Third and Fourth Heart Sounds and Myocardial Fibrosis in Hypertrophic Cardiomyopathy

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Background: The 4th heart sound (S4) is commonly heard in patients with hypertrophic cardiomyopathy (HCM). The 3rd heart sound (S3) is also audible in HCM patients regardless of the presence or absence of heart failure. These extra heart sounds may be associated with myocardial fibrosis because myocardial fibrosis has been suggested to affect left ventricular compliance.

Methods and Results: The present retrospective study evaluated 53 consecutive HCM patients with sinus rhythm who had no symptoms of heart failure and underwent an initial assessment including phonocardiography, echocardiography, and late gadolinium enhancement (LGE) magnetic resonance imaging (MRI). S3 was detected on phonocardiography in 13% of all patients, and S4 was recorded in 75% of patients. Patients with S3 had a higher incidence of LGE and larger LGE volumes (86% and 11.5±2.4 g/cm³, respectively) than patients without S3 (33% and 2.5±0.8 g/cm³, respectively; P=0.02 and P=0.002). The presence of S4 was not associated with MRI findings, including the incidence of LGE and LGE volume. The diagnostic value of S3 for the detection of LGE was highly specific (97%), with a low sensitivity (29%).

Conclusions: Myocardial fibrosis, as assessed by LGE, was associated with S3 but not with S4 in patients with HCM. These results may contribute to the risk stratification of patients with HCM.

Key Words: 3rd heart sound; 4th heart sound; Hypertrophic cardiomyopathy; Late gadolinium enhancement; Phonocardiography
SATO Y et al.

antagonists, 12 had taken β-blockers (but only 1 had taken high doses, defined as carvedilol >10 mg/day, metoprolol >5 mg/day, atenolol >50 mg/day, and propranolol >30 mg/day), 3 had taken diuretics, and 3 had taken antiarrhythmic drugs; none had taken amiodarone. Informed consent for the assessments was obtained from all patients with HCM.

MRI

LGE-MRI was performed using a 1.5-Tesla imaging system (Signa HDx; GE Medical Systems, Milwaukee, WI, USA), as described previously. Briefly, the steady state free procession of cine images was obtained and maximum LV wall thickness and LV mass were calculated using

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**Figure 1.** Representative results of phonocardiography and magnetic resonance imaging in two different cases. (A–C) Case 1. (A) The phonocardiogram shows the 4th heart sound (S4) before the 1st heart sound (S1), as well as the 3rd heart sound (S3) after the 2nd heart sound (S2), in a 49-year-old man with hypertrophic cardiomyopathy (HCM). (B) A cine image at the end-diastolic phase on magnetic resonance imaging (MRI) shows asymmetric septal hypertrophy with a maximum wall thickness of 25.4 mm. (C) Late gadolinium enhancement (LGE) is detected in the ventricular septum (arrows) and the area of the inferior ventricular septum-free wall junction (arrowhead). The late gadolinium enhancement (LGE) volume and %LGE in this patient were calculated to be 3.0 g/cm and 5.0%, respectively. (D–F) Case 2. (D) S4, but not S3, is seen on the phonocardiogram of a 77-year-old man with HCM. Myocardial hypertrophy is observed predominantly in the anterior and inferior walls and ventricular septum (E) without LGE (F).
commercially available software (Plissimo Ex Version 1.0.4.5; Panasonic Medical Solutions, Osaka, Japan). Approximately 10 min after an intravenous injection of 0.1 mmol/kg gadopentetate dimeglumine (Magnevist; Schering, Berlin, Germany), LGE images were obtained in long- and short-axis views at the basal, mid-, and apical LV levels under serial breath-holds using a 2-dimensional, spoiled, and segmented inversion recovery and gradient-echo sequence. LGE was defined as 2 standard deviations above the mean signal intensity of an apparently normal myocardium, and the extent of LGE (LGE volume, expressed in g/cm) and the proportion of the LGE volume to LV mass, expressed as a percentage (%LGE), were calculated. The location of LGE was identified on the basis of a 17-segment model of the LV: 1 apex segment on a vertical long-axis view and 16 segments on 3 short-axis views.

**Phonocardiography**

A phonocardiogram was obtained at the apex as well as at the right and left sternal borders in the half left lateral decubitus position as well as in the supine position at a paper speed of 50 or 100 mm/s using a commercially available device (MES-1000; Fukuda-Denshi, Tokyo, Japan), as shown in Figure 1. Measurements included 4 frequencies: low, lower-middle, higher-middle, and high frequency. The cut-off frequency, attenuation, Nyquist rate, and differential sensitivity were: 50 Hz, −6 dB/oct (oct), 1, and −32 dB, respectively, for the low frequency; 50 Hz, −18 dB/oct, 3, and −32 dB for the lower-middle frequency; 160 Hz, −24 dB/oct, −4, −16 dB for the higher-middle frequency; and 315 Hz, −24 dB/oct, 4, and 0 dB for the high frequency. When an apex cardiogram was recorded, a simultaneous apical phonocardiogram was obtained near the apex because the microphone of the apex cardiogram was placed exactly at the apex.

In the present study, S3 was defined as an extra sound that had a predominant distribution at the apex as well as a low frequency that occurred after the 2nd heart sound (S2) during early diastole and coinciding with the peak of the rapid-filling wave on an apex cardiogram if available. Similarly, S4 was considered present when a low-frequency sound of an electrocardiogram and before the onset of the P wave of an electrocardiogram and after the onset of S2 and S3 and the amplitudes of S3 and S4, as well as the amplitudes of S3 and S4, were measured in the low-frequency range of the phonocardiogram in the same setting. Although the duration of S3 was also measured, that of S4 was not because it is often difficult to clearly separate S4 from the 1st heart sound (S1). The presence or absence of S3 and S4 on auscultation was also assessed in all but 2 patients by a single experienced cardiologist who was unaware of the results of phonocardiography.

**Echocardiography**

An echocardiographic examination was performed using commercially available equipment (Vivid 9; GE Healthcare, Milwaukee, WI, USA) using a standard method. Briefly, LV EDD, LVEF, left atrial end-systolic diameter, mitral early diastolic velocity (E), late diastolic velocity (A), and early septal mitral annular velocity (E′) were measured, and the E:A and E:E′ ratios were calculated. An LV outflow tract obstruction was considered present when the peak flow velocity was $>$2.5 m/s as determined by Doppler imaging under resting conditions or after the Valsalva maneuver.

**Biomarkers**

Serum concentrations of high-sensitivity cardiac troponin T (hs-cTnT) and plasma concentrations of atrial natriuretic peptide (ANP) and B-type natriuretic peptide (BNP) were measured using commercially available kits, as described previously (Elecsys Troponin T hs [Roche Diagnostics, Mannheim, Germany], M102 Shionogi ANP [Shionogi & Co., Osaka, Japan], and M102 Shionogi BNP [Shionogi & Co.], respectively). The analytical range and normal reference range of the assays were as follows: 0.003–99,900,000,000 and <0.014 ng/mL for hs-cTnT, 5.1–1,290.0 and <43.0 pg/mL for ANP, and 4.0–2,000.0 and <18.4 pg/mL for BNP.

**Statistical Analysis**

Categorical variables were compared by the Chi-squared test or Fisher's exact test where appropriate. Continuous variables are expressed as the mean±SD and were compared using Student’s t-test. LGE volume, %LGE, and levels of biomarkers (hs-cTnT, ANP, and BNP) are expressed as the mean±SEM and were compared using the Mann-Whitney U-test or Kruskal-Wallis test followed by Bonferroni correction for multiple comparisons because of possibly skewed distributions. The Spearman rank correlation coefficient was used to examine relationships between indices of S3 and S4 and the LGE volume and %LGE.

**Results**

MRI revealed maximal LV wall thickness of 21.0±5.7 mm and an LV mass of 66.8±21.7 g/cm. The location of myocardial hypertrophy was the ventricular septum in 42 patients (79%), the anterior wall in 16 (31%), the apex in 11 (21%), the lateral wall in 11 (21%), and the inferior wall in 2 (4%). LGE was detected in 21 of 53 patients (44%): the ventricular septum in 15, the anterior wall in 8, the apex in 2 (4%), and the inferior wall in 2. Median LGE volume was 6.0 g/cm (range 0.1–25.3 g/cm) and median %LGE was 11.0% (range 0.2%–38.0%).

S3 was observed in 7 of 53 patients with HCM (13%), and S4 was detected in 40 patients (75%). There were no significant differences in heart rate on phonocardiography between patients with and without S3 (62±13 vs. 63±11 beats/min, respectively; P=0.65) or between patients with and without S4 (62±10 vs. 66±13 beats/min, respectively; P=0.89). Table 1 lists the clinical characteristics of patients with and without S3 or S4. The presence of S3 was
Measurements of hs-cTnT, ANP, and BNP were possible in 52 (98%), 52 (98%), and 51 (96%) patients, respectively, with mean concentrations of 0.014 ng/mL (range 0.003–0.072 ng/mL) for hs-cTnT, 71 pg/mL (range 17–195 pg/mL) for ANP, and 100 pg/mL (range 6–582 pg/mL) for BNP. There were no significant differences in the concentrations of these 3 biomarkers between patients with and without S3 or S4 (Table 1).

In the 7 HCM patients with S3, the time interval from the onset of S2 to S3 was 180 ± 43 ms (range 120–240 ms); 3 patients had a time interval ≥ 200 ms. As shown in Table 2, the time interval from the onset of S2 to S3 was positively correlated with LGE volume (correlation coefficient=0.82, P=0.04) and %LGE (correlation coefficient=0.86, P=0.04). The duration and amplitude of S3 were 82 ± 40 ms and 2.6 ± 2.6 mm, respectively; these parameters were not correlated with LGE variables. The interval period from the P wave to S4 and the amplitude of S4 were 109 ± 33 ms and 6.2 ± 5.1 mm, respectively; these parameters were not correlated with LGE volume or %LGE in any of the 40 patients with S4.

During a mean follow-up period of 24 months (range 3–39 months), 6 patients with S3 and 8 patients without S3 associated with a younger age, but not with echocardiographic indices or hypertrophic sites as assessed by MRI. The incidence of LGE, LGE volume, and %LGE were significantly higher in patients with than without S3. The presence of S4 was not significantly associated with echocardiographic indices or MRI findings, including the incidence of LGE, LGE volume, and %LGE.

There was no significant difference between those with and without S3 in terms of the proportion of patients taking calcium antagonists (14% vs. 43%, respectively; P=0.15), β-blockers (29% vs. 22%, respectively; P=0.42), diuretics (0% vs. 7%, respectively; P=0.77), and antiarrhythmic drugs (0% vs. 7%, respectively; P=0.77). Among all 53 patients, 7 had both S3 and S4, 33 had S4 but not S3, and 13 did not have either S3 or S4; no patients had S4 but not S3. The presence of S3 was associated with an increased incidence of LGE and increased LGE volume and %LGE (Figure 2). Multiple logistic regression analysis after adjustment for age showed that S3 was an independent predictor for the presence of LGE (odds ratio [OR] 10.4; 95% confidence interval 1.1–99.9; P=0.04). The diagnostic value of the presence of S3 was highly specific for the detection of LGE, with a sensitivity of 29%, specificity of 97%, accuracy of 70%, positive predictive value (PPV) of 86%, and a negative predictive value (NPV) of 67%.

Measurements of hs-cTnT, ANP, and BNP were possible in 52 (98%), 52 (98%), and 51 (96%) patients, respectively, with mean concentrations of 0.014 ng/mL (range 0.003–0.072 ng/mL) for hs-cTnT, 71 pg/mL (range 17–195 pg/mL) for ANP, and 100 pg/mL (range 6–582 pg/mL) for BNP. There were no significant differences in the concentrations of these 3 biomarkers between patients with and without S3 or S4 (Table 1).

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During a mean follow-up period of 24 months (range 3–39 months), 6 patients with S3 and 8 patients without S3

### Table 1. Clinical Characteristics of Patients With and Without Third (S3) or Fourth (S4) Heart Sounds

<table>
<thead>
<tr>
<th></th>
<th>S3 Present (n=7)</th>
<th>S3 Absent (n=46)</th>
<th>S4 Present (n=40)</th>
<th>S4 Absent (n=13)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>57±11 competent</td>
<td>67±12 competent</td>
<td>64±12 competent</td>
<td>72±12 competent</td>
</tr>
<tr>
<td>No. women</td>
<td>1 (14)</td>
<td>10 (22)</td>
<td>7 (18)</td>
<td>4 (31)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>23.2±1.7</td>
<td>24.1±3.6</td>
<td>23.6±3.1</td>
<td>25.3±4.0</td>
</tr>
<tr>
<td><strong>Echocardiography</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVEDD (mm)</td>
<td>45±8</td>
<td>44±6</td>
<td>44±6</td>
<td>44±8</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>65±6</td>
<td>65±6</td>
<td>66±6</td>
<td>64±4</td>
</tr>
<tr>
<td>LAD (mm)</td>
<td>37±4</td>
<td>37±6</td>
<td>37±5</td>
<td>38±7</td>
</tr>
<tr>
<td>E wave (cm/s)</td>
<td>73±21</td>
<td>64±18</td>
<td>64±19</td>
<td>70±18</td>
</tr>
<tr>
<td>A wave (cm/s)</td>
<td>52±28</td>
<td>76±21</td>
<td>70±25</td>
<td>83±19</td>
</tr>
<tr>
<td>E/A</td>
<td>1.9±1.6</td>
<td>0.9±0.4</td>
<td>1.1±0.8</td>
<td>0.9±0.4</td>
</tr>
<tr>
<td>Mitral annular E′ (cm/s)</td>
<td>5.0±1.6</td>
<td>4.6±1.6</td>
<td>4.8±1.6</td>
<td>4.2±1.3</td>
</tr>
<tr>
<td>E/E′</td>
<td>16.2±7.0</td>
<td>15.3±5.9</td>
<td>14.6±5.5</td>
<td>17.9±7.0</td>
</tr>
<tr>
<td>LV outflow tract obstruction</td>
<td>2 (29)</td>
<td>3 (7)</td>
<td>3 (6)</td>
<td>2 (15)</td>
</tr>
<tr>
<td><strong>Magnetic resonance imaging</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Location of hypertrophy*</td>
<td>0.96</td>
<td>0.87</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Septal</td>
<td>7 (100)</td>
<td>35 (76)</td>
<td>31 (78)</td>
<td>11 (85)</td>
</tr>
<tr>
<td>Anterior</td>
<td>2 (29)</td>
<td>14 (30)</td>
<td>12 (30)</td>
<td>4 (31)</td>
</tr>
<tr>
<td>Apical</td>
<td>2 (29)</td>
<td>9 (20)</td>
<td>9 (23)</td>
<td>2 (15)</td>
</tr>
<tr>
<td>Lateral</td>
<td>2 (29)</td>
<td>9 (20)</td>
<td>9 (23)</td>
<td>2 (15)</td>
</tr>
<tr>
<td>Inferior</td>
<td>0</td>
<td>2 (4)</td>
<td>1 (3)</td>
<td>1 (8)</td>
</tr>
<tr>
<td>Maximal wall thickness (mm)</td>
<td>23.2±6.6</td>
<td>20.6±5.5</td>
<td>20±5.3</td>
<td>22.6±7</td>
</tr>
<tr>
<td>LV mass (g/cm)</td>
<td>75.1±18.5</td>
<td>65.6±22.1</td>
<td>66.1±19.8</td>
<td>69.1±27.8</td>
</tr>
<tr>
<td>LGE</td>
<td>6 (86)</td>
<td>15 (33)</td>
<td>17 (43)</td>
<td>4 (31)</td>
</tr>
<tr>
<td>LGE volume (g/cm)</td>
<td>11.5±2.4</td>
<td>2.5±0.8</td>
<td>3.8±1.0</td>
<td>2.6±1.3</td>
</tr>
<tr>
<td>%LGE</td>
<td>15.2±2.8</td>
<td>3.3±1.1</td>
<td>4.8±1.3</td>
<td>3.4±1.6</td>
</tr>
<tr>
<td><strong>Biomarkers</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High-sensitivity cTnT (ng/mL)</td>
<td>0.020±0.009</td>
<td>0.013±0.002</td>
<td>0.014±0.003</td>
<td>0.013±0.003</td>
</tr>
<tr>
<td>ANP (pg/mL)</td>
<td>81±16</td>
<td>69±7</td>
<td>69±6</td>
<td>78±15</td>
</tr>
<tr>
<td>BNP (pg/mL)</td>
<td>129±34</td>
<td>96±17</td>
<td>102±19</td>
<td>93±25</td>
</tr>
</tbody>
</table>

Data are given as the mean±SD or as n (%), except late gadolinium enhancement (LGE) indices and biomarkers, which are given as the mean±SE. *Some patients had 2 or more hypertrophic sites. ANP, atrial natriuretic peptide; BMI, body mass index; BNP, B-type natriuretic peptide; cTnT, cardiac troponin T; LAD, left atrial dimension; LV, left ventricular; LVEDD, LV end-diastolic diameter; LVEF, LV ejection fraction.

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Figure 2. Late gadolinium enhancement (LGE) and extra heart sounds. (A) Incidence of LGE, (B) LGE volume, and (C) %LGE are significantly higher in patients with both 3rd (S3) and 4th (S4) heart sounds (n=7) than in patients who have S4 but not S3 (n=33), or in patients who have neither S3 nor S4 (n=13). No patient had S3 but not S4. Data are the mean±SD. *P<0.05 compared with patients who have S4 but not S3 and patients who do not have either S3 or S4.

Table 2. Relationships Between LGE Indices and Features of Third (S3) or Fourth (S4) Heart Sounds

<table>
<thead>
<tr>
<th></th>
<th>LGE volume (g/cm)</th>
<th>%LGE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Correlation coefficient</td>
<td>P value</td>
</tr>
<tr>
<td>S3 (n=7)</td>
<td>Interval from S2 (ms)</td>
<td>0.82</td>
</tr>
<tr>
<td></td>
<td>Amplitude (mm)</td>
<td>−0.01</td>
</tr>
<tr>
<td></td>
<td>Duration (ms)</td>
<td>−0.13</td>
</tr>
<tr>
<td>S4 (n=40)</td>
<td>Interval from P wave (ms)</td>
<td>−0.24</td>
</tr>
<tr>
<td></td>
<td>Amplitude (mm)</td>
<td>−0.035</td>
</tr>
</tbody>
</table>

LGE, late gadolinium enhancement.

Figure 3. Follow-up phonocardiography. (A) Neither 3rd (S3) nor 4th (S4) heart sounds were observed at the initial assessment of a 65-year-old woman with hypertrophic cardiomyopathy (HCM). (B, C) Magnetic resonance imaging showed a hypertrophied ventricular septum (B) with mildly positive late gadolinium enhancement (LGE) in the inferior ventricular septum-free wall junction (C; arrow). (D) Note that 27 months later soft S3 develops (arrow), along with soft S4 (arrowhead); the inset shows the same data on an enlarged vertical scale.
underwent repeated phonocardiography. All 6 HCM patients with S3 at initial phonocardiography had S3 at the time of the follow-up study. None of the remaining 8 patients without S3 at the initial study had S3 in the follow-up study, except for 1 patient, in whom LGE was positive and soft S3 and S4 developed 27 months after initial phonocardiography (Figure 3).

Among the 51 patients in whom auscultation assessment was performed by a single experienced cardiologist, S3 was detected on auscultation in 4 of 7 patients who had S3 on phonocardiography. Two patients had S3 on auscultation despite the absence of S3 on phonocardiography. The concordance regarding S3 between auscultation and phonocardiography was 71%. The incidence of LGE, LGE volume, and %LGE were significantly higher in patients with S3 on auscultation than in those without S3 on auscultation (83% vs. 36% [P=0.02], 8.8±3.4 vs. 3.0±0.9 g/cm³ [P=0.04], and 10.4±3.7% vs. 3.9±1.1% [P=0.03], respectively). The presence of S3 on auscultation for the detection of LGE had a sensitivity of 24%, specificity of 97%, accuracy of 67%, PPV of 83%, and NPV of 64%. S4 was heard in 28 of 39 patients with S4 on phonocardiography, whereas 5 patients were diagnosed with S4 on auscultation despite the absence of evidence of S4 on phonocardiography (concordance=69%). The presence of S4 on auscultation was not significantly associated with the incidence of LGE, LGE volume, or %LGE (52% vs. 22% [P=0.08]; 4.6±1.2 vs. 1.9±1.0 g/cm³ [P=0.10], and 5.8±1.6% vs. 2.5±1.2% [P=0.10], respectively).

Discussion
The present study showed that S4 was commonly observed (75%) and that S3 was not rare (13%) in patients with HCM. The presence of S3 was correlated with a high incidence of LGE and an increased LGE volume and %LGE, but not with echocardiographic indices or biomarkers (i.e., hs-cTnT, ANP, and BNP). The diagnostic value of S3 for the detection of LGE was highly specific (97%), with a low sensitivity (29%). Conversely, the presence of S4 was not correlated with echocardiographic indices, LGE findings, or biomarker levels.

Since the description of S3 by Pontains in the 19th century, its detection has been valuable because it is a good indicator of ventricular dysfunction and is independently associated with adverse outcomes. The proposed mechanisms responsible for S3 include internal production (valvular origin or ventricular origin) and external production (chest wall origin). Although debate regarding the mechanisms underlying S3 has persisted, a ventricular origin (i.e., ventricular vibrations as a consequence of rapid filling in early diastole) is most widely accepted. It is important to note that physiological S3 is common in healthy children and adolescents, even in adults approaching their 40s. Nevertheless, S3 in the present study was considered to be pathological because of the age of the patients (i.e., 57 years on average) and underlying cardiac conditions (i.e., myocardial hypertrophy associated with HCM).

The incidence of S3 in HCM patients in the present study was 13%. In other studies, the incidence varied, ranging from 4% to nearly 40%. This discrepancy may be explained by a number of factors, such as detection methods (i.e., auscultation vs. phonocardiography) and detection skills (i.e., experts vs. non-experts). In the present study, phonocardiography was used to assess S3 with clear definitions in all patients. The age of subjects also needs to be taken into consideration. In a previous study, a higher incidence of S3 (39.7% in non-obstructive HCM and 36.5% in obstructive HCM) was observed in relatively young patients (on average, 34.1 years, including other dilated cardiomyopathies) compared with those in the present study. Even in the present study, HCM patients with S3 were significantly younger than HCM patients without S3. In addition, heart rate has been identified as a factor affecting S3, with slower heart rates more likely to produce S3. In the present study, no significant differences were observed in the heart rate between patients with and without S3 at the time of phonocardiography.

Conditions associated with the development of pathological S3 include a high left atrial pressure, ventricular enlargement, and, most commonly, impaired LV function. Thus, S3 is often observed in patients with dilated cardiomyopathy and extensive ischemic heart disease as well as valvular heart diseases (e.g., severe mitral regurgitation). In a study on unselected patients subjected to phonocardiography, echocardiography, and cardiac catheterization within a 4-h period in which more than 70% of patients had coronary artery disease, important determinants of S3 included heart failure symptoms, increased E:A and E:E' ratios, lower LVEF, and higher BNP concentrations. None of these findings is consistent with the results of the present study. This may be explained by differences in baseline characteristics (i.e., patients with ischemic heart disease and patients with HCM). It is also important to note that pathological S3 appears to be heard in non-compliant LV, for example HCM regardless of heart failure. In the present study, S3 was associated with myocardial fibrosis as assessed by LGE-MRI. Because determinants of LV compliance are supposed to include myocardial fibrosis, the results of the present study are acceptable; however, direct evidence of the underlying mechanisms has not yet been obtained.

In the present study, the interval from the onset of S2 to S3 was positively correlated with LGE volume and %LGE, despite the limited number of patients with S3. Time intervals were ≥200 ms in 3 of 7 patients with S3, although S3 generally appears almost 100–200 ms after S2. These findings indicate that the mechanisms responsible for S3 in patients with HCM may differ from those in other diseases (e.g., dilated cardiomyopathy and mitral regurgitation) because a pressure-flow study performed on dogs revealed that the relatively early timing of S3 may be due to a high LV filling rate produced by volume loading and elevated afterload. The results of the present study suggest that a high LV filling rate is not a major cause of the development of S3 in patients with HCM. This appears to be supported by the fact that neither BNP nor ANP concentrations were associated with the presence or absence of S3 in the present study, because levels of these biomarkers may become elevated with increases in ventricular and atrial pressure. Further studies are warranted to examine the features of S3 in association with filling rates, as well as myocardial fibrosis in HCM patients. S4 is considered to be derived primarily from vibrations in the mitral valve leaflets and chordae tendineae when the ventricles expand as a result of the rapid inflow of blood by atrial contractions. Because S4 has its origins in impaired ventricles, such as a non-compliant LV or one with limited distensibility, it is reasonable to assume that myocardial fibrosis is related to the development of S4. However, this
S3 and S4 and Myocardial Fibrosis in HCM

mean follow-up period of 3.1 years showed that LGE had a diagnostic value of S3 on auscultation, auscultation may be a limitation in clinical practice, even among experienced clinicians. More recently, in a meta-analysis of 3,067 patients with HCM during an average follow-up of 3.05 years, the rates of all-cause mortality, sudden cardiac death, and cardiac death in patients with LGE were significantly higher than those in patients without LGE, and LGE was correlated with these adverse outcomes, even in patients with non-high-risk HCM according to conventional risk factors. The results of the present study indicate that the detection of S3 is of importance in the management and risk stratification of patients with HCM, and this is possible using phonocardiography because of its convenience and cost-effectiveness with very few contraindications. Further research is needed in order to assess the predictive value of S3 on outcomes in patients with HCM.

Clinical Implications
Myocardial fibrosis as assessed by LGE-MRI has been associated with adverse outcomes in patients with HCM. A systemic review including 1,063 HCM patients over a mean follow-up period of 3.1 years showed that LGE had significant prognostic value for all-cause mortality (OR 4.46) and for cardiac death (OR 2.92). More recently, in a meta-analysis of 3,067 patients with HCM during an average follow-up of 3.05 years, the rates of all-cause mortality, sudden cardiac death, and cardiac death in patients with LGE were significantly higher than those in patients without LGE, and LGE was correlated with these adverse outcomes, even in patients with non-high-risk HCM according to conventional risk factors. The results of the present study indicate that the detection of S3 is of importance in the management and risk stratification of patients with HCM, and this is possible using phonocardiography because of its convenience and cost-effectiveness with very few contraindications. Further research is needed in order to assess the predictive value of S3 on outcomes in patients with HCM.

Study Limitations
The present analyses have several limitations. First, this study was a retrospective study conducted in a single center on selected patients. Therefore, the results may not be generalizable to the global HCM population. Some conditions affect the detection of S3; for example, reduced inflow to the heart or a decreased ventricular volume may diminish the loudness of S3. Although the reproducibility of S3 on phonocardiography was excellent in the present study, it is important to recognize that S3 may wax and wane, particularly in the case of a soft S3. Given the concordance of S3 between auscultation and phonocardiography and the diagnostic value of S3 on auscultation, auscultation may also be used to identify S3 as a marker of myocardial fibrosis in patients with HCM. Nevertheless, it is important to note that a physical examination has inherent inaccuracies and the reliance of S3 on auscultation over phonocardiography may be a limitation in clinical practice, even among experienced clinicians.

Conclusions
The detection of S3 on phonocardiography was associated with the presence of myocardial fibrosis, as assessed by LGE-MRI, in patients with HCM. The diagnostic value of S3 was highly specific, but not sufficiently sensitive for the detection of myocardial fibrosis. These results may contribute to the risk stratification of patients with HCM, even in the era of advanced imaging technologies.

Acknowledgments
The authors thank Drs Hiroki Sugihara, Haruhiko Adachi, and Hiroshi Katsume for their thoughtful comments on the manuscript.

Conflict of Interest
None declared.

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