Application of Signal-Averaged Electrocardiogram to Myocardial Damage in the Late Stage of Kawasaki Disease

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Background  Myocardial damage occurs in the late stage of Kawasaki disease (KD) regardless of whether coronary artery lesions (CALs) are present.

Methods and Results  A signal-averaged electrocardiogram (ECG) was performed in 23 patients who were in the late stage of KD (CAL was found in 12 and no CAL (non-CAL) was found in 11) and 10 healthy controls. Filtered QRS duration and the root-mean-square voltage in the last 40 ms of the QRS complex were measured using time-domain analysis. Additionally, the area ratio (AR), (area of 20–50 Hz)/(area of 0–20 Hz)×100, was calculated by frequency domain analysis. These findings were compared with the clinical data and histopathological findings. In time-domain analysis, there were no significant differences among the 3 groups. In frequency domain analysis, the AR in CAL was significantly higher than that in the other 2 groups. Furthermore, all 4 patients who underwent an endomyocardial biopsy showed a high AR and abnormal histopathological features.

Conclusions  The findings of the present study suggest that patients in the late stage of KD have abnormal findings on signal-averaged ECG even without stenotic lesions, arrhythmia or ischemia, a condition that might reflect histopathological changes in the myocardium in the late stage of KD. (Circ J 2006; 70: 1443–1445)

Key Words: Frequency domain analysis; Histopathological findings; Kawasaki disease; Signal-averaged electrocardiogram

Kawasaki disease (KD) was first described in 1967 as an acute febrile illness of young children that is complicated by a vasculitis preferentially affecting the coronary arteries. Myocarditis is also a complication of patients in the acute stage of KD, and might cause histological alterations of the myocardium, such as interstitial fibrosis. Several reports have demonstrated that histological abnormalities persist, even in patients in the late stage of KD without coronary involvement.1–3 However, it is difficult to perform non-invasive tests that quantitatively assess the severity of the myocardial changes.

Time-domain and frequency domain analysis of the signal-averaged electrocardiogram (SAECG) have been introduced to detect abnormal myocardial electrical activity and to predict significant ventricular arrhythmia.4 More histological alterations of the myocardium might induce the greater electrical turbulence instability. Thus, this study was prospectively designed to determine whether SAECG analysis is a useful tool for assessing myocardial histological changes after KD in patients in the late stage of KD.

Methods

Subjects  Twenty-three patients after KD, aged 2–16 years (mean 8.6 years), were divided into 2 groups according to their coronary status on echocardiogram (Table 1): 12 patients with coronary dilatation and/or aneurysms comprised the coronary artery lesion (CAL) group and the remaining 11 patients without coronary complications comprised the non-CAL group. There were no differences between the 2 groups in gender, age, onset of KD, and interval after onset. None had coronary ischemia or significant ventricular arrhythmia, and none had a significant medical history or underlying chronic disease. Ten healthy age-matched volunteers comprised a control group, and were investigated using the same protocol. Written informed consent was obtained from all children and their parents.

Time-Domain Analysis  The SAECG was recorded from a modified X-, Y- and Z-lead system using the Multicardiner VCM-3000 (Fukuda

Table 1  Coronary Status of 23 Post-Kawasaki Disease Patients

<table>
<thead>
<tr>
<th></th>
<th>Acute stage</th>
<th>Late stage</th>
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</thead>
<tbody>
<tr>
<td>CAL</td>
<td>12</td>
<td>5</td>
</tr>
<tr>
<td>Aneurysm/dilatation</td>
<td>12</td>
<td>5</td>
</tr>
<tr>
<td>Normal</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Non-CAL</td>
<td>11</td>
<td>11</td>
</tr>
<tr>
<td>Normal</td>
<td>11</td>
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CAL, coronary artery lesion.
Denshi Co Tokyo, Japan) in an electrically shielded room. The gain of the amplifier was 1,000 and the noise input was <0.6 μV. The signal from each lead was recorded from analog to digital data with 12-bit accuracy at a sampling rate of 1 kHz. All of the digital data were stored on a floppy disk. The signals were amplified, digitized and averaged with a bidirectional filter at frequencies of 25–250 Hz. The duration of the filtered QRS complex (fQRS) and the root-mean-square voltage in the last 40 ms of the fQRS (RMS) were determined by algorithm.6

**Frequency Domain Analysis**

Frequency domain analysis was performed on a 100-ms segment from 40 ms before to 60 ms after the end of the QRS wave on the signal averaged Z-lead as described by Yamada et al.7,8 This component was identified by using the cursor of a computer graphic program and standard ECG criteria. These data were multiplied by the Blackmann–Harris 4-term window function to reduce spectral leakage from edge discontinuities after a direct-current component was removed from the data. The data were padded with zeros to fill a 512-point array, and the fast Fourier transform was applied to determine frequency content. After the analysis, the magnitude vs frequency plot curve was obtained, and the area ratio (AR) was calculated by dividing the area under the spectrum curve between 20 and 50 Hz, multiplied by 100, and by the area between 0 and 20 Hz.

**Statistical Analysis**

All values are expressed as mean±SD. ANOVA followed by Scheffe’s equation was used to compare the results for the 3 groups. A p value <0.05 was accepted as being statistically significant.

**Results**

**Comparison of Time-Domain Analysis Among the 3 Groups**

The respective fQRS and RMS values were 105.1±8.6 ms and 36.0±13.8 μV in the CAL group, 109.0±11.4 ms and 35.6±19.9 μV in the non-CAL group, and 109.7±9.3 ms and 33.5±10.3 μV in the control group. There were no significant differences among the 3 groups (Fig 1A,B).

**Comparison of Frequency Domain Analysis Among the 3 Groups**

The AR value was 21.4±5.2 in the CAL group, 15.1±2.9 in the non-CAL group, and 11.7±1.8 in the control group. AR in the CAL group was significantly higher than in the other 2 groups (p<0.01). The AR did not significantly differ between the non-CAL and control groups (Fig 1C).

**Histopathological Study in Patients With a High AR**

Four patients with extremely high AR underwent a right ventricular endomyocardial biopsy, at a mean of 2.9 years after the onset of KD. Several biopsy samples were obtained from the septal aspect of the right ventricle. The specimens were fixed in 10% neutral formaldehyde and stained with hematoxylin-eosin and elastica van Gieson. Each specimen was evaluated by light microscopy for endocardial surface alterations, myocardial cell changes, vascular abnormalities,
Inflammatory cell infiltrates and the degrees of fibrosis.

These 4 patients had abnormal histological features such as hypertrophy of the myocytes (100%), interstitial and replacement fibrosis (100%), and abnormal branching and bizarre nuclei of myocytes (50%). None of the biopsy specimens demonstrated significant cellular infiltration (Fig 2).

Discussion

The long-term clinical issue in KD mainly concerns coronary artery lesions, which are involved in aneurysm formation, thrombotic occlusion, progression to ischemic heart disease and premature atherosclerosis. Mild coronary artery lesions tend to regress gradually in the late stage of KD. However, myocardial changes, such as myocardial hypertrophy and degeneration, and interstitial fibrosis, are found in all KD patients regardless of the presence or absence of the coronary artery lesions. These findings are attributed to the myocarditis in the acute stage of KD and might become persistent over time.

SAECG has been introduced as a non-invasive and useful method of evaluating electric instability and a late conduction site, which provides the basis for re-entrant ventricular arrhythmia. Ogawa et al. used this method in patients with myocardial ischemia and old myocardial infarction in KD and were able to demonstrate these disorders non-invasively by using time-domain analysis. In the present study, time-domain analysis did not demonstrate significant differences among the CAL, non-CAL, and control groups. We speculate that there are 2 reasons for this. First, the present study population comprised children aged 2–16 years. We did not consider their growth and development. Ogawa et al. estimated an abnormality of time-domain analysis using 3 factors (fQRS, RMS and 1 other factor) with consideration of body surface area. However, we did not measure body surface areas during the examination, and set only 2 parameters to detect abnormality. Consequently, we compared age-matched groups instead of considering body surface area. Second, there were no patients with myocardial ischemia or significant ventricular arrhythmia, which are the 2 main conditions investigated by time-domain analysis.

Frequency domain analysis clearly demonstrated that the AR in the CAL group was significantly higher than in the other 2 groups, suggesting a dominant high-frequency electrical component in the CAL group. Although the clinical significance of increased AR remains to be determined, our study offers some advantage over time-domain analysis, using frequency domain variables in signal-averaged electrocardiograms during sinus rhythm in patients with paroxysmal atrial fibrillation. J Am Coll Cardiol 1992; 19: 559–563.

Frequency domain analysis may play a role in assessing the grade of myocardial change rather than in predicting ventricular arrhythmia in late-stage KD patients.

There are no well-established criteria for frequency domain analysis of the SAECG regarding choice of window function, segment length of the window, or AR. In the present study, we performed frequency domain analysis according to the method described by Yamada et al. The possibility that another AR might have obtained better results cannot be excluded, because we used only one AR. In addition, further histological studies are necessary in patients with low AR to confirm the relationship between AR and myocardial histological changes.

In conclusion, the present study results indicate that AR, using frequency domain SAECG analysis, was significantly higher in the CAL group than in the other groups, probably because of histological changes in the myocardium.

References