Prediction of Serious Adverse Events of Patients with Hypertrophic Cardiomyopathy by Magnetic Resonance

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Summary

Although it is well known that patients with hypertrophic cardiomyopathy (HCM) have serious adverse events, such as life-threatening arrhythmia and heart failure, the prediction of such events is still difficult. Recently, it has been reported that one of the causes of these serious adverse events is microvascular dysfunction, which can be noninvasively evaluated by employing cardiac magnetic resonance (CMR) imaging.

We analyzed 32 consecutive HCM patients via CMR imaging and myocardial scintigraphy and divided them into two groups: ventricular tachycardia (VT) group and non-VT group. Myocardial perfusion studies were conducted quantitatively using the QMass software, and each slice image was divided into six segments. The time-intensity curve derived from the perfusion image by CMR imaging was evaluated, and the time to 50% of the peak intensity (time 50% max) was automatically calculated for each segment.

Although no difference was observed in various parameters of myocardial scintigraphy between the two groups, the VT group exhibited a higher mean of time 50% max and wider standard deviation (SD) of time 50% max in each segment than the non-VT group. The cutoff values were obtained by the receiver operating characteristic curves derived from the mean of time 50% max and SD of time 50% max. The two groups divided by the cutoff values exhibited significant differences in the occurrence of serious adverse events.

CMR imaging may be useful for predicting serious adverse events of patients with HCM.

Key words: Cardiac magnetic resonance, Myocardial perfusion, Life-threatening arrhythmia, Heart failure

Hypertrophic cardiomyopathy (HCM), which is characterized by marked ventricular hypertrophy, causes life-threatening arrhythmia, sudden cardiac death (SCD), heart failure, and stroke mainly due to the embolism caused by atrial fibrillation (AF).12 It has been reported that left ventricular wall thickness and SCD are related,9 and that non-sustained ventricular tachycardia (VT), which is observed in 20% to 46% of HCM patients, is also closely related to SCD.5 The greatest risk factor for SCD is a personal history of cardiac arrest, ventricular fibrillation (VF), and sustained VT, and the SCD rate in HCM patients with these risk factors is approximately 10%/year.7 Therefore, the detection of ventricular arrhythmias, such as VT and VF, is crucial for the management of patients with HCM.

It has been reported that ventricular arrhythmia is caused by various mechanisms, such as overactivation of the autonomic nervous system, fibrosis, myocyte disarray, and microvascular dysfunction.9 Microvascular dysfunction has been reported to be involved in cardiac dysfunction and ventricular arrhythmia in patients with HCM.7 A wide range of mechanisms for microvascular dysfunction have also been reported, such as decreased arteriolar density, fibrosis, myocyte disarray, and increased left ventricular end-diastolic pressure.5 The severity of microvascular dysfunction is associated with an independent predictor of long-term clinical deterioration and death from cardiovascular events in patients with HCM.7 Positron emission tomography (PET) is often used for evaluating microvascular function. In this study, regional myocardial blood flow was measured via PET using nitrogen-13-labeled ammonia. The response of myocardial blood flow to dipyridamole infusion was severely blunted in patients with HCM compared with the control subjects.7,8 However, vasodilators, which are used to examine microvascular function via PET,9 can enhance pressure gradient and can be dangerous for patients with HCM.9 Cardiac magnetic resonance (CMR) imaging is used to evaluate cardiac function, hypertrophy, and fibrosis in HCM patients.10 However, it has been reported recently that the perfusion imaging of CMR imaging can be employed to evaluate microvascular function.11,12 Therefore, we first examined whether the VT group and non-VT group can be discriminated by myocardial perfusion images based on CMR imaging. Furthermore, we examined whether we can predict serious adverse events in HCM patients by the...
cutoff values obtained from the myocardial perfusion images.

**Methods**

**Study population:** All the study participants provided written informed consent. The study protocol complied with the Declaration of Helsinki and was approved by the ethics committee of the Sakakibara Heart Institute. We retrospectively analyzed 32 consecutive HCM patients who had myocardial hypertrophy in the septal wall from the basal to the mid-portion using both CMR imaging and myocardial scintigraphy (β-methyl-p-iodophenylpentadecanoic acid (BMIPP)/thallium (Tl) or technetium (Tc)) at our hospital from 2013 to 2015. The mean of the time interval between myocardial scintigraphy and CMR imaging was 212 ± 401 hours in all, whereas the means of the time interval of the VT group and non-VT group were 179 ± 341 hours and 248 ± 454 hours (P = 0.401), respectively. The mean age and the number of males in this study were 62 ± 16 years old and 15 (48%), respectively. The numbers of those who had a family history of cardiac disease and severe arrhythmia.

**Myocardial scintigraphy:** Most patients underwent the 1-day thallium (Tl)-201/123I-BMIPP dual-isotope imaging protocol. However, some underwent the 99mTc-methoxyisobutylisonitrile (MIBI)/123I-BMIPP dual-isotope imaging protocol upon arrival at our hospital. Tl-201 and 99mTc-MIBI were supplied by Fujifilm RI Pharma Co., Ltd. (Tokyo, Japan), whereas 123I-BMIPP was supplied by Nihon Medi-Physics Co., Ltd. (Tokyo, Japan). Patients were instructed to refrain from consuming caffeine-containing beverages for at least 24 hours before the test. A weight-adjusted dose of Tl-201 and 99mTc-MIBI and a uniform dose of 123I-BMIPP were injected simultaneously.

**CMR imaging:** All participants were examined in the supine position using a 1.5 T magnetic resonance imaging system (Magnetom Sonata; Siemens Medical Solution, Erlangen, Germany) and a six-channel phased-array body and supine coil. All images were taken by employing the electrocardiography (ECG)-gated breath-holding technique. There were three patients with AF, and for these patients, we employed CMR imaging to make 2-3 slices for 30 millisecond after the R wave of ECG during the perfusion study. After obtaining a scout image, steady-state free-precession cine images were acquired in three long-axis and five short-axis views covering the left ventricle from the base to the apex.

The image parameters were as follows: slice thickness 8 mm, minimum TR, minimum TE, and flip angle of 60°-80°, with 20 phases per cardiac cycle. Dynamic perfusion imaging was performed in three short-axis views (base, mid-ventricle, and apex) in the same views used in cine imaging. Gadolinium-diethylenetriamine pentaacetic acid (Magnevist, Bayer Schering Pharma AG, Germany), a type of gadolinium chelate contrast agent, was intravenously injected at a dose of 0.2 mL/kg body weight and an injection rate of 4.0 mL/sec, followed by injection of a 20-mL saline flush at the same rate.

**Image analysis:** Myocardial perfusion studies were conducted, and four short-axis slices were quantitatively analyzed using the QMass® software. Each slice image was divided into six segments (Figure 1A). The time-intensity curve derived from the perfusion image was assessed, and the time to 50% of the peak intensity (time 50% max) was automatically calculated (Figure 1B). We used the mean of time 50% max of each segments as an index for whole heart microvascular dysfunction and standard deviation (SD) of time 50% max of each segment as an index for inhomogeneous myocardial perfusion to consider the relationship with life-threatening arrhythmia and microvascular dysfunction or inhomogeneous myocardial perfusion. The patients were divided into two groups: one group consisted of those who experienced sustained VT, non-sustained VT, or VF (VT group) before the MRI examination, and the other group consisted of those who had not experienced VT or VF (non-VT group). We determined the primary end point as composite events, such as all-cause death, re-hospitalization for heart failure, and occurrence of life-threatening arrhythmia (Figure 2). We checked the sustained VT and non-sustained VT using the Holter monitor.

**Statistical analysis:** Statistical analysis was conducted using the commercially available software packages, namely, JMP 12 (SAS Institute Inc. Cary, NC), IBM SPSS Statistics, Version 24 (Armonk, NY, USA), and Microsoft Excel 97-2003 (version 97-2003, Microsoft Excel, USA). Continuous variables were expressed as mean ± SD. The Kolmogorov-Smirnov test was employed for the normality test, and Student’s t test or Mann-Whitney U test for unpaired data was employed to compare the baseline characteristics of continuous variables. In addition, the χ2 test was used for the categorical variables. By determining the cutoff value of the mean of time 50% max and SD of time 50% max, the receiver operating characteristic (ROC) curve and Kaplan-Meier curve were drawn for survival.
Figure 1. Analysis of first-pass myocardial perfusion images by CMR imaging. A: Four short-axis slices: basal (a1), mediobasal (b1), medioapical (c1), and apical (d1), for first-pass myocardial perfusion analysis were analyzed quantitatively using the QMass® software package (MEDIS, Leiden, Netherlands). B: Time-intensity curve. For this analysis, epicardial (green line) and endocardial (red line) contours were manually drawn. Each slice image was divided into six segments (S1–S6), and the time-intensity curve of each segment derived from the perfusion image was evaluated. Of the four short-axis slices, the slice with the greatest LV wall thickness was analyzed.

Figure 2. The study flow chart. We divided the patients into two groups: the VT group consisted of patients with sustained or non-sustained VT or VF, whereas the non-VT group consisted of patients without VT or VF.

Results

Baseline characteristics: There were 15 patients in the VT group and 16 patients in the non-VT group. The baseline characteristics of the study population are presented in Table I. No significant difference was observed between the two groups in terms of the age, history of heart failure, heart size, and maximum wall thickness. The numbers of males, patients with family history of SCD, and history of syncope were larger in the VT group than in the non-VT group (VT versus non-VT; male, 10 (67%) versus 5 (31%), \( P = 0.049 \); family history of sudden
Myocardial scintigraphy: No difference was observed between the VT group and non-VT group in various parameters of myocardial scintigraphy, such as decay correction activity of Tl, decay correction activity of Tc, decay correction activity of BMI, acquisition time, left ventricular (LV) counts (Tl), LV counts (Tc), and LV counts (BMI) (Table I).

We evaluated myocardial injury using BMI (53) and the mismatch score, which was defined as the difference between Tl-201 (or 99mTc-MIBI) and 123I-BMIPP defect score, according to the previous report (16, 17). Although there were significant myocardial injuries in the hearts of both groups, no difference was observed between the VT group and non-VT group (VT versus non-VT; BMI mismatch score, 4.1 ± 3.9 versus 3.6 ± 3.7, P = 0.72) in the degree of injuries determined by the BMI mismatch score, indicating that predicting life-threatening arrhythmia in HCM patients via myocardial scintigraphy, including myocardial injury evaluated by BMI, is difficult.

Myocardial perfusion examined via CMR imaging and its relation with life-threatening arrhythmia: In the myocardial perfusion studies of CMR imaging, we investigated the parameters from the time-signal intensity curve, which exhibited differences between the VT group and non-VT group. The patients in the VT group exhibited higher mean of time 50% max than the patients in the non-VT group (VT versus non-VT; 24 ± 10 seconds versus 17 ± 4.3 seconds, P = 0.026). Moreover, the patients in the VT group exhibited wider SD of time 50% max in each segment than the patients in the non-VT group (VT versus non-VT; SD; 1.9 ± 1.6 seconds versus 0.87 ± 0.4 seconds, P = 0.028) (Figure 3A). These results were also consistent with the analyses regardless of the history of syncope and family history of SCD. We conducted additional analyses by excluding those who had history of syncope and/or family history of SCD. The results were as follows: (1) results without patients who have history of syncope: mean of time 50% max (VT group versus non-VT group; 2.1 ± 1.7 seconds versus 0.87 ± 0.40 seconds, P = 0.011) and SD of time 50% max (VT group versus non-VT group; 17 ± 4.3 seconds versus 0.87 ± 0.4 seconds, P = 0.023) (Figure 3A).

Table I. Baseline Characteristics Between the VT Group and Non-VT Group

|                      | VT group       | Non-VT group   | P   |
|----------------------|----------------|----------------|-----|
| Age                  | 63 ± 14        | 61 ± 19        | 0.73|
| Gender (Male)        | 10 (67%)       | 5 (31%)        | 0.048|
| BMI                  | 24 ± 5.2       | 25 ± 3.7       | 0.15|
| FH (+)               | 5 (36%)        | 0 (0%)         | 0.011|
| Syncope (+)          | 4 (27%)        | 0 (0%)         | 0.027|
| Heart Failure (+)    | 1 (6.7%)       | 2 (13%)        | 0.58|
| Left ventricular end-diastolic diameter | 40 ± 5.2 | 43 ± 3.5 | 0.12|
| Left ventricular end-systolic diameter | 26 ± 4.3 | 28 ± 2.7 | 0.16|
| Max wall thickness   | 20 ± 6         | 18 ± 2         | 0.31|
| Ejection fraction    | 66 ± 3         | 63 ± 3         | 0.015|
| Decay correct activity (Tl/Tc) | 124 ± 18/292 ± 43 MBq | 127 ± 18/274 ± 25 MBq | 0.64/0.18|
| Decay correct activity (BMIPP) | 109 ± 13 MBq | 107 ± 9.8 MBq | 0.65|
| Acquisition time     | 13 minutes 29 seconds | 14 minutes 31 seconds | 0.24|
| Heart rate during MRI| 60 ± 9.3       | 61 ± 10.9      | 0.65|
| Atrial fibrillation during MRI | 2 (13%) | 1 (6.3%) | 0.48|
| LV counts (Tl/Tc)    | 3439 ± 1124/4789 ± 1082 kC | 3530 ± 929/4423 ± 216 kC | 0.29/0.066|
| LV counts (BMIPP)    | 2109 ± 601 kC  | 2056 ± 447 kC  | 0.11|
| BMI mismatch         | 4.1 ± 3.9      | 3.6 ± 3.7      | 0.72|
| LGE (+)              | 15 (100%)      | 15 (94%)       | 0.52|

Table II. Baseline Characteristics of Medicine between the VT Group and Non-VT Group

|                      | VT group       | Non-VT group   | P   |
|----------------------|----------------|----------------|-----|
| Before hospitalization |               |                |     |
| Loop diuretics       | 2 (13%)        | 3 (19%)        | 0.68|
| Thiazide diuretics   | 0 (0%)         | 2 (13%)        | 0.16|
| ACE-I                | 0 (0%)         | 1 (6.7%)       | 0.31|
| ARB                  | 4 (27%)        | 1 (6.3%)       | 0.12|
| AAA                  | 1 (6.7%)       | 2 (13%)        | 0.58|
| CCB                  | 4 (29%)        | 6 (38%)        | 0.60|
| β-blocker            | 10 (67%)       | 13 (81%)       | 0.35|
| Amiodarone           | 1 (6.7%)       | 0 (0%)         | 0.29|
| Statin               | 4 (27%)        | 5 (31%)        | 0.78|
| At discharge |               |                |     |
| Loop diuretics       | 2 (13%)        | 4 (25%)        | 0.41|
| Thiazide diuretics   | 1 (6.7%)       | 2 (13%)        | 0.58|
| ACE-I                | 1 (6.7%)       | 1 (6.3%)       | 0.96|
| ARB                  | 2 (13%)        | 0 (0%)         | 0.13|
| AAA                  | 1 (6.7%)       | 2 (13%)        | 0.58|
| CCB                  | 4 (27%)        | 6 (38%)        | 0.52|
| β-blocker            | 15 (100%)      | 15 (94%)       | 0.33|
| Amiodarone           | 2 (13%)        | 0 (0%)         | 0.13|
| Statin               | 6 (40%)        | 6 (38%)        | 0.89|

definite, 5 (36%) versus 0 (0%), P = 0.011; syncope, 4 (27%) versus 0 (0%), P = 0.027). The left ventricular ejection fraction was higher in the VT group than in the non-VT group (VT versus non-VT; 66% ± 3% versus 63% ± 3%, P = 0.015). The medications before hospitalization and upon discharge are presented in Table II. No difference was observed between the two groups in terms of the general medication, such as loop diuretics, angiotensin-converting enzyme inhibitor/angiotensin II type 1 receptor blocker, β-blocker, and antiarrhythmic drugs.
time 50% max (VT group versus non-VT group; 28 ± 12 seconds versus 17 ± 4.1 seconds, \( P = 0.0050 \)) and SD of time 50% max (VT group versus non-VT group; 2.7 ± 1.8 seconds versus 0.87 ± 0.40 seconds, \( P = 0.0010 \)). These results indicate that CMR imaging may be useful for predicting serious adverse events in patients with HCM, regardless of the history of syncope and family history of SCD. The cutoff values of the mean of time 50% max and SD of time 50% max determined by the ROC curves were 15.6 and 1.32 seconds, respectively (Figure 3B).

**Prognosis of patients:** There were more events, such as all-cause death, hospitalization for heart failure after inspection of MRI, and the occurrence of life-threatening arrhythmia, in the VT group than in the non-VT group (VT versus non-VT; 11 (73%) versus 1 (6.3%), \( P = 0.0001 \)) (Table III). Next, we evaluated whether CMR imaging can be used for predicting serious adverse events in HCM patients. We first set the cutoff value of the mean of time 50% max to 15.6 seconds and divided the patients into two groups. The group whose value was less than the cutoff value of the mean of time 50% max was named “Group A,” whereas the group whose value was the same as or more than the cutoff value was named “Group B.” The Kaplan-Meier curves for composite events, including all-cause death, hospitalization for heart failure after inspection of MRI, and the occurrence of life-threatening arrhythmia, revealed that Group B had higher serious adverse events than Group A (Figure 4A). Subsequently, we set the cutoff value of the SD of time 50% max to 1.32 seconds and divided the patients into two groups. The group whose value was less than the cutoff value of the SD of time 50% max was named “Group C,” whereas the group whose value was the same or more than the cutoff value was named “Group D.” Group D also had higher serious adverse events than Group C (Figure 4B).

**Discussion**

In this study, we examined whether CMR imaging can predict serious adverse events in patients with HCM using noninvasive perfusion images. Although no difference was observed between the VT group and non-VT group in the various parameters of myocardial scintigraphy, including BMIPP mismatches score, a significant difference between the two groups was observed in the perfusion scores obtained by CMR imaging. BMIPP mismatch score is thought to evaluate myocardial injury by visualizing the nuclide intake of cardiomyocyte, whereas myocardial perfusion studies on CMR imaging is thought to dynamically evaluate microvascular dysfunction. Therefore, the results of this study indicate that microvascular dysfunction may be more deeply related to life-threatening arrhythmia than myocardial injury. The perfusion scores obtained by CMR imaging were also closely related to the major events, including all-cause death, hospitalization for heart failure, and the occurrence of life-threatening arrhythmia. These results indicate that CMR imaging is more useful than myocardial scintigraphy for predicting serious adverse events in HCM patients.

**Table III. Major Events**

| Event                  | VT group | Non-VT group | \( P \)     |
|------------------------|----------|--------------|-------------|
| VT/VF                  | 11 (73%) | 0 (0%)       | <0.0001     |
| Sustained VT           | 2        | 0            | 0.13        |
| Non-sustained VT       | 9        | 0            | 0.0002      |
| HF                     | 0 (0%)   | 1 (6.3%)     | 0.33        |
| All-cause death        | 3 (20%)  | 0 (0%)       | 0.060       |
| Primary endpoints      | 11 (73%) | 1 (6.3%)     | 0.0001      |

*1 out of 3 was non-cardiac death.
It has been reported that microvascular dysfunction causes life-threatening arrhythmia and is an independent predictor of poor prognosis in HCM patients. Cecchi et al. reported that microvascular dysfunction in patients with HCM evaluated by PET is a strong and independent predictor of clinical deterioration and death. Although PET is a good and standard method for evaluating microvascular dysfunction, vasodilators that are generally used during PET examination can exacerbate pressure gradient and can be harmful to HCM patients. CMR imaging is a gold standard for evaluating cardiac function and morphology. Moreover, it is useful for assessing fibrosis using gadolinium. Yin et al. recently reported that the utilization of first-pass myocardial perfusion CMR imaging with semiquantitative perfusion parameters enables early assessment of microvascular dysfunction without late gadolinium enhancement. Thus, in this study, we used myocardial perfusion images based on CMR imaging, instead of PET, to evaluate microvascular dysfunction in HCM patients. Among several parameters, we found that the mean of time 50% max and SD of time 50% max, both of which are automatically obtained from the time-intensity curve, clearly discriminated the VT group from the non-VT group. The differences in the mean of time 50% max and SD of time 50% max seem to indicate that microvascular dysfunction in the whole heart is worse and inhomogeneous myocardial perfusion is larger among each segment in the VT group than in the non-VT group. It has been reported that lower myocardial perfusion is induced by microvascular damage and that microvascular damage causes reentrant circuit around the ischemic area, which results in VT/VF. Our studies suggest that the risk of VT/VF of HCM patients can be predicted by myocardial perfusion examined by CMR imaging.

Since significant differences were observed between the VT group and non-VT group in the mean of time 50% max and SD of time 50% max obtained from the time-intensity curve, we next evaluated whether we can predict the major adverse events, including all-cause death, hospitalization for heart failure, and the occurrence of life-threatening arrhythmia, using the cutoff values of each index obtained by the ROC curves. We divided the patients into two groups by the cutoff values and examined the major adverse events using the Kaplan-Meier method. Significant differences in the serious adverse events were observed between the two groups divided by the cutoff values, indicating that myocardial perfusion examined by CMR imaging may be used to predict the serious adverse events and prognosis of patients with HCM. Since the prognosis of HCM patients without serious adverse events, such as life-threatening arrhythmia and cardiac dysfunction, is usually good, it is very important to discriminate the patients with serious adverse events from those without. This study indicates the potential usefulness of myocardial perfusion examined by CMR imaging for predicting serious adverse events in HCM patients. To prove this, further studies are necessary.

Limitation: This study has several limitations. This is a retrospective study and only includes a small number of participants. Thus, larger prospective studies are necessary to prove our conclusion. In terms of CMR imaging, spatially varying phase shifts may also occur in stationary tissue, and background phase errors may arise due to concomitant magnetic fields and/or eddy currents caused by the gradient pulse distorting the respective flow measurement.

Conclusion
CMR imaging may be useful for predicting serious adverse events in patients with HCM.

Disclosure
Conflicts of interest: None. There is nothing to declare.

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