



# Prognostic impact of mitral L-wave in patients with hypertrophic cardiomyopathy without risk factors for sudden cardiac death

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## Abstract

Hypertrophic cardiomyopathy (HCM) with severe diastolic dysfunction is a major cause of heart failure and sudden cardiac death (SCD) associated with lethal arrhythmia. Although various risk factors for cardiac events have been reported in HCM patients, previous studies have reported that some HCM patients exhibit either no risk or a low risk of SCD experienced cardiac events. The mid-diastolic transmitral flow velocity curve (mitral L-wave) is an echocardiographic index of left ventricular compliance, and it has been reported as one of the parameters of advanced diastolic dysfunction assessed noninvasively. However, little is known about the association between the mitral L-wave and long-term clinical outcomes in HCM patients without SCD risk factors. Between July 2005 and February 2016, 112 patients were diagnosed with HCM and 96 patients without risk factors were enrolled. After excluding 3 patients whom we could not detect L-wave more than once, 93 patients (mean age  $57.7 \pm 13.1$  years, 33 females) were divided into the following two groups, according to the presence or absence of the mitral L-wave: Group L (+) (with the mitral L-wave) and Group L (−) (without the mitral L-wave). The correlations between the mitral L-wave and rates of cardiac events were investigated. The mitral L-wave was present in 14 (15.1%) patients [Group L]. During the follow-up period [4.7 (2.9–7.5) years], patients experienced 7 cardiac events. Kaplan–Meier survival analysis showed that the event-free rate was significantly lower in Group L (+) than in Group L (−) (log-rank  $P=0.002$ ). Additionally, in multivariate analysis, L-wave positivity was identified as independent predictors of cardiac events. Existence of the mitral L-wave can predict cardiac events, even in HCM patients without SCD risk factors.

**Keywords** Hypertrophic cardiomyopathy · Mitral L-wave · Diastolic dysfunction · Prognosis

## Introduction

Hypertrophic cardiomyopathy (HCM) is a genetically transmitted myocardial disease that affects 1 in 500 individuals in the general population [1–3]. It involves a structural cardiac abnormality associated with an abnormal diastolic function, and this dysfunction is considered to be responsible for heart failure (HF) [4–6] and cardiac arrhythmia, which can cause sudden cardiac death (SCD) [7–9]. Contemporary guidelines for HCM recommend the use of SCD risk factors, including non-sustained ventricular tachycardia, massive left

ventricular (LV) hypertrophy, unexplained syncope, abnormal blood pressure response to exercise, and family history of SCD, to guide clinical decision-making with regard to the treatment strategy [3, 10–12]. However, cardiac events can occur even in patients with no risk or a low risk of SCD [9, 13]. Thus, clinically, it is important to stratify patients with latent myocardial impairment of HCM in the setting of asymptomatic stages to reduce the risk of subsequent cardiac events. Mitral inflow velocities detected using pulsed-wave Doppler echocardiography usually involve the following two forward-flow velocities: an early diastolic peak from early rapid filling (E-wave) and a late filling peak from atrial contraction (A-wave). In some cases, a triphasic mitral inflow-filling pattern with a mid-diastolic flow velocity (L-wave) could be noninvasively identified using echocardiography [14]. This pattern reflects elevated filling pressures and/or delayed myocardial relaxation [15] and has been reported to

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be a prognostic predictor in patients with ventricular hypertrophy [16]. Recently, it was shown that L-wave-positive HF with preserved ejection fraction (EF) is associated with a poor prognosis [17, 18]. The L-wave is considered as a valid marker of diastolic dysfunction; however, its prognostic implications in low-risk and asymptomatic HCM patients are unclear. Thus, we investigated the role of the mitral L-wave as a predictor of cardiac events in HCM patients without SCD risk factors.

## Materials and methods

### Study population

From June 2005 to September 2016, we retrospectively enrolled 112 consecutive patients with HCM at the timing of first diagnosis of HCM. HCM was defined as a maximum LV wall thickness  $\geq 15$  mm in the absence of another cardiac or systemic disease that can cause LV hypertrophy. At the time of registration, patients with cardiac hypertrophy caused by syndromic or metabolic diseases, those with coronary artery stenosis requiring therapy, those with prior evidence of primary valvular disease, and those with an implanted cardiac pacemaker or defibrillator were excluded. Additionally, patients were excluded if they had the following SCD risk factors: (1) non-sustained ventricular tachycardia (2) massive LV hypertrophy (maximum wall thickness  $\geq 30$  mm) (3) unexplained syncope (4) abnormal systolic blood pressure responses to exercise, and (5) family history of SCD [3, 10, 15]. All patients underwent blood examinations, transthoracic echocardiography, and cardiac catheterization at Nagoya University Hospital. Thus, of the 96 patients without SCD risk factor, 93 patients who had echocardiography more than once at over 2 weeks intervals were included in further analyses. The patients were classified into the following two groups: Group L (+) (included those with the mitral L-wave) and Group L (−) (included those without the mitral L-wave). This study was approved by the Ethics Review Board of Nagoya University School of Medicine, and written informed consent was obtained from all study patients.

### Echocardiography

Two-dimensional and Doppler echocardiography and tissue Doppler imaging (TDI) were performed in accordance with the American Society of Echocardiography guidelines using a Vivid 7 system (Vivid 7, GE Healthcare, WI, USA) [19]. LV ejection fraction was calculated using modified Simpson's method. In apical images, the pulsed Doppler sample volume was placed at the mitral valve tip and recorded. Diastolic filling indexes, including peak early (E), mid-diastolic

(L), and late (A) velocities, and the deceleration time (Dct) of the E-wave velocity were measured from mitral inflow velocities. The mid-diastolic flow (mitral L-wave) was identified as a distinct forward flow occurring during diastasis with peak velocity  $> 0.2$  m/s [15, 16]. TDI was used to measure mitral annular velocities, and assessments were performed at the septal corner of the mitral annulus.

### Cardiac catheterization

Right heart catheterization was performed using a 7-F triple-lumen Swan-Ganz thermodilution pulmonary artery catheter (Edwards Life Science Co., Irvine, CA, USA) at rest. After collecting baseline hemodynamic data, coronary angiography was performed to confirm the presence of coronary artery lesions, and a 6-F fluid-filled pigtail catheter with a high-fidelity micromanometer (CA-61000-PLB Pressure-tip Catheter, CD Leycom, Zoetermeer, the Netherlands) was advanced into the LV cavity through the upper limb artery to measure LV pressure. LV end-diastolic volume (LVEDV) and LV end-systolic volume (LVESV) were calculated by performing left ventriculography.

### Endomyocardial biopsy samples and collagen volume fraction measurement

Endomyocardial biopsy was performed ( $n = 69$ ) to exclude secondary cardiomyopathies. Three-to-five biopsy specimens were obtained from the right side of the intraventricular septum using a 6-F cardiac biptome catheter (Myocardial Biopsy Forceps, Technowood, Tokyo, Japan). To assess myocardial fibrosis in biopsy specimens, the collagen volume fraction was quantified by evaluating the region with positive Sirius red staining using the BZ-9000 Microscope (Keyence, Osaka, Japan).

### HCM risk score for SCD

HCM risk score for 5-year SCD was estimated using the European Society of Cardiology online risk calculator (HCM Risk-SCD Calculator: Available via <https://doc2do.com/hcm/webHCM.html>).

### Endpoints and follow-up

The primary endpoints were cardiac events, including SCD and lethal arrhythmia [ventricular tachycardia (VT) or ventricular fibrillation (VF)]. SCD was defined as instantaneous and unexpected death in patients previously in stable clinical conditions. The occurrence of lethal arrhythmia as an endpoint was defined the substitute of SCD consisted of sudden death events such as ventricular tachycardia or fibrillation which recover without treatment, or resuscitated by

appropriate treatment or implantable defibrillator discharge. Cardiac events were tracked and survival was confirmed by assessing the medical records and contacting the patients by telephone.

## Statistical analysis

Proportions are shown in percentages. Normally distributed continuous variables are expressed as mean  $\pm$  standard deviation, and non-normally distributed variables are expressed as median and interquartile range. Student's *t* test was used to compare normally distributed continuous variables, and the Mann–Whitney *U* test was used to compare non-normally distributed continuous variables. The Chi-square test or Fisher's exact test was used to compare categorical variables. The follow-up period was calculated from the date of evaluation to the date of reaching an endpoint. In patients not reaching the endpoint, the follow-up period was extended to the most recent evaluation. Cumulative survival curves were estimated using the Kaplan–Meier method. Hazard ratios (HRs) and 95% confidence intervals were calculated using Cox proportional hazards regression models. In bivariate and multivariate analyses, the variable with  $p < 0.05$  was included. Receiver operating characteristic (ROC) analysis was performed to assess the clinical utility of L wave for discriminating the cardiac events. All statistical analyses were performed using the Statistical Package for the Social Sciences version 18.0 (IBM Corp., Armonk, NY, USA). A *P* value  $< 0.05$  was considered statistically significant.

## Results

### Baseline clinical characteristics

Initially, the study cohort included 112 patients. The baseline clinical characteristics are summarized in Table 1. The mean patient age was  $58.5 \pm 13.1$  years, and 36 (32.1%) were female. Of the 112 patients, 96 (85.7%) did not have SCD risk factors and 16 (14.3%) had conventional risk factors. There were no differences in clinical characteristics at baseline between these groups. To estimate the prognostic efficacy of the L-wave in HCM patients without risk factors, after excluding 3 patients not detecting L-wave more than once, 93 patients in 96 patients without SCD risk factor were selected for further investigation. The baseline clinical characteristics of these patients without risk factors are summarized in Table 2. Of these 93 patients, 14 (15.1%) had the mitral L-wave [Group L (+)] and 79 (84.9%) did not have the mitral L-wave [Group L (-)]. A representative mitral Doppler inflow pattern with triphasic mitral inflow is shown in Fig. 1. All patients were classified as New York Heart Association (NYHA) functional class I or II. The heart

rate (HR) was significantly lower in Group L (+) and prescription rates of beta-blockers, diuretics, and Ca channel blockers and the mean plasma brain natriuretic peptide level tended to be higher in Group L (+) than in Group L (-). However, there were no significant differences in baseline characteristics, including age, blood pressure, medical history, hemoglobin level, and estimated glomerular filtration rate, between the groups. When calculated 5-year SCD risk score based on the HCM-Risk calculator, no patients had over 4% SCD risk score and these risk score were no significant difference between Group L (+) ( $1.6 \pm 0.8$ ) and Group L (-) ( $1.4 \pm 0.4$ ) ( $P = 0.345$ ) and between cardiac events (+) ( $1.7 \pm 1.0$ ) and cardiac events (-) ( $1.4 \pm 0.4$ ) ( $P = 0.367$ ).

### Baseline echocardiographic and cardiac catheterization characteristics

Echocardiographic and cardiac catheterization data are presented in Table 3. *E/A* ratio in Group L (+) was significantly higher than Group L (-). However, there were no significant differences in the baseline LV end-diastolic diameter (LVDd), LV end-systolic diameter (LVDs), left arterial (LA) diameter, LV ejection fraction, Dct, and *E/e'* ratio on echocardiography between the groups. At cardiac catheterization, although the mean pulmonary artery wedge pressure (PAWP) and mean pulmonary artery pressure (mPAP) tended to be higher and cardiac index (CI) was lower in Group L (+) than in Group L (-), there were no differences in LV end-diastolic volume index (LVEDVI), LV end-diastolic pressure (LVEDP), maximum rate of change in LV pressure ( $LVdp/dt_{max}$ ), minimum rate of change in LV pressure ( $LVdp/dt_{min}$ ) and half-time constant of isovolumic pressure decay ( $T_{1/2}$ ) between the groups. On assessing the degree of cardiac fibrosis using Sirius red staining, we found no differences between Group L (+) ( $n = 9$ ; median, 9.0% [range 4.0–14.5%]) and Group L (-) ( $n = 60$ ; median 11.0% [range 8.0–19.0%]) ( $P = 0.441$ ).

### Predictors of cardiac events

On comparing the incidence of cardiac events between risk factor-positive patients and risk factor-negative patients during the follow-up period [4.7 (2.9–7.5) years], we found that the cardiac event-free survival rate was significantly lower in risk factor-positive patients than in risk factor-negative patients ( $P < 0.001$ , Fig. 2). Of the 93 patients without risk factors, 7 had cardiac events [2 (2.1%) involving SCD, 5 (5.4%) involving lethal arrhythmia]. In the Kaplan–Meier survival analysis for cardiac events, the event-free survival rate was lower in Group L (+) than in Group L (-) (log-rank,  $P = 0.002$ ; Fig. 3). We stratified the risk factors for composite cardiac events with respect to patient characteristics and hemodynamic variables using a Cox proportional

**Table 1** Baseline characteristics of the study patients ( $n = 112$ )

|   | Total ( $n = 112$ ) | Risk factor (+) ( $n = 16$ ) | Risk factor (−) ( $n = 96$ ) | <i>P</i> value |
|---|---------------------|------------------------------|------------------------------|----------------|
| Age (years)                               | 58.5 ± 13.1         | 61.2 ± 12.4                  | 58.1 ± 13.2                  | 0.378          |
| Female [ <i>n</i> (%)]                    | 36 (32.1)           | 2 (12.5)                     | 34 (35.4)                    | 0.069          |
| BMI (kg/m <sup>2</sup> )                  | 23.9 ± 3.8          | 24.8 ± 2.0                   | 23.8 ± 4.0                   | 0.130          |
| Heart rate (beats/min)                    | 66.4 ± 12.9         | 64.8 ± 8.6                   | 66.7 ± 13.5                  | 0.575          |
| Systolic BP (mmHg)                        | 133.0 ± 25.0        | 131.1 ± 28.7                 | 133.4 ± 24.4                 | 0.733          |
| Diastolic BP (mmHg)                       | 73.9 ± 12.9         | 71.7 ± 13.8                  | 74.2 ± 12.8                  | 0.467          |
| Laboratory measurements                   |                     |                              |                              |                |
| Hemoglobin (g/dL)                         | 13.9 ± 1.8          | 14.0 ± 1.4                   | 13.9 ± 1.8                   | 0.788          |
| Creatine (mg/dL)                          | 0.81 ± 0.22         | 0.88 ± 0.21                  | 0.79 ± 0.22                  | 0.125          |
| Estimate GFR (mL/min/1.73m <sup>2</sup> ) | 72.6 ± 16.4         | 69.2 ± 16.4                  | 73.2 ± 16.4                  | 0.368          |
| BNP (pg/mL)                               | 104.5 (41.6–213.6)  | 165.5 (83.6–219.0)           | 91.0 (36.3–183.5)            | 0.118          |
| Echocardiography                          |                     |                              |                              |                |
| LVDd (mm)                                 | 46.8 ± 7.3          | 46.5 ± 8.8                   | 46.8 ± 7.0                   | 0.862          |
| LVDs (mm)                                 | 28.46 ± 7.9         | 28.0 ± 7.9                   | 28.6 ± 7.9                   | 0.760          |
| LV ejection fraction (%)                  | 68.7 ± 11.8         | 68.9 ± 9.7                   | 68.7 ± 12.2                  | 0.955          |
| LA dimension (mm)                         | 40.2 ± 7.0          | 44.3 ± 8.2                   | 39.5 ± 6.6                   | <b>0.010</b>   |
| <i>E/A</i> ratio                          | 0.98 ± 0.38         | 0.96 ± 0.44                  | 0.98 ± 0.36                  | 0.826          |
| <i>E/e'</i> ratio                         | 16.7 ± 9.2          | 17.4 ± 10.9                  | 16.6 ± 8.9                   | 0.765          |
| Deceleration time (ms)                    | 244.4 ± 81.0        | 250.1 ± 108.9                | 243.3 ± 75.9                 | 0.743          |
| Cardiac catheterization                   |                     |                              |                              |                |
| PAWP (mmHg)                               | 12.1 ± 5.7          | 13.4 ± 7.5                   | 11.9 ± 5.3                   | 0.345          |
| mPAP (mmHg)                               | 17.7 ± 5.9          | 18.4 ± 6.7                   | 17.6 ± 5.8                   | 0.631          |
| CI (L/min/m <sup>2</sup> )                | 2.8 ± 0.6           | 2.8 ± 0.7                    | 2.9 ± 0.6                    | 0.683          |
| LVEDVI (mL/m <sup>2</sup> )               | 74.0 ± 19.9         | 74.2 ± 21.1                  | 74.6 ± 19.1                  | 0.948          |
| LVdp/dt <sub>max</sub> (mmHg/s)           | 1585.0 ± 382.4      | 1557.6 ± 332.7               | 1589.7 ± 391.8               | 0.766          |
| LVdp/dt <sub>min</sub> (mmHg/s)           | − 1405.1 ± 375.0    | − 1279.4 ± 318.8             | − 1426.8 ± 381.3             | 0.161          |
| <i>T</i> <sub>1/2</sub> (ms)              | 39.7 ± 8.5          | 42.0 ± 8.9                   | 39.3 ± 8.4                   | 0.269          |

Bold value indicates statistically significant

Data are mean ± SD or median (interquartile range)

*BMI* body mass index, *BP* blood pressure, *eGFR* estimated glomerular filtration rate, *BNP* B-type natriuretic peptide, *LVDd* left ventricular end-diastolic diameter, *LVDs* left ventricular end-systolic diameter, *LA* left atrial, *E/A ratio* ratio of early transmitral flow velocity to atrial flow velocity, *E/e' ratio* ratio of early transmitral flow velocity to early diastolic mitral annular velocity, *PAWP* pulmonary arterial wedge pressure, *mPAP* mean pulmonary artery pressure, *CI* cardiac index, *LVEDVI* left ventricular end-diastolic volume index, *LVdp/dt<sub>max</sub>* maximum rate of change in left ventricular pressure, *LVdp/dt<sub>min</sub>* minimum rate of change in left ventricular pressure, *T*<sub>1/2</sub> half-time constant of isovolumic pressure decay

hazards analysis (Table 4). In univariate analysis, BNP (HR 1.035,  $P = 0.023$ ), L-wave (HR 7.636,  $P = 0.008$ ), *E/e'* ratio (HR 1.084,  $P = 0.038$ ), and mPAP (HR 1.123,  $P = 0.028$ ) were found to be predictors of cardiac events. Estimating the predictive power of L wave for other prognostic indicators, the bivariate analyses demonstrated that the L wave (+) predicted increased cardiac events risk-independent of BNP, *E/e'* ratio and mPAP. In multivariate analysis, L-wave positivity was found to be an independent predictor of cardiac events. When calculated a ROC-analysis using L wave score (m/s), ROC curve analysis identified L wave score cutoff value for cardiac events of 0.2 (AUC: 0.732, sensitivity: 57.1%, specificity: 88.4%) (Fig. 4).

## Discussion

Although few indexes have been identified for the prediction of cardiac events in HCM patients without risk factors, our study showed that among all parameters assessed, the existence of the mitral L-wave was independently associated with cardiac events. Generally, SCD is considered the most crucial complication in the natural clinical course of HCM. Previous studies have reported that the overall mortality rate among HCM patients was 0.53–1.3% per year [20, 21] and that patients exhibiting multiple SCD risk factors had high cardiac event incidence rates (1.3–5.0% per year) [9, 13]. However, HCM patients

**Table 2** Baseline characteristics of the study patients without risk factors ( $n=93$ )

|   | Total ( $n=93$ )  | L-wave (+) ( $n=14$ ) | L-wave (-) ( $n=79$ ) | <i>P</i> value |
|---|-------------------|-----------------------|-----------------------|----------------|
| Age (years)                               | 57.7 ± 13.1       | 62.1 ± 13.4           | 56.9 ± 13.0           | 0.177          |
| Female [ <i>n</i> (%)]                    | 33 (35.4)         | 6 (42.9)              | 27 (34.2)             | 0.367          |
| BMI (kg/m <sup>2</sup> )                  | 23.8 ± 4.0        | 23.9 ± 3.4            | 23.8 ± 4.1            | 0.913          |
| Systolic BP (mmHg)                        | 133.4 ± 24.7      | 133.5 ± 21.5          | 133.4 ± 25.4          | 0.984          |
| Diastolic BP (mmHg)                       | 74.6 ± 12.8       | 71.0 ± 11.3           | 75.2 ± 13.0           | 0.254          |
| Heart rate (beats/min)                    | 67.2 ± 13.4       | 59.4 ± 10.4           | 68.6 ± 13.5           | <b>0.008</b>   |
| HOCM [ <i>n</i> (%)]                      | 17 (18.3)         | 4 (28.6)              | 13 (16.5)             | 0.232          |
| Af [ <i>n</i> (%)]                        | 9 (9.7)           | 3 (21.4)              | 6 (7.6)               | 0.132          |
| 5-year SCD risk score (%)                 | 1.4 ± 0.5         | 1.6 ± 0.8             | 1.4 ± 0.4             | 0.345          |
| Medical history [ <i>n</i> (%)]           |                   |                       |                       |                |
| Hypertension                              | 34 (36.6)         | 8 (57.1)              | 26 (32.9)             | 0.083          |
| Diabetes                                  | 11 (11.8)         | 3 (21.4)              | 8 (10.1)              | 0.214          |
| Dyslipidemia                              | 29 (31.1)         | 4 (28.6)              | 25 (31.6)             | 0.545          |
| Current smoker                            | 26 (28.0)         | 6 (42.9)              | 20 (25.3)             | 0.153          |
| Prevalent heart failure                   | 6 (6.5)           | 0 (0.0)               | 6 (7.6)               | 0.365          |
| Medication [ <i>n</i> (%)]                |                   |                       |                       |                |
| ACE-Is/ARBs                               | 28 (30.1)         | 7 (50.0)              | 21 (26.6)             | 0.077          |
| Beta-blockers                             | 38 (40.9)         | 10 (71.4)             | 28 (35.4)             | <b>0.012</b>   |
| Aldosterone antagonists                   | 5 (5.4)           | 1 (7.1)               | 4 (5.1)               | 0.566          |
| Loop diuretics                            | 13 (16.1)         | 3 (21.4)              | 10 (12.7)             | 0.305          |
| Ca channel blockers                       | 19 (20.4)         | 6 (42.9)              | 13 (16.5)             | <b>0.035</b>   |
| Laboratory measurements                   |                   |                       |                       |                |
| Hemoglobin (g/dL)                         | 13.9 ± 1.8        | 14.1 ± 1.8            | 13.8 ± 1.8            | 0.662          |
| Creatine (mg/dL)                          | 0.79 ± 0.22       | 0.78 ± 0.17           | 0.80 ± 0.23           | 0.839          |
| Estimate GFR (mL/min/1.73m <sup>2</sup> ) | 73.3 ± 16.6       | 69.2 ± 11.1           | 74.1 ± 17.3           | 0.182          |
| BNP (pg/mL)                               | 87.9 (34.0–171.4) | 205.5 (84.7–300.0)    | 72.0 (26.7–159.2)     | <b>0.010</b>   |

Bold values indicate statistically significant

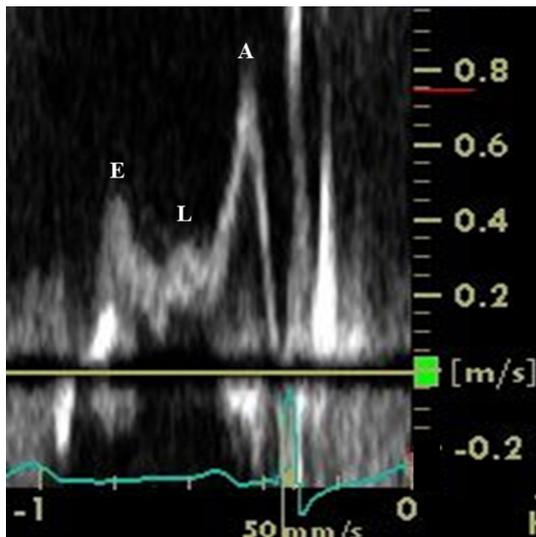
Data are mean ± SD or median (interquartile range)

*BMI* body mass index, *BP* blood pressure, *HOCM* hypertrophic obstructive cardiomyopathy, *Af* atrial fibrillation, *SCD* sudden cardiac death, *ACE-I* angiotensin-converting enzyme inhibitor, *ARB* angiotensin II receptor blocker, *eGFR* estimated glomerular filtration rate, *BNP* B-type natriuretic peptide

who have no risk or a low risk of SCD were reported to have a HCM-related mortality rate of 0.53–0.6% per year, [20, 22] and in our study, the overall SCD rate was 0.46% per year (2 events) during follow-up, although there were no SCD risk factors. The annual mortality rate in this study was equal to the rate reported previously and these findings confirmed that HCM patients without risk factors experienced SCD events with a certain probability.

Diastolic dysfunction is associated with various mechanical factors such as impaired myocardial relaxation, diastolic calcium overload, increased resistance to ventricular inflow, and activation of the renin–angiotensin system [4] and has adverse effects on the condition of HCM patients [3]. Severe hypertrophy of the myocardium increases chamber stiffness, and diffuse myocardial ischemia further influences chamber stiffness and relaxation; [3] therefore, the LV filling pressure progressively increases and diastolic HF worsens despite preserved systolic function. On the other hand,

microvascular ischemia associated with cell death causes replacement myocardial fibrosis, and increased interstitial fibrosis causes lethal arrhythmias [7]. Myocardial fibrosis, which is detected by late gadolinium enhancement (LGE) on contrast-enhanced cardiovascular magnetic resonance (CMR) imaging, has been shown to be associated with increased occurrence of VT on ambulatory Holter electrocardiography [23]. Additionally, Chan et al. have reported that the extent of LGE on CMR imaging was associated with an increased risk of HCM-related adverse events, including SCD [24]. However, CMR imaging with LGE is hard to introduce for every institution. With regard to noninvasive examination, previous studies have reported that mitral annulus mid-diastolic velocity is useful for the estimation of LV filling pressure and impaired LV relaxation [25, 26]; however, in the clinical course, pseudo-normalization was detected at progressed stages, and the use of this approach was not easy in daily practice. Geske et al. have reported



**Fig. 1** Representative Mitral Doppler inflow patterns for patient with triphasic mitral inflow. *E* peak velocity of mitral inflow early filling, *A* peak velocity of mitral inflow late filling during atrial contraction, *L* mid-diastolic filling

that it is difficult to clinically evaluate diastolic function in HCM because noninvasive measurements do not reflect LV filling pressure accurately [27]. On the other hand Ha et al. have reported that the existence of the mitral L-wave on echocardiography was associated with advanced diastolic dysfunction [15]. The mid-diastolic flow is associated with continued atrial filling from the pulmonary veins into the left ventricle after initial rapid mitral inflow during diastole in normal hearts [14]. Although the precise genesis and mechanism of L-wave formation have not been identified, the mitral L-wave in abnormal hearts is considered to result from delayed and prolonged LV relaxation and/or elevated LA pressure [28]. Either condition or both conditions could produce a pressure gradient between the left atrium and left ventricle during mid-diastole, resulting in mid-diastolic LV filling [16]. Therefore, mid-diastolic flow, a noninvasive surrogate of diastolic dysfunction, is well suited for assessing diastolic dysfunction. Even though the result of this study is partially inconsistent with the results of previous reports because there were no differences in the  $Dct$ ,  $E/e'$

**Table 3** Echocardiographic and cardiac catheterization data without risk factors ( $n=97$ )

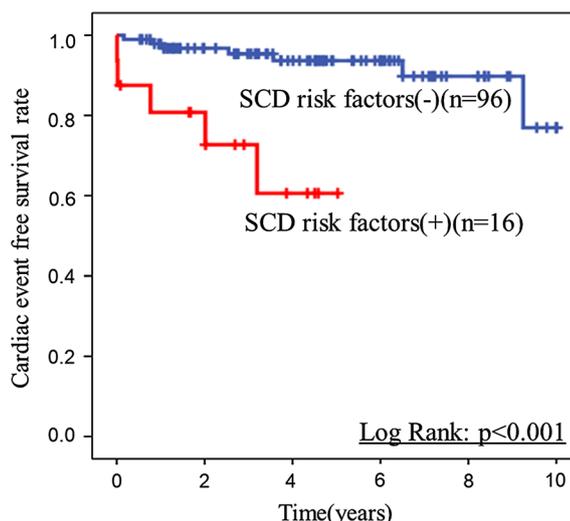
|                                 | Total ( $n=93$ ) | L-wave (+) ( $n=14$ ) | L-wave (−) ( $n=79$ ) | <i>P</i> value |
|---------------------------------|------------------|-----------------------|-----------------------|----------------|
| Echocardiography                |                  |                       |                       |                |
| LVDd (mm)                       | 46.8±7.1         | 49.6±5.7              | 46.3±7.2              | 0.104          |
| LVDs (mm)                       | 28.7±8.0         | 29.2±7.2              | 28.6±8.2              | 0.806          |
| LV wall maximum (mm)            | 17.1±2.6         | 18.0±3.1              | 17.0±2.5              | 0.157          |
| LV ejection fraction (%)        | 68.4±12.2        | 69.4±13.0             | 68.2±12.1             | 0.733          |
| LA dimension (mm)               | 39.5±6.6         | 41.2±7.3              | 39.1±6.4              | 0.160          |
| Peak E wave velocity (cm/s)     | 72.0±21.4        | 75.1±15.4             | 71.4±22.3             | 0.550          |
| Peak A wave velocity (cm/s)     | 76.5±24.8        | 67.1±24.0             | 77.9±24.8             | 0.179          |
| <i>E/A</i> ratio                | 0.99±0.37        | 1.21±0.41             | 0.96±0.35             | <b>0.033</b>   |
| <i>E/e'</i> ratio               | 16.6±8.9         | 18.5±8.2              | 16.3±9.1              | 0.446          |
| Deceleration time (ms)          | 242.1±74.2       | 234.4±78.2            | 243.5±74.0            | 0.675          |
| Cardiac catheterization         |                  |                       |                       |                |
| LVEDVI (mL/m <sup>2</sup> )     | 74.6±19.2        | 80.1±17.3             | 73.6±19.5             | 0.252          |
| LVESVI (mL/m <sup>2</sup> )     | 24.2±16.8        | 26.7±19.3             | 23.7±16.4             | 0.546          |
| PAWP (mmHg)                     | 11.8±5.5         | 14.4±6.4              | 11.4±5.1              | 0.057          |
| mPAP (mmHg)                     | 17.6±5.9         | 20.9±6.6              | 17.0±5.3              | 0.084          |
| RAP (mmHg)                      | 5.5±3.2          | 6.2±3.5               | 5.54±3.1              | 0.364          |
| CI (L/min/m <sup>2</sup> )      | 2.9±0.6          | 2.6±0.6               | 2.9±0.6               | 0.053          |
| LVdp/dt <sub>max</sub> (mmHg/s) | 1588.9±395.9     | 1476.9±263.9          | 1609.4±413.7          | 0.270          |
| LVdp/dt <sub>min</sub> (mmHg/s) | −1429.4±385.4    | −1318.9±258.3         | −1449.6±402.5         | 0.264          |
| $T_{1/2}$ (ms)                  | 39.2±8.6         | 42.6±7.7              | 38.6±8.6              | 0.123          |
| CVF [% ( $n=69$ )]              | 9.0 (4.5–15.5)   | 9.0 (4.0–14.5)        | 11.0 (8.0–19.0)       | 0.441          |

Bold value indicates statistically significant

Data are mean ±SD or median (interquartile range)

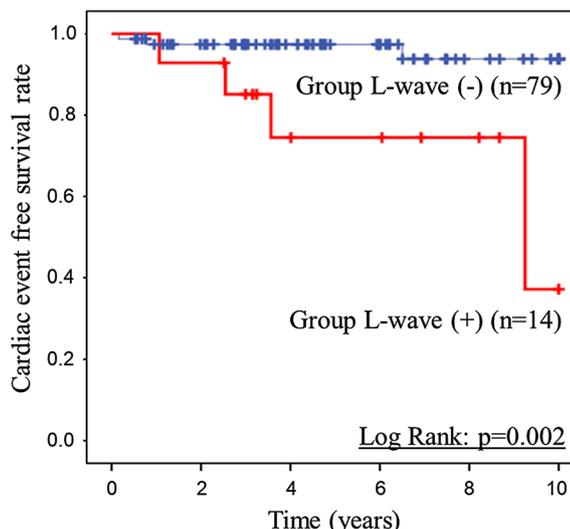
*LVDd* left ventricular end-diastolic diameter, *LVDs* left ventricular end-systolic diameter, *LV* left ventricular, *LA* left atrial, *E/A ratio* ratio of early transmitral flow velocity to atrial flow velocity, *E/e' ratio* ratio of early transmitral flow velocity-to-early diastolic mitral annular velocity, *LVEDVI* left ventricular end-diastolic volume index, *LVESVI* left ventricular end-systolic volume index, *PAWP* pulmonary arterial wedge pressure, *mPAP* mean pulmonary artery pressure, *RAP* right atrial pressure, *CI* cardiac index, *LVdp/dt<sub>max</sub>* maximum rate of change in left ventricular pressure, *LVdp/dt<sub>min</sub>* minimum rate of change in left ventricular pressure,  $T_{1/2}$  half-time constant of isovolumic pressure decay, *CVF* collagen volume fraction

**Fig. 2** Kaplan–Meier event-free survival between patients with SCD risk factors and those without. The probability of event-free survival in SCD risk factors (-) was significantly higher than SCD risk factors (+) by the log-rank test ( $P < 0.001$ ) (SCD risk factors; non-sustained ventricular tachycardia, massive left ventricular hypertrophy, unexplained syncope, abnormal blood pressure response to exercise and family history)



| Cardiac events                     |     |
|------------------------------------|-----|
| <b>SCD risk factors (-) (n=96)</b> |     |
| Sudden cardiac death               | n=2 |
| Lethal arrhythmia                  | n=5 |
| <b>SCD risk factors (+) (n=16)</b> |     |
| Sudden cardiac death               | n=2 |
| Lethal arrhythmia                  | n=3 |

**Fig. 3** Kaplan–Meier event-free survival between Group L-wave (+) and Group L-wave (-) in patients without risk factors for sudden cardiac death (SCD). The probability of event-free survival in Group L-wave (-) was significantly higher than that in Group L-wave (+) by the log-rank test ( $P = 0.002$ ) (SCD risk factors; non-sustained ventricular tachycardia, massive left ventricular hypertrophy, unexplained syncope, abnormal blood pressure response to exercise and family history)



| Cardiac events                 |     |
|--------------------------------|-----|
| <b>Group L-wave (-) (n=79)</b> |     |
| Sudden cardiac death           | n=1 |
| Lethal arrhythmia              | n=2 |
| <b>Group L-wave (+) (n=14)</b> |     |
| Sudden cardiac death           | n=1 |
| Lethal arrhythmia              | n=3 |

ratio, LVEDP,  $LVdp/dt_{min}$ , and  $T_{1/2}$  according to the mitral L-wave status, BNP and  $E/A$  were significantly higher and PAWP and mPAP tended to be higher and CI was lower in Group L (+) than in Group L (-). These findings suggest the existence of the mitral L-wave mean an increase in cardiac overload and this index could be useful for risk stratification of HCM patients even not having SCD risk factors. In HCM patients with the L-wave, additional therapies like ICD implantation would be considered to reduce the rate of lethal cardiac events.

### Study limitations

First, this was a retrospective study with a small number of patients at a single center. Second, because the mitral L-wave may be generated by delayed myocardial relaxation, elevated filling pressure, and reduced heart rate, it may be influenced by altered loading conditions including the administration of beta-blockers and Ca channel blockers. Further studies including groups without drug effects

**Table 4** Bivariate and multivariate cox regression analysis for the composite endpoint

|                                    | HR 95% CI              | P value      |
|------------------------------------|------------------------|--------------|
| Univariate analysis                |                        |              |
| Age                                | 1.014 (0.949–1.083)    | 0.679        |
| Female                             | 0.256 (0.031–2.133)    | 0.361        |
| BMI                                | 1.025 (0.858–1.220)    | 0.786        |
| BNP <sup>a</sup>                   | 1.035 (1.005–1.065)    | <b>0.023</b> |
| L-wave (+)                         | 7.636 (1.705–34.173)   | <b>0.008</b> |
| E/A ratio                          | 0.491 (0.025–9.685)    | 0.640        |
| E/e' ratio                         | 1.084 (1.005–1.171)    | <b>0.038</b> |
| CI                                 | 0.853 (0.230–3.170)    | 0.812        |
| mPAP                               | 1.123 (1.013–1.246)    | <b>0.028</b> |
| LVEDVI                             | 1.023 (0.981–1.067)    | 0.292        |
| LVdp/dt <sub>max</sub>             | 1.000 (0.998–1.02)     | 0.833        |
| LVdp/dt <sub>min</sub>             | 1.001 (0.999–1.004)    | 0.329        |
| T <sub>1/2</sub>                   | 1.002 (0.922–1.090)    | 0.956        |
| Bivariate analysis                 |                        |              |
| L-wave (+)                         | 5.356 (1.012–28.357)   | <b>0.048</b> |
| BNP <sup>a</sup>                   | 1.019 (0.984–1.055)    | 0.284        |
| L-wave (+)                         | 6.877 (1.106–42.762)   | <b>0.039</b> |
| E/e' ratio                         | 1.082 (0.991–1.181)    | 1.181        |
| L-wave (+)                         | 5.437 (1.094–27.013)   | <b>0.038</b> |
| mPAP                               | 1.079 (0.970–1.200)    | 0.160        |
| Multivariate analysis <sup>b</sup> |                        |              |
| BNP <sup>a</sup>                   | 0.962 (0.895–1.034)    | 0.321        |
| L-wave (+)                         | 19.470 (1.235–306.883) | <b>0.035</b> |
| E/e' ratio                         | 1.137 (0.994–1.300)    | 0.061        |
| mPAP                               | 1.033 (0.901–1.184)    | 0.643        |

Bold values indicate statistically significant

HR hazard ratio, CI confidence interval, other abbreviations as in Table 1

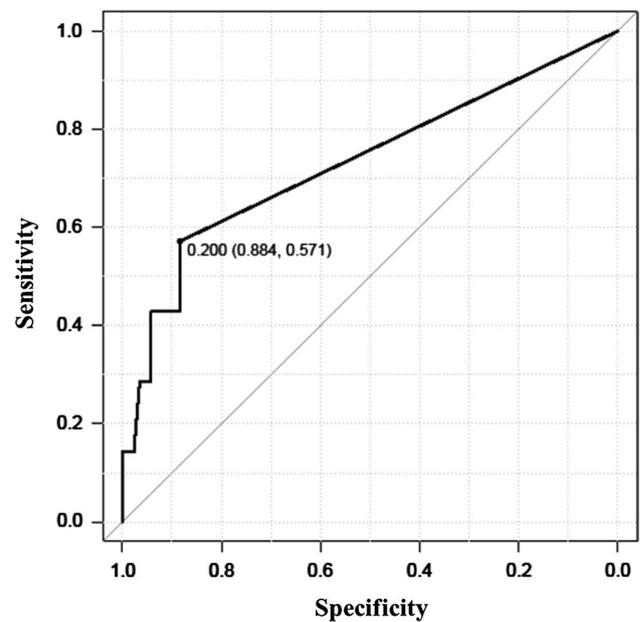
<sup>a</sup>Per 10-pg/mL increments

<sup>b</sup>The final model included all univariate predictors

are needed. Third, though left atrial volume is known as a powerful parameter that has an influence on diastolic function, there are no data in this study.

## Conclusions

Our study suggested that the appearance of the mitral L-wave was an abnormal echocardiographic index and could predict cardiac events in HCM. It is important to detect the existence of the mitral L-wave for monitoring and treating HCM patients, including stable HCM patients without SCD risk factors.



**Fig. 4** ROC curve analysis identified L wave score cutoff value for cardiac events of 0.2 (AUC: 0.732, sensitivity: 57.1%, specificity: 88.4%)

## Compliance with ethical standards

**Conflict of interest** The authors declare no competing financial interest.

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