Electrocardiographic Diagnosis of Hypertrophic Cardiomyopathy in the Pre- and Post-Diagnostic Phases in Children and Adolescents

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Background: The usefulness of electrocardiographic (ECG) voltage criteria for diagnosing hypertrophic cardiomyopathy (HCM) in pediatric patients is poorly defined.

Methods and Results: ECGs at the 1st grade (mean ± SD age 6.6±0.3 years) were available for 11 patients diagnosed with HCM at around the 7th grade (13.2±0.3 years). ECGs were available for another 64 patients diagnosed with HCM in the 1st (n=15), 7th (n=32), and 10th (n=17) grades. Fifty-one voltage criteria were developed by grade and sex using 62,841 ECGs from the general population. Voltage criteria were set at the 99.95th percentile (1/2,000) point based on the estimated prevalence of childhood HCM (2.9 per 100,000 [1/34,483]) to decrease false negatives. Conventional criteria were from guidelines for school-aged children in Japan. Of 11 patients before diagnosis, 2 satisfied conventional criteria in 1st grade; 5 (56%) of the remaining 9 patients fulfilled 2 voltage criteria (R wave in limb-lead I [RI]+S wave in lead V3 [SV3] and R wave in lead V3 [RV3]+SV3). Robustness analysis for sensitivity showed RV3+SV3 was superior to RI+SV3. For all patients after diagnosis, RI+SV4 was the main candidate. However, conventional criteria were more useful than voltage criteria.

Conclusions: Early HCM prediction was possible using RV3+SV3 in >50% of patients in 1st grade. Voltage criteria may help diagnose prediagnostic or early HCM, and prevent tragic accidents, although further prospective studies are required.

Key Words: Children; Diagnosis; Electrocardiography; Hypertrophic cardiomyopathy; Prevention
Hypertrophic cardiomyopathy (HCM) remains one of the major causes of sudden cardiac death (SCD) or aborted cardiac arrest (ACA) in youth. Electrocardiographic (ECG) findings overlap between HCM and athletes. Current recommendations for ECG interpretation are based on asymptomatic athletes aged 12–35 years. In contrast, the median age of patients with childhood-onset HCM was reported to be 12.2 years. A recommendation for ECG interpretation is required for asymptomatic children because many potential competitive or professional athletes may start sports activities before these ages. Early diagnosis and early intervention, such as lifestyle modification or the introduction of medications, may prevent children and adolescents from competitive or professional sports-related SCD or ACA.

A standard 12-lead ECG in HCM patients shows a variable combination of left ventricular hypertrophy (LVH), ST and T wave abnormalities, and pathological Q waves. Of these, voltage criteria have been reported for LVH screening. However, despite interventricular hypertrophy being a characteristic feature of HCM, few studies have investigated whether single R or S waves or a combination of R and S waves can be used to detect interventricular hypertrophy in pediatric HCM patients.

A nationwide, school-based ECG screening program for heart diseases in the 1st, 7th, and 10th graders (aged 6, 12 and 15 years, respectively) in Japan was set by law in 1994; the program is also performed in 4th graders in some regions. As part of this screening program in Japan, HCM is most frequently diagnosed around the 7th grade. A previous study showed that approximately 60% (27/44) of school-aged children and adolescents who experienced SDS or ACA were not diagnosed with HCM before their school-aged children and adolescents who experienced cardiac events, suggesting that the current screening system may not be effective for the early diagnosis of HCM and may not allow for interventions before the appearance of symptoms. When participants are diagnosed with HCM at the 7th grade screening or later, the 1st grade ECGs are available for review in some areas in Japan where the ECGs of participants are digitally stored.

The aim of the present study was to determine whether voltage criteria could be used to predict a potential diagnosis of HCM at the 1st grade screening in patients who were diagnosed at the 7th grade or later screening (i.e., approximately 6 years before the actual HCM diagnosis). Furthermore, we examined the utility of voltage criteria and conventional criteria for diagnosing HCM patients who were diagnosed at the 1st, 7th, and 10th grade screening.

### Methods

#### Subjects

In all, 124 patients with HCM who visited 1 of 14 hospitals in Japan from 2000 to 2019 and who were <20 years old at their first visit were included in this study. Of 202 ECGs from 124 patients, 44 ECGs from 24 patients with secondary HCM and 37 ECGs from 24 patients with findings that affect the QRS voltages (i.e., complete bundle branch block) were excluded (Figure 1). Patients were divided into pre- and post-diagnostic groups.

This study was approved by the Ethics Committee of the National Hospital Organization Kagoshima Medical Center (27-9 and 27-28).

#### Prediagnostic Group

The prediagnostic group included 11 patients (9 boys, 2 girls) who visited the National Hospital Organization Kagoshima Medical Center and were diagnosed with HCM at a mean (±SD) age of 13.2±2.0 years and whose ECGs at the 1st grade screening program were retrospectively available (Table 1). The mean (±SD) interval between the 1st grade ECG recordings and actual diagnosis was 6.4±1.8 years. A diagnosis of HCM was made when the left ventricular (LV) wall thickness was ≥15mm; this is a robust diagnostic criterion for adults in this group. Two patients with LV wall thickness <15mm were pathologically diagnosed by myocardial biopsy (Cases 10 and 11).

The genetic background in this group was determined using the ClearSeq Halo HS cardiomyopathy panel (Agilent Technologies, Santa Clara, CA, USA), which included 34 genes, and using a bench top-type next-generation sequencing machine (MiSeq; Illumina, San Diego, CA, USA). Data were analyzed using SureCall software (Agilent Technologies). Detected variants were confirmed using the Sanger method and variants classified as pathogenic or likely pathogenic in ClinVar (https://www.ncbi.nlm.nih.gov/clinvar/) were judged as pathogenic mutations.

#### Post-Diagnostic Group

The post-diagnostic group included 64 patients who were...
ECG Diagnosis of an Early Stage of Childhood HCM

Criteria, ECGs of 1st, 7th, and 10th graders among the general population who participated in screening programs were obtained. ECGs were recorded at school at a speed of 25 mm/s and a sampling rate of 500 Hz using a portable PC-based system (Fukuda Denshi, Tokyo, Japan). In the Japanese screening programs, where numerous ECGs of children are recorded at the same time, narrow bandwidth filters (0.5–35 Hz) were occasionally used to remove noise. Thus, we prepared 2 ECG reference values for a narrow bandwidth and a routine bandwidth (0.05–150 Hz), as detailed below.

Reference ECGs for the Narrow Bandwidth

The process used to develop the ECG reference values was previously reported. Briefly, 56,753 digitally stored ECGs of participants in a school-based ECG screening system in Kagoshima, Japan, were obtained. Each ECG was manually reviewed by 2 pediatric cardiologists, and only ECGs with sinus rhythm were included. ECGs of subjects with arrhythmias, ST/T changes, or inappropriate recordings were excluded. Finally, 48,401 ECGs from 16,773 1st graders (8,350 boys, 8,423 girls), 18,126 7th graders (8,943 boys, 9,183 girls), and 13,502 10th graders (6,477 boys, 7,025 girls) were selected.

Reference ECGs to Establish Screening Criteria for Increased R/S Wave Voltages

To establish the screening voltage criteria, ECGs of 1st, 7th, and 10th graders among the general population who participated in screening programs were obtained. ECGs were recorded at school at a speed of 25 mm/s and a sampling rate of 500 Hz using a portable PC-based system (Fukuda Denshi, Tokyo, Japan). In the Japanese screening programs, where numerous ECGs of children are recorded at the same time, narrow bandwidth filters (0.5–35 Hz) were occasionally used to remove noise. Thus, we prepared 2 ECG reference values for a narrow bandwidth and a routine bandwidth (0.05–150 Hz), as detailed below.
Screening Criteria for Increased R/S Wave Voltages. The following 51 voltage criteria were assessed as screening criteria for screening HCM patients at 1/2,000 point in the general population:

1. R/S waves of each single lead
   • An R wave of each of the 12 leads (the voltages of the R and R’ waves were summed if present)
   • An S wave of each of the 12 leads

2. A combination of R/S waves of different leads that have already been published
   • Cornell criteria: R wave in lead aVL (RaVL)+S wave in lead V3 (SV3) [RaVL+SV3] (Criterion A)
   • Pediatric-specific criteria (RaVL+SV2) (Criterion B)
   • Gubner-Ungerleider criteria: R wave in lead I (RI)+S wave in lead III (SIII) [RI+SIII] (Criterion C)
   • Lewis criteria: R1+SIII–(R wave in lead III [RIII]+S wave in lead I [SI]) [RII+SII] (Criterion D)
   • Sokolow-Lyon criteria: SV1+RV5 and SV1+RV6 (Criterion E)
   • The deepest S wave in any lead (S0) and the S wave in lead V4 (SV4) (Criterion F)
   • RaVL+SV4, So+SV3, R1+S2, and R1+SV3 were included to compare Criteria of A, B, and C. Approximately 80% of

The reference population showed the deepest S wave in lead V2. Thus, So+SV2 was not investigated. In addition, the total 12-lead QRS voltage was not investigated in the present study because it is difficult to use in the clinical setting.

3. A combination of an R wave in lead V1 (RV1) and S waves in the mid-precordial leads: RV1+SV2, RV1+SV3, and RV1+SV4

In one case in the prediagnostic group, high voltage R waves in lead V1 and relatively deep S waves in the precordial leads were seen. Thus, a combination of RV1 and S waves in the precordial leads was included.

4. A combination of R/S waves in the mid-precordial leads:
   • RV2+SV2, RV2+SV3, and RV2+SV4
   • RV3+SV2, RV3+SV3, and RV3+SV4
   • RV4+SV2, RV4+SV3, and RV4+SV4

5. A combination of S waves of different mid-precordial leads: SV2+SV3, SV2+SV4, and SV3+SV4.

Screening Criteria for Cardiovascular Disease in the School-Based Screening Program in Japan

Screening criteria in the school-based screening program in Japan are available in published form and include

<table>
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<tr>
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<th>Sex</th>
<th>Age at Dx (years)</th>
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<th>IVSTh at Dx (mm)</th>
<th>PWTh at Dx (mm)</th>
<th>Type of HCM</th>
<th>Age at 1st ECG (years)</th>
<th>Interval (years)</th>
<th>Prognosis</th>
<th>Genes</th>
<th>Variants</th>
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<td>Screening</td>
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<td>10.2</td>
<td>ASH</td>
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<td>Sudden death</td>
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<tr>
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<td>13.1</td>
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</tr>
<tr>
<td>4</td>
<td>F</td>
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<td>Screening</td>
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<td>9.1</td>
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<tr>
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<td>Apical</td>
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<tr>
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<td>M</td>
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<td>Familial study</td>
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<td>13.1</td>
<td>ASH</td>
<td>6.8</td>
<td>6.2</td>
<td>Alive</td>
<td>MYH7</td>
<td>c.1357C&gt;T, p.R453C, rs121913625</td>
</tr>
<tr>
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<td>M</td>
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<td>Screening</td>
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<td>12.0</td>
<td>Diffuse</td>
<td>6.4</td>
<td>6.2</td>
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<td></td>
</tr>
<tr>
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<td>M</td>
<td>12.9</td>
<td>Screening</td>
<td>18.7</td>
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<td>ASH</td>
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<td>Screening</td>
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<td>11.9</td>
<td>Diffuse</td>
<td>6.7</td>
<td>8.9</td>
<td>Alive</td>
<td>Not identified</td>
<td></td>
</tr>
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<td>M</td>
<td>16.3</td>
<td>OHCA</td>
<td>14.0</td>
<td>10.0</td>
<td>ASH</td>
<td>6.5</td>
<td>9.9</td>
<td>ACA</td>
<td>TNNT2</td>
<td>c.418C&gt;T, p.R140C, homozygous, rs397516463</td>
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</table>

Mean ± SD: 13.2±2.0, 18.6±4.9, 10.6±2.1, 6.6±0.3, 6.4±1.8
HCM-related findings (abnormal Q waves, ST depression, and T wave inversion), right ventricular hypertrophy, and LVH. The “conventional criteria” used in the present study are those included in these guidelines. In the present study, an ECG was considered abnormal if the patient fulfilled one of the criteria of “Group A” in those guidelines.

Additional Criteria for Pathological Q Waves

The deepest Q wave of leads III and V6 was less than −0.7 mV in all 3 (1st, 7th, and 10th) grades in the general population for both the narrow and routine bandwidth groups. We defined a deep Q wave greater than −0.7 mV as an abnormal Q wave.

Statistical Analysis

All data are presented as the mean±SD. Statistical analyses were performed using IBM® SPSS® Statistics v23.0 (IBM Japan, Tokyo, Japan). Tentative criteria for increased R/S voltages at the 99.95th percentile (1/2,000) point were calculated by grade and sex. To estimate the 99.95th percentile (1/2,000) point, the bundled PERCENTILE.EXC function in EXEL 2016® (Microsoft Japan, Tokyo, Japan) was used if the size of a group exceeded 2,000, where the percentile of the maximum value exceeds the 99.95th percentile (2,000/2,001=0.99950025>0.9995). When the size of a group, n, was <2,000 (e.g., n=1,611), the 99.95th percentile (2,000/2,001=0.99950025>0.9995). When the size of a group exceeded 2,000, where the percentile of the maximum value exceeds the 99.95th percentile (2,000/2,001=0.99950025>0.9995). When the size of a group exceeded 2,000, where the percentile of the maximum value exceeds the 99.95th percentile (2,000/2,001=0.99950025>0.9995).

Formula:

\[ x = \frac{(p_{n-1} - 0.9995)x_{n-1} + (0.9995 - p_{n-1})x_{n}}{(p_n - p_{n-1})} \]

where \( p_{n-1} = n/(n+1) = 1,611/1,612 (0.99938) \), \( p_n-1 = (n-1)/(n+1) = 1,610/1,612 (0.99875) \), and \( x_{n-1} \) and \( x_{n} \) are the largest and the second largest values of the group of size n, respectively.

When the sensitivity at the 99.95th percentile (1/2,000) screening point was the same between several voltage criteria, the robustness of the sensitivity of each voltage criterion was determined using additional 1/1,500 and 1/2,500 screening points. The sensitivity of a criterion was considered to be more robust than others when the square of the distance to the ideal sensitivity and specificity (i.e., \([1−\text{sensitivity}]^2 + [1−\text{specificity}]^2\)) was unchanged.

Results

Tentative Screening Criteria for Increased R/S Voltage Criteria in Each Lead

Tentative criteria for the increased R/S voltages at the 99.95th percentile (1/2,000) point for the narrow and routine bands are shown in Supplementary Table 1A and 1B, respectively.

Patients Fulfilling the Increased Voltage Criteria

First Graders of the Prediagnostic Group

For the 11 patients in the 1st grade in the prediagnostic group, the highest sensitivity (45%) was found for the screening criteria of RI+SV3, RV2+SV3, and RV3+SV3; all these criteria included the S wave voltage in lead V3 (Supplementary Table 2). Two of these 11 patients were screened using the conventional criteria during the 1st grade screening program (QS pattern [Case 10] and right ventricular hypertrophy [Case 11]). However, they were diagnosed as normal because they did not have an increased ventricular wall thickness or congenital heart diseases on echocardiography.20

The ECGs of all 11 patients are shown in Supplementary Figure 1. The remaining 9 patients who showed a promi-

<table>
<thead>
<tr>
<th>Table 2. Characteristics of the Post-Diagnostic Groups</th>
</tr>
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<tbody>
<tr>
<td>1st grade (n=15)</td>
</tr>
<tr>
<td>-----------------------------------</td>
</tr>
<tr>
<td>No. males/females</td>
</tr>
<tr>
<td>Age at ECG+ (years)</td>
</tr>
<tr>
<td>Age at diagnosis (years)</td>
</tr>
<tr>
<td>Interval+ (years)</td>
</tr>
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<td>Through symptoms</td>
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<td>Familial study</td>
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<tr>
<td>By chance</td>
</tr>
<tr>
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<tr>
<td>Age at echocardiography+ (years)</td>
</tr>
<tr>
<td>IVSTh (mm)</td>
</tr>
<tr>
<td>PWTh (mm)</td>
</tr>
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<td>Prognosis</td>
</tr>
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<tr>
<td>OHCA</td>
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<td>Transplantation</td>
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<td>Death</td>
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</table>

Unless indicated otherwise, data are given as the mean±SD or n (%). *Age at which electrocardiograms (ECG) used in this study were recorded. **Interval between the age at diagnosis and the age at the time of ECG recording. ***Age at which echocardiography was performed in the 1st, 7th, or 10th grades. **The same patient. IVSTh, interventricular septum thickness; OHCA, out-of-hospital cardiac arrest; PWTh, posterior wall thickness.
nent LV wall thickness that fulfilled the diagnostic criteria for adults at their 7th grade screening did not fulfill conventional criteria at their 1st grade screening. Of these 9 patients, the highest sensitivity (56%) was still found for the screening criteria of RI+SV3 and RV3+SV3. The RV3+SV3 criterion was preferable to the RI+SV3 criterion because robustness analysis showed that the sensitivity, specificity, and deviation from the ideal point of the sensitivity and specificity \((1−\text{sensitivity})^2 + (1−\text{specificity})^2\) of RV3+SV3 was unchanged (robust), even when the screening point changed from 1/2,000 to 1/1,500 or 1/2,500 (Table 3). Thus, the tentative criterion of RV3+SV3 for the early diagnosis of 1st graders in the clinical setting was 6.0 and 5.0 mV in boys and girls, respectively, for the narrow bandwidth group and 6.5 and 6.1 mV in boys and girls, respectively, for the routine bandwidth group (Supplementary Table IA, IB). Nevertheless, these criteria should be further revised after obtaining a larger number of ECGs for the routine bandwidth from the general population.

**First Graders of the Post-Diagnostic Group** Of the 15 patients in the 1st grade in the post-diagnostic group, the highest sensitivity (60%) was found for SV2+SV4, whereas the criteria with the second-highest (53%) sensitivity were RaVL+SV3, SD+SV3, RI+SV3, RI+SV4, and SV2+SV3.

**Table 3. Robustness of Sensitivity of the Voltage Criteria of R Wave in Limb-Lead I (RI)+S Wave in Lead V3 (SV3) and R Wave in Lead V3 (RV3)+SV3 at the 1/1,500, 1/2,000, and 1/2,500 Screening Points**

<table>
<thead>
<tr>
<th>Screening point</th>
<th>RI+SV3</th>
<th>RV3+SV3</th>
</tr>
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<tbody>
<tr>
<td>1/1,500</td>
<td>0.5556 0.9993 0.1975</td>
<td>0.5556 0.9993 0.1975</td>
</tr>
<tr>
<td>1/2,000</td>
<td>0.5556 0.9995 0.1975</td>
<td>0.5556 0.9995 0.1975</td>
</tr>
<tr>
<td>1/2,500</td>
<td>0.4444 0.9996 0.3087</td>
<td>0.5556 0.9996 0.1975</td>
</tr>
</tbody>
</table>

Value refers to the square of the distance to the ideal sensitivity and specificity (i.e., \((1−\text{sensitivity})^2 + (1−\text{specificity})^2\)), with smaller values indicating a better candidate criterion.

**Table 4. Number of Patients Who Fulfilled the Criteria and the Sensitivity of All Surrogate Markers in the Pre- and Post-Diagnostic Groups**

<table>
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<th>Pre-diagnostic phase</th>
<th>Post-diagnostic phase</th>
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<tbody>
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<td></td>
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<td>1st grade (n=15)</td>
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<tr>
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<td>RIII</td>
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<td>RaVL+SV3</td>
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</tr>
<tr>
<td>RaVL+SV4</td>
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</tr>
<tr>
<td>RI+SIII</td>
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(Table 4 continued the next page.)
ECG Diagnosis of an Early Stage of Childhood HCM

<table>
<thead>
<tr>
<th></th>
<th>Pre-diagnostic phase</th>
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<td>Conventional criteria</td>
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<td>10 (67)</td>
</tr>
</tbody>
</table>

Data show the number of patients with the sensitivity (%) of each marker given in parentheses. HCM, hypertrophic cardiomyopathy; RVH, right ventricular hypertrophy.

Figure 2. Changes in the sensitivity of the representative criteria. Some voltage criteria showed a higher sensitivity than conventional or hypertrophic cardiomyopathy (HCM)-related criteria in 1st graders in the prediagnostic group. The prediagnostic group included 2 patients who had conventional screening criteria. The RV3+SV3 criterion had a sensitivity of 45% in the prediagnostic group, but failed in the post-diagnostic group. The RI+SV4 criterion showed a low sensitivity in the pre-diagnostic group, but showed a relatively high sensitivity for 1st and 7th graders in the post-diagnostic groups. Conventional and HCM-related criteria showed a low sensitivity for the pre-diagnostic group, but had a higher sensitivity than voltage criteria in the post-diagnostic groups, particularly at the 7th and 10th grades. RI, R wave in limb-lead I; RV3, R wave in lead V3; SV3, S wave in lead V3; So, deepest S wave in any lead; SV4, S wave in lead V4.
(Supplementary Table 3). In the post-diagnostic group, 10 of 15 patients (67%) met conventional criteria. Of remaining 5 patients who did not meet conventional criteria, 4 were diagnosed by chance (Supplementary Table 3). RaVL+SV3, Sa+SV3, R1+SV3, R1+SV4, SV2+SV3, and SV2+SV4, which included the S wave voltages in leads V3 or V4 (SV3 or SV4, respectively), had a sensitivity of 60%. These 6 screening criteria had the same sensitivity at 1/1,500 and 1/2,500 (data not shown), suggesting that they are all candidate criteria for screening 1st graders in the post-diagnostic group who do not meet conventional criteria.

Seventh Graders of the Post-Diagnostic Group The highest sensitivity was found for R1+SV4 (44%; Table 4). Of the 32 patients in this group, 29 (91%) fulfilled the conventional criteria. Of the 3 remaining patients who did not meet the conventional criteria, 2 fulfilled the voltage criterion of R1+SV4. However, of these 3 patients, 2 showed a flat T wave (and not an inverted T wave as in the conventional criteria) in the left precordial leads and 1 showed a very low voltage R wave in the left precordial leads. Overall, these findings suggest that nearly all 7th graders with HCM may be screened using conventional criteria and abnormal findings.

Tenth Graders of the Post-Diagnostic Group The highest sensitivity was found for R1+SV4, although the sensitivity was low (35%; Table 4). Of the 17 patients, 14 (82%) fulfilled the conventional criteria, whereas the remaining 3 patients also had a flat T wave in lead V6, a deep S wave (1.3 mV) in lead V6, and fulfilled the voltage criteria of RV2+SV2 and RV3+SV3.

Candidate Criteria for 1st, 7th, and 10th Graders in the Post-Diagnostic Groups The sensitivity of representative voltage criteria for the pre- and post-diagnostic groups, including subjects who fulfilled the conventional screening criteria, is shown in Figure 2. R1+SV4 was a potential candidate criterion for all post-diagnostic groups because it had one of the highest sensitivities in 1st graders who did not meet conventional criteria, and showed the highest sensitivity in 7th and 10th graders. However, conventional diagnostic criteria were better at diagnosing patients with HCM than the voltage criteria, particularly in the case of 7th and 10th graders (Figure 2; Table 4). The tentative criterion of R1+SV4 for 1st graders in the clinical setting was 3.2 and 3.0 mV for boys and girls, respectively, and 3.6 mV for both boys and girls with a routine bandwidth (Supplementary Table 1). Nevertheless, these criteria should be further revised after obtaining a larger number of ECGs for the routine bandwidth from the general population.

Summary of Sensitivity and Specificity A summary of the sensitivity of each criterion is presented in Table 4. The specificity of each criterion was approximately 99.95% for all screening criteria because the criteria were set to screen 1/2,000 of the general population.

Discussion The present study showed that early prediction of a potential diagnosis of HCM was possible using the voltage criteria of R1+SV3 and RV3+SV3 in >50% of patients in the 1st grade who were diagnosed in the 7th grade. The robustness of sensitivity data showed that RV3+SV3 was superior to R1+SV3. This strategy may help prevent tragic accidents in patients, although future prospective studies are required. R1+SV4 was also useful for diagnosing patients with HCM in the post-diagnostic groups. The present study showed that the voltage criteria had a lower sensitivity for screening patients with HCM than the conventional criteria for post-diagnostic groups, particularly for 7th and 10th graders.

ECG findings in HCM patients are known to precede echocardiographic findings. Early diagnosis via ECG may prevent children and adolescents from competitive sports-related SCD or ACA. One strategy may be to compare ECG findings between normal controls and patients with positive pathogenic variants without overt LVH using imaging techniques such as echocardiography. A limitation of this strategy is the low penetrance of HCM during childhood. Previous studies in children with positive mutations reported that 2 (17%) of 12 children (12±5 years old) and 8 (7%) of 119 children (12±3 years old) developed overt HCM during follow-up.

In the present study we used a unique strategy of retrospectively examining ECGs approximately 6 years before the actual HCM diagnosis to determine whether they fulfilled our voltage criteria. We used the 99.95th percentile (1/2,000) point as the voltage criterion for screening criteria, indicating that specificity was approximately 99.95% for all screening criteria. This strategy showed that 2 screening criteria (RI+SV3 and RV3+SV3) could predict a potential diagnosis of HCM in 5 of 9 patients (56% sensitivity) in the prediagnostic group. These patients did not fulfill the conventional criteria while in 1st grade, but showed a prominent LV wall thickness approximately 6 years later, suggesting that screening with voltage criteria is a useful strategy for the early screening of patients at risk of future marked LVH, although the efficacy was not optimal.

Both criteria included the SV3 (Supplementary Table 2). Of the 5 first graders in the post-diagnostic group who did not fulfill the conventional criteria, 3 fulfilled the voltage criteria that included SV3 or SV4 (Supplementary Table 3). In 7th and 10th graders in the post-diagnostic group, the highest sensitivity (44%) was found for R1+SV4, although nearly all patients met conventional criteria or had some abnormal findings. Our data suggest that the efficacy of the deep S wave in the mid-precordial leads shifts from V3 to V4 with age and/or with the development of HCM phenotypes. Our findings are consistent with reports that Sa+SV4 or R1+SV4 were the most effective screening criteria for adult patients with LVH, both of which include SV4.

With regard to the effect of the R wave voltage, the voltage criterion of RV3+SV3 (effective for the prediagnostic group) showed a low sensitivity (20%) for patients who did not meet conventional criteria in 1st grade in the post-diagnostic group. Rather, the combined voltage criteria, including the R wave voltage in leads aVL or I, showed high sensitivity (Table 4). These findings are consistent with previous studies in adults showing the importance of the R wave vector progresses leftward and slightly upward of the frontal plane with age and/or phenotypic LVH progression.

The voltage criteria had a lower sensitivity for screening children and adolescents with HCM than the conventional criteria for the post-diagnostic groups. A potential reason for this is that the ECG may change with the development of the HCM phenotype. The ORS voltages of children and adolescents with HCM (Supplementary Figure 2), as well as those in the general population, increase with age.
particularly in males. Nevertheless, only a small number of patients showed a constant increase in the QRS. Furthermore, many patients will develop HCM-related ECG abnormalities rather than an increase in QRS voltages after developing the HCM phenotype and pathological changes.

The present study showed that the voltage criterion of RV3+SV3 is effective in predicting a potential diagnosis of HCM in the 1st grade for the prediagnostic group. For the 1st grader’s post-diagnostic group, 6 screening criteria, including R1+SV4, were candidates for screening 1st graders who did not meet conventional criteria. In the 7th and 10th grade screening programs, the conventional criteria may be sufficient, but the voltage criterion of R1+SV4 may be applicable in the 7th grade screening program because 14 of 32 (44%) patients in the 7th grade post-diagnostic group (Figure 2; Table 4) and 2 of 3 (67%) patients who did not fulfill the conventional criteria in the 7th grade post-diagnostic group fulfilled the criterion of R1+SV4. These data indicate that the voltage criteria of RV3+SV3 and R1+SV4 could be included in the 1st grade screening program and that the voltage criterion of R1+SV4 may be applicable to the 7th grade screening program.

This study has some limitations. First, the number of patients in the prediagnostic group was very small. Nevertheless, this is the first report examining the ECGs of patients 6 years before a diagnosis of HCM. Furthermore, our strategy was able to detect 5 of 9 patients (56%) with increased QRS voltages who did not meet conventional criteria. If we expand the number of patients using this strategy, the early diagnosis of HCM before the development of a phenotype may be possible. Second, we only presented tentative voltage criteria. QRS voltages have been reported to differ between races and/or studies.19 Thus, future studies are required to develop the exact diagnostic voltage criteria for different races and/or ethnicities based on ECGs from their general populations. Third, the number of reference ECGs for the routine bandwidth was relatively small compared with that for the narrow bandwidth. This should be expanded in future studies. Finally, we did not discuss approaches to minimize the concerns of patients and families regarding the potential for developing HCM in the future. Further studies are required to confirm the sensitivity and specificity of our voltage criteria to provide sufficient information to minimize their concerns and develop requirements for follow-up.

In conclusion, early prediction of a potential diagnosis of HCM was possible using the voltage criterion of RV3+SV3 in >50% of patients in the 1st grade who were diagnosed in the 7th grade. This strategy may help prevent competitive activities-associated tragic accidents in these patients, although further prospective studies are required. For example, patients should be followed-up every few years, with the interval based on their ECG and echocardiography findings. Finally, the conventional criteria for HCM or abnormal findings can diagnose nearly all patients in the 7th and 10th grades.

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Disclosures
H. Tsutsui is a member of Circulation Journal’s Editorial Team. The remaining authors have no conflicts of interest to declare.

IRB Information
This study was approved by the Ethics Committee of the National Hospital Organization Kagoshima Medical Center (27-9 and 27-28).

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17. Yoshinaga M, Kudo Y, Nishibatake M, Ogata H, Nomura Y, H. Tsutsui is a member of Circulation Journal’s Editorial Team. The remaining authors have no conflicts of interest to declare.

ECG Diagnosis of an Early Stage of Childhood HCM
9

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Supplementary Files

Please find supplementary file(s): http://dx.doi.org/10.1253/circj.CJ-21-0376