Prognostic Significance of Non-Dilated Left Ventricular Size and Mitral Regurgitation in Patients With Dilated Phase of Hypertrophic Cardiomyopathy

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SUMMARY

Although a subtype of hypertrophic cardiomyopathy (HCM), dilated phase of HCM (D-HCM) characterized by left ventricular (LV) systolic dysfunction, has been reported to have a poor prognosis, some patients with D-HCM survive for a relatively long period. The degree of LV dilatation and functional mitral regurgitation (MR) are generally thought to be important predictors of poor prognosis in patients with LV systolic dysfunction. However, there is little information available on the relations among LV size, presence of significant MR, and prognosis in D-HCM patients.

We retrospectively studied 31 patients with D-HCM to determine whether echocardiographic assessment of LV size and MR provides incremental prognostic information.

During a follow-up period of 5.6 ± 4.2 years, there were 13 cardiovascular deaths. When the patients were divided into two groups by LV size at diagnosis of D-HCM, a non-dilated LV group (LV end-diastolic diameter (LVEDD) < 50 mm, n = 9) and a dilated LV group (LVEDD ≥ 50 mm, n = 22), the clinical course in the non-dilated LV group was significantly worse. As for the clinical impact of MR, no patient in the non-dilated LV group showed significant MR and 7 of the patients with dilated LV size showed significant MR during follow-up. Once significant MR was reached, cardiovascular deaths were significantly more frequent in patients with MR.

Patients with D-HCM, particularly those with less LV dilatation at diagnosis of dilated phase and with significant MR during follow-up, have a poor prognosis. (Int Heart J 2017; 58: 63-68)

Key words: Prognosis

Hypertrrophic cardiomyopathy (HCM) is a primary myocardial disorder that is generally associated with mild disability and normal life expectancy if sudden death can be prevented. On the other hand, it is well known that HCM in a subset of patients progresses to “dilated” or “end-stage” phase characterized by left ventricular (LV) systolic dysfunction, and patients with dilated phase of HCM (D-HCM) have a poor prognosis. However, various treatments such as the use of an implantable cardioverter-defibrillator (ICD) for prevention of sudden cardiac death and several medications and devices for prevention of heart failure are now available even for patients with D-HCM.

In patients with LV systolic dysfunction, the degree of LV dilatation associated with LV remodeling is generally thought to be one of the predictors of poor prognosis. Furthermore, patients with heart failure and LV dilatation often have functional mitral regurgitation (MR), and the presence of MR is also known to be associated with a poor clinical outcome. Although patients with D-HCM have been reported to show diverse clinical expression, there is little information on the relations among LV size, presence of significant MR, and prognosis. This study was performed to determine whether echocardiographic assessment of LV size and MR provides incremental prognostic information for patients with D-HCM.

METHODS

Subjects: We retrospectively studied 31 consecutive patients with D-HCM. All of the patients were evaluated at Kochi Medical School Hospital for confirmation of diagnosis, risk assessment, and symptom management between 1990 and 2014. The diagnosis of HCM was based on echocardiographic demonstration of unexplained left ventricular hypertrophy (LVH), ie, maximum left ventricular wall thickness (MLVWT) ≥ 15 mm. D-HCM was defined as LV systolic dysfunction of global ejection fraction (EF) < 50% at study entry or during follow-up with (1) unexplained hypertrophied LV (MLVWT ≥ 15 mm) or (2) previous documentation of unexplained LVH on echocardiography (MLVWT ≥ 15 mm) or (3) proven familial HCM in at least one relative who had an unequivocal diagnosis. Patients in whom LV systolic dysfunction was first docu-
mented at more than 80 years of age were excluded. Concomi-
tant coronary artery disease was excluded by coronary
angiography and/or myocardial scintigraphy. The study was
approved by the Ethics Committee on Medical Research of
Kochi Medical School.

Clinical evaluation: Evaluation of patients included history,
clinical examination, 12-lead electrocardiography, convention-
aland Doppler echocardiography, and ambulatory 24-hour
Holter ECG analysis. Left ventricular end-diastolic diameter
(LVEDD) and end-systolic diameter (LVESD) were measured
from M-mode and 2-D images obtained from parasternal long-
axis views by modified Simpson’s method. Global EF was
determined from apical 2- and 4-chamber views. Assessment of
MR included a comprehensive evaluation of 2D and Doppler
color flow echocardiographic images. We defined MR as sig-
nificant MR if the degree was moderate or severe. Moderate
MR was defined as a jet penetrating any depth and encompass-
ing 30% to 50% of the left atrium. Severe MR was considered
present when the MR jet encompassed > 50% of the left atrial
area. Mitral inflow velocities were determined using pulsed-
wave Doppler with the sample volume positioned at the tips of
the mitral leaflets in the 4-chamber view. Peak early (E) trans-
mitral filling velocity was measured. Tissue Doppler imaging
was performed in the pulse-Doppler mode to allow for a spec-
tral display and recording of mitral annulus velocities at the
septal corner. Peak early diastolic (Ea) velocity was measured
and the E/Ea ratio was calculated. Peripheral venous blood
samples were collected for measurements of several biomark-
ers including plasma brain natriuretic peptide at initial diagno-
sis of D-HCM.

For survival analysis, 3 modes of cardiovascular death
were defined: (1) sudden and unexpected death (including re-
suscitated cardiac arrest), in which collapse occurred in the
absence of or < 1 hour from the onset of symptoms in patients
who previously experienced a relatively stable or uneventful
clinical course (Appropriate ICD discharge was not included
in this study.); (2) heart failure-related death, which was in the
context of progressive cardiac decompensation ≥ 1 year before
death (including patients who had undergone heart transplanta-
tion); and (3) stroke-related death, which occurred as a result
of probable or proven embolic stroke.

Statistical analysis: All data are expressed as the mean ± SD
(range) or frequency (percentage). Baseline data were used in
initial diagnosis of D-HCM under a clinically stable condition.
Differences in continuous variables were assessed using Stu-
dent’s t test. Pearson’s chi-square test was used for compar-
sions between non-continuous variables, and Fisher’s exact
test was used when expected frequency was lower than 5. The fol-
low-up period was from the initial diagnosis of D-HCM. Sur-
vival estimates were calculated by the Kaplan-Meier method
and logrank test. Five-year survival values are expressed to-
gether with their 95% confidence intervals defined as survival
± 1.96 x SE. Statistical significance was defined by P ≤ 0.05.
Statistical analysis was performed using SPSS (version 14.0J)
statistical software (SPSS Japan Inc., Tokyo).

RESULTS

Baseline evaluation: The 31 patients with D-HCM included
20 men and 11 women. Twenty-three (74%) of the patients
were confirmed as having familial HCM. The ages of the pa-
tients at diagnosis of HCM and at diagnosis of D-HCM were
46 ± 15 and 58 ± 11 years, respectively.

LV size and outcome: We divided the patients into two groups
by LV size at initial diagnosis of D-HCM: a non-dilated LV
size (< 50 mm) and a dilated LV group (LVESD ≥
50 mm). The baseline data of clinical characteristics of the two
groups are summarized in Table I. The ages of the patients at
diagnosis of HCM and at diagnosis of D-HCM were not dif-
ferent between the two groups. The percentage of male pa-
tients in the non-dilated LV group was lower than that in the
dilated LV group. Results of echocardiography are also shown
in Table I; LVESD and LVESD were smaller and MLVWT
was larger in patients with non-dilated LV size than in patients
with dilated LV size.

The mean follow-up period from the initial diagnosis of
D-HCM for the whole patient cohort was 5.6 ± 4.2 years.
There were 13 cardiovascular deaths, including sudden death
in 4 patients, heart failure-related death in 7 patients, and em-
bolic stroke-related death in 2 patients. Patients with D-HCM
had a poor prognosis with a cardiovascular survival rate of
64% at 5 years from diagnosis of the dilated phase. During the
follow-up period, cardiovascular deaths occurred in 6 (67%) of
the patients with non-dilated LV size (sudden death in 3 pa-
tients, heart failure-related death in one patient, and embolic
stroke-related death in two patients). In the cases of sudden
death, one case was due to a ventricular fibrillation storm de-
spite cardiac resynchronization therapy with a cardioverter-de-
fibrillator (CRT-D) and another case had CRT without a cardi-
overter-defibrillator for medically refractory heart failure. On
the other hand, cardiovascular deaths occurred in 7 (32%) of
the patients with dilated LV size; 6 of those deaths were heart
failure-related deaths and one was sudden cardiac death. The
clinical course in the non-dilated LV group was significantly
worse than that in the dilated LV group (Figure 1). Medical
treatment and device implantation during follow-up are shown
in Table II.

MR and outcome: Next, we evaluated the significance of MR
in patients with D-HCM. The presence of significant MR was
defined as moderate or severe MR at study entry or during fol-
low-up. Because there was no patient with significant MR in
the non-dilated LV group, we focused on the dilated LV group
(n = 22). Seven of the patients with dilated LV size showed
significant MR: 3 of the 7 patients already had significant MR
at initial diagnosis of D-HCM and the other 4 patients pro-
gressed to significant MR during follow-up. In the etiology of
MR, all of the 7 patients showed not organic MR but function-
al MR mainly due to its tethering associated with depressed
LV systolic function. Baseline data for clinical and echocardio-
graphic characteristics of the two groups at diagnosis of D-
HCM are summarized in Table III. Patients with significant
MR tended to be diagnosed with D-HCM later and to have
lower LV systolic function.

During the follow-up period, cardiovascular deaths oc-
curred in 5 (71%) of the patients with significant MR (heart
failure-related death in all 5 patients) and in 2 (13%) of the
patients without significant MR (sudden cardiac death in one
patient and heart failure death in one patient) in the dilated LV
group. Medical treatment and device implantation during fol-
low-up are shown in Table IV. The rate of cardiovascular
deaths in patients with MR was significantly higher than that.
in patients without significant MR during the follow-up period after the presence of MR (Figure 2).

Figure 3 shows Kaplan-Meier curves of cardiovascular deaths in the 31 patients from initial diagnosis of D-HCM according to LV size and presence of significant MR.

**Discussion**

Hypertrophic cardiomyopathy (HCM) is a heterogeneous myocardial disorder with a broad spectrum of clinical presentations and morphologic features.\(^1,3,17,18\) Although LV systolic function is supernormal or preserved in most cases of HCM, progression to systolic impairment occurs in about 5-10% of patients when they are followed for a long period.\(^4,9\) It is usually associated with LV remodeling with wall thinning and cavity dilatation, resembling the morphologic features of dilated cardiomyopathy (DCM).\(^4,9\) Although this subtype of HCM, so-called D-HCM, has been reported to have a poor prognosis, some patients with D-HCM survive for a relatively long period in the current era of advanced arrhythmia and heart failure management.\(^2,11\)

In the present study, less LV enlargement at diagnosis of D-HCM and presence of significant MR during follow-up were associated with markedly worse clinical outcome, although cardiovascular mortality was originally poor in the whole cohort of D-HCM. To the best of our knowledge, this is the first report showing that LV size and presence of significant MR seem to have additional predictive value for cardiovascular deaths in patients with D-HCM.

Greater LV dilatation is generally considered to be one of the predictors of poor prognosis in patients with LV systolic dysfunction.\(^12\) In myocardial infarction, a severe degree of myocardial injury was associated with a greater degree of chamber remodeling over time.\(^12,19\) On the other hand, several investigators have reported that the prognosis of DCM patients with mild LV dilatation is variable and that end-stage heart failure occurs in a subgroup of patients with DCM despite mild LV dilatation.\(^20-23\) We previously reported that DCM patients with mild LV dilatation have two important features: one group of patients with early and mild DCM may stabilize or improve through the natural course or with appropriate medi-
Table II. Treatment of Patients With D-HCM

<table>
<thead>
<tr>
<th></th>
<th>Non-dilated LV size (&lt; 50 mm)</th>
<th>Dilated LV size (≥ 50 mm)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follow-up duration, years</td>
<td>4.5 ± 3.2</td>
<td>6.1 ± 4.5</td>
<td>0.342</td>
</tr>
<tr>
<td>Device implantation, n (%)</td>
<td>3 (33%)</td>
<td>11 (50%)</td>
<td>0.456</td>
</tr>
<tr>
<td>Appropriate ICD discharge, n (%)</td>
<td>1 (11%)</td>
<td>3 (14%)</td>
<td>1.000</td>
</tr>
<tr>
<td>ACEI or ARB, n (%)</td>
<td>6 (67%)</td>
<td>21 (95%)</td>
<td>0.063</td>
</tr>
<tr>
<td>Beta blocker, n (%)</td>
<td>5 (56%)</td>
<td>12 (55%)</td>
<td>1.000</td>
</tr>
<tr>
<td>Spironolactone, n (%)</td>
<td>3 (33%)</td>
<td>9 (41%)</td>
<td>1.000</td>
</tr>
<tr>
<td>Amiodarone, n (%)</td>
<td>2 (22%)</td>
<td>10 (45%)</td>
<td>0.418</td>
</tr>
<tr>
<td>Diuretics, n (%)</td>
<td>6 (67%)</td>
<td>19 (86%)</td>
<td>0.320</td>
</tr>
<tr>
<td>Warfarin, n (%)</td>
<td>6 (67%)</td>
<td>15 (68%)</td>
<td>1.000</td>
</tr>
</tbody>
</table>

Data are shown as mean ± SD or number (percent). D-HCM indicates dilated phase of hypertrophic cardiomyopathy; LV, left ventricular; ICD, implantable cardioverter-defibrillator; ACEI, angiotensin-converting enzyme inhibitors; and ARB, angiotensin II receptor blockers.

Table III. Clinical Characteristics of Patients With Dilated LV Size at Initial Diagnosis of D-HCM

<table>
<thead>
<tr>
<th></th>
<th>Significant MR presence (n = 7)</th>
<th>Significant MR absence (n = 15)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at diagnosis of HCM, years</td>
<td>47.0 ± 12.9</td>
<td>45.5 ± 15.7</td>
<td>0.832</td>
</tr>
<tr>
<td>Age at diagnosis of D-HCM, years</td>
<td>62.1 ± 8.4</td>
<td>55.1 ± 11.5</td>
<td>0.167</td>
</tr>
<tr>
<td>Gender; men, n (%)</td>
<td>6 (86%)</td>
<td>12 (80%)</td>
<td>1.000</td>
</tr>
<tr>
<td>Familial HCM, n (%)</td>
<td>4 (57%)</td>
<td>11 (73%)</td>
<td>0.630</td>
</tr>
<tr>
<td>NYHA functional class, n (%)</td>
<td></td>
<td></td>
<td>0.565</td>
</tr>
<tr>
<td>II</td>
<td>5 (71%)</td>
<td>13 (87%)</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>2 (29%)</td>
<td>2 (13%)</td>
<td></td>
</tr>
<tr>
<td>Atrial fibrillation, n (%)</td>
<td>5 (71%)</td>
<td>7 (47%)</td>
<td>0.381</td>
</tr>
<tr>
<td>Non-sustained ventricular tachycardia*, n (%)</td>
<td>4 (57%)</td>
<td>12 (80%)</td>
<td>0.334</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Echocardiographic data</th>
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<tbody>
<tr>
<td>Maximum LV wall thickness, mm</td>
<td>15.0 ± 3.1</td>
<td>15.7 ± 1.6</td>
<td>0.568</td>
</tr>
<tr>
<td>Interventricular wall thickness, mm</td>
<td>13.6 ± 4.0</td>
<td>15.7 ± 3.8</td>
<td>0.236</td>
</tr>
<tr>
<td>Posterior wall thickness, mm</td>
<td>10.1 ± 2.3</td>
<td>11.5 ± 2.6</td>
<td>0.268</td>
</tr>
<tr>
<td>LV end-diastolic diameter, mm</td>
<td>58.3 ± 3.3</td>
<td>57.1 ± 5.1</td>
<td>0.572</td>
</tr>
<tr>
<td>LV end-systolic diameter, mm</td>
<td>45.6 ± 2.9</td>
<td>43.5 ± 6.5</td>
<td>0.425</td>
</tr>
<tr>
<td>Ejection fraction, %</td>
<td>39.4 ± 6.1</td>
<td>43.3 ± 5.3</td>
<td>0.146</td>
</tr>
<tr>
<td>Left atrial diameter, mm</td>
<td>51.7 ± 14.9</td>
<td>46.1 ± 10.3</td>
<td>0.317</td>
</tr>
<tr>
<td>E, cm/second</td>
<td>71.0 ± 20.6 (n = 5)</td>
<td>64.5 ± 20.6 (n = 15)</td>
<td>0.546</td>
</tr>
<tr>
<td>E/Ea septal</td>
<td>12.0 ± 3.3 (n = 2)</td>
<td>15.9 ± 7.0 (n = 7)</td>
<td>0.479</td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th>Laboratory data</th>
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<tbody>
<tr>
<td>BNP, pg/mL</td>
<td>700.1 ± 532.5 (n = 3)</td>
<td>328.5 ± 307.1 (n = 10)</td>
<td>0.144</td>
</tr>
<tr>
<td>Creatinine, mg/dL</td>
<td>1.03 ± 0.49 (n = 3)</td>
<td>0.93 ± 0.16 (n = 10)</td>
<td>0.753</td>
</tr>
<tr>
<td>Sodium, mmol/L</td>
<td>140.7 ± 3.2 (n = 3)</td>
<td>139.9 ± 2.5 (n = 11)</td>
<td>0.667</td>
</tr>
<tr>
<td>Total bilirubin, mg/dL</td>
<td>1.30 ± 1.13 (n = 2)</td>
<td>0.72 ± 0.22 (n = 11)</td>
<td>0.599</td>
</tr>
</tbody>
</table>

Data are shown as mean ± SD or number (percent). The * indicates during follow-up period. LV indicates left ventricular; D-HCM, dilated phase of hypertrophic cardiomyopathy; MR, mitral regurgitation; HCM, hypertrophic cardiomyopathy; NYHA, New York Heart Association functional class; E, septal, peak early transmitral filling velocity; E/Ea septal, peak early transmitral filling velocity/mitral annulus peak early diastolic velocity at septal; and BNP, plasma brain natriuretic peptide.

Table IV. Treatment of D-HCM Patients With Dilated LV Size

<table>
<thead>
<tr>
<th></th>
<th>Significant MR presence (n = 7)</th>
<th>Significant MR absence (n = 15)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follow-up duration, years</td>
<td>7.2 ± 5.4</td>
<td>5.5 ± 4.1</td>
<td>0.418</td>
</tr>
<tr>
<td>Device implantation, n (%)</td>
<td>5 (71%)</td>
<td>6 (40%)</td>
<td>0.361</td>
</tr>
<tr>
<td>Appropriate ICD discharge, n (%)</td>
<td>0 (0%)</td>
<td>3 (20%)</td>
<td>0.523</td>
</tr>
<tr>
<td>ACEI or ARB, n (%)</td>
<td>7 (100%)</td>
<td>14 (93%)</td>
<td>1.000</td>
</tr>
<tr>
<td>Beta blocker, n (%)</td>
<td>2 (29%)</td>
<td>10 (67%)</td>
<td>0.172</td>
</tr>
<tr>
<td>Spironolactone, n (%)</td>
<td>4 (57%)</td>
<td>5 (33%)</td>
<td>0.376</td>
</tr>
<tr>
<td>Amiodarone, n (%)</td>
<td>3 (43%)</td>
<td>7 (47%)</td>
<td>1.000</td>
</tr>
<tr>
<td>Diuretics, n (%)</td>
<td>7 (100%)</td>
<td>12 (80%)</td>
<td>0.523</td>
</tr>
<tr>
<td>Warfarin, n (%)</td>
<td>6 (86%)</td>
<td>9 (60%)</td>
<td>0.350</td>
</tr>
</tbody>
</table>

Data are shown as mean ± SD or number (percent). D-HCM indicates dilated phase of hypertrophic cardiomyopathy; LV, left ventricular; MR, mitral regurgitation; ICD, implantable cardioverter-defibrillator; ACEI, angiotensin-converting enzyme inhibitors; and ARB, angiotensin II receptor blockers.
cations, whereas the other group shows definite impairment of hemodynamics together with left atrial dilatation despite modest LV dilatation, and these patients have a poorer prognosis and must be carefully followed.\textsuperscript{13} In the current study, the prognosis of patients with non-dilated LV size was significantly poorer than that of patients with dilated LV size despite similar baseline characteristics and treatment during follow-up, although some D-HCM patients with small LV size might be in an early phase of D-HCM with large LV size. The reason for these results is not clear, but we speculate that patients with non-dilated LV size have greater LV stiffness, leading to restricted LV dilatation and more elevated LV end-diastolic pressure. In general, advanced heart failure unrelated to LV outflow obstruction in HCM is associated with LV remodeling accompanied by LV systolic impairment and chamber dilatation. On the other hand, there is another proposed LV remodeling in HCM, which may eventually lead to a “restrictive-stage” phase with a small LV chamber, progression of biatrial dilatation, markedly restrictive diastolic filling, and poor outcome.\textsuperscript{23-26} The D-HCM patients with non-dilated LV size in our study may be characterized partly by the restrictive type. Recently Wada, et al reported that the severity of fibrosis in myocardial biopsy and lower LV ejection fraction were associated with a greater risk of lethal arrhythmic events in HCM patients.\textsuperscript{13} Although we did not have pathological data in our study, the D-HCM patients with non-dilated LV size might have more severe fibrosis.

Functional MR is a common finding in patients with heart failure as a complication of LV systolic impairment and LV enlargement of any cause and is known to be associated with poorer prognosis.\textsuperscript{13,16} Chronic MR leads to progressive heart failure status through a vicious circle of LV dilatation leading to MR leading to further LV dilatation. In addition to the mechanical process, neurohormonal overload is thought to hasten the deaths of these patients. In our study, about one third of the D-HCM patients with dilated LV size showed functional MR during follow-up of 6.1 ± 4.5 years, and cardiovascular deaths were more frequent in these patients once they had developed significant MR.

The least we can do is to recognize that though slightly reduced global LV systolic function appears subtle, it is indeed an important sign of evolution to dilated phase, since LV systolic function is supernormal in most patients with HCM. Considering the more rapid clinical deterioration mainly to sudden cardiac death and embolic stroke death in D-HCM patients with non-dilated LV size, early intervention with ICD implantation and strict anticoagulation should be considered for these patients. In D-HCM patients with dilated LV size, because heart failure rapidly progresses once significant functional MR is reached, appropriate assignment of limited treatment such as transplantation or valve repair/replacement surgery may be needed, although there is very little evidence of the effectiveness of invasive treatment for D-HCM patients with significant functional MR.

There are several limitations to be acknowledged in the present study. First, the number of subjects was relatively small and some of the statistical analyses might have been affected. Second, due to the retrospective design of the study, it is possible that there is a selection bias, although the study population consisted of consecutive patients with D-HCM. Third, we could not fully evaluate diastolic functions such as tissue Doppler indices because these echo techniques were not available for some patients at the time of initial diagnosis of D-HCM although we speculate that patients with non-dilated LV size have greater LV stiffness, leading to restricted LV dilatation and more elevated LV end-diastolic pressure. We did not have enough data supporting our speculation, including pulmonary artery wedge pressure, degree of late gadolinium enhancement in cardiac magnetic resonance, and endomyocardial biopsy. A prospective study to clarify the mechanism is needed.

In conclusion, patients with D-HCM, particularly those with less LV dilatation at diagnosis of D-HCM and with significant MR during follow-up, have a poor prognosis. This information will be helpful for appropriate interventions such as early deployment of an ICD, strict anticoagulation, and cardiac surgery for these patients.
DISCLOSURE

None of the authors have conflict of interest to disclose in connection with our manuscript.

REFERENCES