at rest and in 77.8% with stress. The sensitivity for myocardial ischemia was 72.7% at rest and 87.5% with stress (p < 0.05), and the specificity was 86.5% at rest and 94.2% with stress. Conclusion: LPs associated with dobutamine stress testing are useful for identifying myocardial ischemia in children with Kawasaki disease, especially in those who cannot tolerate testing involving physical exercise.

Keywords: Signal-averaged electrocardiography; Dobutamine stress test; Myocardial ischemia; Kawasaki disease

1. Introduction

Coronary artery aneurysm occurs in about 10–20% of patients with Kawasaki disease, a form of systemic vasculitis [1,2] that often leads to coronary obstruction [3]. Myocardial ischemia and myocardial infarction affect the lives of patients with a history of Kawasaki disease by restricting their activity. These disorders, especially silent myocardial ischemia, are not easy to assess by noninvasive, objective, and convenient methods.

Signal-averaged electrocardiograph (SAE) ventricular late potentials (LPs) represent the delayed and fragmented activation potentials of the damaged myocardium. Such data provide information useful in evaluating the prognosis of patients with underlying heart disease such as cardiomyopathy, ischemic heart disease, and serious spontaneous ventricular arrhythmia [4–12]. As we previously reported, children with Kawasaki disease with myocardial ischemia and old myocardial infarction often exhibit signal-averaged LPs [13].

In 1984, Mason et al. [14] proposed using dobutamine, a sympathomimetic amine, in a stress test in combination with 201Tl scintigraphy. In adults, the dobutamine stress test is reported to readily detect regions of myocardial ischemia [15–25]. We sought a noninvasive, relatively easy, repeatable method that would be suitable for use in detecting myocardial ischemia in children with Kawasaki disease. We thought that silent myocardial ischemia would be relatively easy to detect by SAE in patients with Kawasaki disease in whom the location of the coronary artery lesions was already known from echocardiography.
Table 1
Characteristics of patients with Kawasaki disease

<table>
<thead>
<tr>
<th>Group</th>
<th>Subjects (M:F)</th>
<th>Average age (yr)</th>
<th>Average BSA (m²)</th>
<th>Average dose of dobutamine (µg/kg/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>48 (32:16)</td>
<td>8.0</td>
<td>1.0</td>
<td>29.7</td>
</tr>
<tr>
<td>C</td>
<td>19 (14:5)</td>
<td>8.1</td>
<td>1.1</td>
<td>29.7</td>
</tr>
<tr>
<td>I</td>
<td>18 (13:5)</td>
<td>11.6</td>
<td>1.3</td>
<td>28.6</td>
</tr>
</tbody>
</table>

M: male; F: female; BSA: body surface area; Group N: without coronary lesions; Group C: with coronary artery lesions but without ischemia and old myocardial infarction; Group I: with myocardial ischemia.

and coronary angiography. Accordingly, we evaluated the usefulness of dobutamine stress LPs in identifying myocardial ischemia in children with Kawasaki disease.

2. Methods

2.1. Subjects

We studied 85 Japanese patients with Kawasaki disease in the chronic stage who had been observed at the Nippon Medical School Hospital between 1993 and 1995. The ages of the 59 males and 26 females ranged from 10 months to 20 years (mean 9.1 years). All subjects underwent coronary angiography, left ventriculography, and echocardiography. If coronary dilation and/or stenosis were found subjects were studied by exercise ²⁰¹Tl myocardial scintigraphy and exercise electrocardiography. On the basis of these test results, subjects were divided into three groups. Group N consisted of 48 children (aged from 10 months to 16 years) without coronary artery lesions. Group C comprised 19 children (aged from 5 years to 18 years) with coronary artery lesions but without myocardial ischemia and old myocardial infarction. The 18 subjects (aged from 5 years to 20 years) with myocardial ischemia were designated Group I (Table 1). No patient had a history of myocardial infarction, documented sustained ventricular tachycardia, or ventricular arrhythmia greater than grade II (Lown’s classification), as confirmed by 24-hour electrocardiographic monitoring. Patients with evidence of bundle branch block were excluded from study. Children with coronary artery lesions were administered aspirin (5 mg/kg/day), but none was receiving antiarrhythmic agents. The purpose of this study was fully explained, and informed consent was obtained from each patient and/or the parents. The investigation conformed with the principles outlined in the Declaration of Helsinki.

2.2. SAE

The SAE was recorded using a multipurpose electrocardiograph (VCM 3000, Fukuda Electronics Ltd., Tokyo, Japan) and standard bipolar X, Y, and Z leads by the method of Simson [4]. A total of 200 cycles was averaged in each child. The band pass filters were set at 40–300 Hz, and the noise level was less than 1 µV. The measurement

![Fig. 1](image-url) Measurement of signal-averaged electrocardiographic parameters. (A) f-QRSd: filtered QRS duration, RMS: root mean square voltage during 40 ms in the filtered QRS terminal part. (B) LAS: duration of signal under 40 µV.
Table 2
BSA-related criteria for positive LPs in children

<table>
<thead>
<tr>
<th>BSA (m²)</th>
<th>RMS (µV)</th>
<th>f-QRSd (ms)</th>
<th>LAS (ms)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 0.3</td>
<td>&lt; 30</td>
<td>&gt; 95</td>
<td>&gt; 25</td>
</tr>
<tr>
<td>0.3 &lt; 0.5</td>
<td>&lt; 25</td>
<td>&gt; 110</td>
<td>&gt; 30</td>
</tr>
<tr>
<td>0.5 &lt; 1.2</td>
<td>&lt; 20</td>
<td>&gt; 115</td>
<td>&gt; 30</td>
</tr>
<tr>
<td>≥ 1.2</td>
<td>&lt; 20</td>
<td>&gt; 125</td>
<td>&gt; 30</td>
</tr>
</tbody>
</table>

BSA: body surface area; LPs: late potentials; RMS: root mean square voltage during the last 40 msec; f-QRSd: filtered QRS duration; LAS: duration of signal under 40 µV.

of late potentials utilized the vector magnitude method. The vector magnitude of the voltage was calculated as \( V = \sqrt{X^2 + Y^2 + Z^2} \).

The LPs were evaluated by filtered QRS duration (f-QRSd), root mean square voltage during the last 40 ms (RMS), and duration of the signal under 40 µV (LAS) (Fig. 1). Rest and dobutamine stress LPs were considered to be present if the patient exhibited more than one of these three parameters, using our criteria for the differences in body surface area [13,26] (Table 2).

The investigators who interpreted the SAE were blinded to the results of clinical tests.

2.3. Dobutamine administration

Dobutamine was administered at initial dose of 5 µg/kg/min for 3 minutes, increased by 5 µg/kg/min every 3 minutes to a maximum of 30 µg/kg/min. Young children were sedated during the dobutamine stress test. The administration of dobutamine was halted when intolerable chest pain, palpitations, headache, nausea, or other symptoms were present; when the systolic blood pressure rose above 200 mmHg; when there were frequent episodes of ventricular arrhythmias, or when sustained ventricular tachycardia intervened.

2.4. Statistical evaluation

Data are reported as mean values ± SD. Results were analyzed by one-way analysis of variance (ANOVA) (Scheffe’s method), two-way ANOVA (Scheffe’s method), the paired t test, and the proportion test (binomial distribution). Differences between groups were considered statistically significant at a level of \( p < 0.05 \).

3. Results

3.1. Hemodynamics

The heart rate and systolic blood pressure were significantly higher at rest than during dobutamine stress testing in each group (Fig. 2). The double product, defined as heart rate multiplied by systolic pressure, showed a significant increase, nearly twice doubling with dobutamine stress compared with the value at rest in each group.

3.2. SAE

According to criteria based on body surface area (Table 2), we observed LPs at rest in 2 of the 48 children (4.2%) in Group N, in 1 of the 19 children (5.3%) in Group C, and in 8 of the 18 children (44.4%) in Group I. After the maximum dose of dobutamine, LPs were exhibited by 1 child (2.1%) in Group N, 1 child (5.3%) in Group C, and 14 children (77.8%) in Group I (Figs. 3 and 4). The incidence of LPs in Group I was significantly higher than that in the other groups, both at rest and with stress (\( p < 0.01 \)). The incidence of LPs was significantly higher after dobutamine stress compared with the incidence at rest in Group I (\( p < 0.05 \)).

The value of RMS in Group I was significantly decreased with dobutamine stress, being 22.7 ± 8.0 at rest and 18.2 ± 8.4 after stress (\( p < 0.05 \)). The same tendency was seen for f-QRSd (116.5 ± 8.8 at rest and 121.2 ± 9.1 after stress in Group I, \( p < 0.01 \)). There were no statistically significant differences in the values of RMS and f-QRSd in Group N and Group C at rest and after stress.

Fig. 2. Hemodynamic changes produced by dobutamine stress testing. (A) Heart rate. (B) Systolic blood pressure. (C) Double product (heart rate × systolic blood pressure). Group N: children with Kawasaki disease without coronary artery lesions. Group C: children with coronary artery lesions but without myocardial ischemia and old myocardial infarction. Group I: children with myocardial ischemia. Hatched bars show the value at rest, and solid bars show the value during dobutamine stress testing. * \( p < 0.01 \).
There was no significant difference in the LAS among the three groups at rest and after stress.

The sensitivity of each parameter for detecting myocardial ischemia was as follows: 36.4% at rest and 72.4% with stress for RMS ($p < 0.05$), 18.2% both at rest and with stress for f-QRSd, and 54.5% at rest and 72.7% with stress for LAS ($p < 0.05$) (Fig. 5). The sensitivity of f-QRSd was significantly lower than that of the other parameters, which were equally sensitive. Overall, the sensitivity of LPs for detecting myocardial ischemia was

![Fig. 3. Incidence of LPs in each group. Hatched bars show the value at rest, and solid bars show the value during dobutamine stress testing. * $p < 0.05$](image)

![Fig. 4. LPs at rest and during dobutamine stress testing in a 5.5 year old boy (Group I). (A) At rest, LPs were negative (heart rate: 80–92 beats/min, f-QRSd: 109 ms; RMS: 20.6 $\mu$V; LAS: 29.3 ms). (B) During dobutamine stress (30 $\mu$g/kg/min), LPs were positive (heart rate: 162–184 beats/min; f-QRSd: 122 ms; RMS: 9.5 $\mu$V; LAS: 35.4 ms).](image)
Fig. 5. The specificity and sensitivity for myocardial ischemia of RMS, f-QRSd, and LAS at rest and during dobutamine stress testing. Hatched bars show the value at rest, and solid bars show the value during dobutamine stress. * $p < 0.01$

72.7% at rest and 87.5% during dobutamine stress ($p < 0.05$). The specificity for detecting myocardial ischemia was 86.5% at rest and 94.2% during stress.

3.3. Adverse effects

Dobutamine was discontinued because of adverse events before the maximum dose was administered in one child in Group N (final dose 20 $\mu$g/kg/min), in one child in Group C (25 $\mu$g/kg/min), and in 3 children in Group I (15, 20, 25 $\mu$g/kg/min). These adverse events consisted of headache in 3 patients and elevation of systolic blood pressure above 200 mmHg in 2 patients. These adverse events disappeared quickly after the infusion of dobutamine was discontinued. Ventricular arrhythmia was not observed in any patients.

4. Discussion

Kawasaki disease has its onset at a mean age of about 1 year. Early detection of myocardial ischemia using a noninvasive, convenient, and repeatable method is needed for identifying these young patients. The presence of myocardial hibernating and stunning can be determined by exercise echocardiography [27,28] and exercise myocardial scintigraphy [29,30]. However, exercise myocardial scintigraphy is invasive and cannot be repeated frequently. It is difficult to evaluate the presence of myocardial ischemia in children by means of exercise echocardiography, because the heart rate is significantly increased during dobutamine stress. Signal-averaged electrocardiographic LPs are objective, noninvasive, convenient, and can be assessed repeatedly. However, it is necessary to determine first the criteria related to body surface area in children [13,31], because the thickness of the ventricular wall and intraventricular conduction in children vary according to their growth and development.

The LPs on the SAE represent the delayed and fragmented activation potentials of the damaged myocardium. The presence of LPs is associated with an increased risk of arrhythmias and sudden death in patients with coronary artery disease and in those with myocardial infarction [3–8].

When used in combination with radionuclide scintigraphy, pharmacological stress testing is more sensitive than exercise testing for detecting coronary artery disease [17–26]. Stress can be induced pharmacologically in young children who cannot tolerate physical exercise testing, and can induce myocardial ischemia by increasing the myocardial demand for oxygen. Such potent coronary vasodilators as dipyridamole or adenosine [16] can cause nonhomogeneous myocardial perfusion.

A high dose (> 15 $\mu$g/kg/min) increases the heart rate, arterial pressure, and contractility, and may cause a heterogeneous distribution of myocardial blood flow. However, such effects are not as marked as those produced by specific coronary vasodilators such as dipyridamole and adenosine. Comparison of various pharmacological stress tests performed in conjunction with radionuclide scintigraphy showed a similar sensitivity and specificity [22–25].

Because their assessment is based on micropotentials, the presence of LPs should be carefully determined. Ventricular wall thickness and intraventricular conduction vary considerably in children, according to their growth and development. Therefore, different criteria for the presence of LPs should be formulated according to the BSA. We had no problem in recording, calculating and determining the LPs during the rapid heart rate induced by dobutamine stress (Fig. 4).

The presence of our BSA-related criteria was considered to verify the presence of LPs induced by dobutamine
stress testing. We judged whether dobutamine stress LPs were positive or negative using the same criteria as those applied to healthy controls at rest. The incidence of LPs was significantly increased by dobutamine stress testing in Group I. We suspected that the mass of ischemic regions was increased by dobutamine stress. With the infusion, the incidence of conversion from negative to positive LPs in the ischemic myocardium was significantly increased vs. the incidence observed at rest. We also detected LPs in a few children with a history of Kawasaki disease who were free of myocardial ischemia (Groups N and C). Although the clinical implications of LPs in these children are unclear, it is possible that myocarditis occurs in the acute stage of Kawasaki disease, and cardiomyopathy may develop late, contributing to the appearance of LPs.

The sensitivities of RMS and LAS were higher than that of f-QRSd at rest and were markedly increased by dobutamine stress, especially RMS. The change rate of RMS in Group I was the highest of the three parameters of LPs in the three groups. We therefore consider RMS to be the most sensitive of the three parameters. However, we could not determine the relationship between the degree of myocardial ischemia and incidence of positive LPs in this study.

We conclude that LPs become more sensitive to myocardial ischemic change in children with Kawasaki disease during dobutamine stress testing. Although the presence of LPs does not indicate the presence of myocardial ischemia, this parameter provide quantitative information on the ischemic area of the myocardium. This procedure was used safely in infants and was relatively noninvasive, repeatable, and convenient. The method is thus useful for detecting myocardial ischemia in children with a history of Kawasaki disease.

References


