Clinical Features of the Dilated Phase of Hypertrophic Cardiomyopathy in Comparison With Those of Dilated Cardiomyopathy

Address for correspondence:
Yoshinori L. Doi, MD
Department of Medicine and Geriatrics,
Kochi Medical School, Oko-cho,
Nankoku-shi, Kochi 783–8505,
Japan
ydoi@kochi-u.ac.jp

Tomoyuki Hamada, MD; Toru Kubo, MD; Hiroaki Kitaoka, MD; Takayoshi Hirota, MD; Eri Hoshikawa, MD; Kayo Hayato, MD; Yuji Shimizu, MD; Makoto Okawa, MD; Naohito Yamasaki, MD; Yoshihisa Matsumura, MD; Toshikazu Yabe, MD; Jun Takata, MD; Yoshinori L. Doi, MD

Department of Medicine and Geriatrics, Kochi Medical School, Kochi, Japan

ABSTRACT

Background: Although the dilated phase of hypertrophic cardiomyopathy (D-HCM) characterized by left ventricular (LV) systolic dysfunction and cavity dilatation has been reported to be a poor prognosis, this is now in contrast to the improved prognosis of dilated cardiomyopathy (DCM) in the era of advancements in heart failure management. There has been no investigation of the clinical features of D-HCM compared with those of DCM from the point of management of systolic dysfunction.

Hypothesis: The aim of this study was to investigate the clinical features of D-HCM in comparison with those of DCM in a single institute.

Methods: We studied 20 consecutive patients with D-HCM (global ejection fraction $<50\%$) and 115 consecutive patients with DCM.

Results: At diagnosis of D-HCM, 8 (40%) of the D-HCM patients already experienced dyspnea (New York Heart Association [NYHA] class $\geq$ III). Left atrial diameter was larger and prevalence of atrial fibrillation was higher in the D-HCM group, although LV size was larger and LV ejection fraction was lower in the DCM group. During the follow-up period (4.0 years), 11 (55%) of the patients with D-HCM died. The 5-year survival rate from all-cause mortality including cardiac transplantation was 45.6% in patients with D-HCM vs 81.6% in patients with DCM (log-rank $P = .0001$).

Conclusions: Patients with D-HCM were more symptomatic at diagnosis, although LV dilatation and impaired fractional shortening seemed more severe in patients with DCM. The prognosis for D-HCM patients was worse than that for patients with DCM despite similar or even more intensive treatment for heart failure.

Introduction

Hypertrophic cardiomyopathy (HCM) is a primary myocardial disorder, generally associated with mild disability and normal life expectancy, if sudden death can be prevented.[1–3] However, patients with the dilated phase of HCM (D-HCM), characterized by left ventricular (LV) systolic dysfunction and cavity dilatation, have been reported to have a poor prognosis.[4–7] On the other hand, the prognosis of patients with dilated cardiomyopathy (DCM) has significantly improved over the past 20 years. This improvement seems to be partly due to the increased use of angiotensin-converting enzyme inhibitors (ACEI), angiotensin II type 1 receptor blockers (ARB), and β-blockers for the treatment of heart failure due to systolic impairment.[8]

The purpose of this study was to investigate the clinical features of D-HCM in comparison with those of DCM treated in a single institute from the point of management of heart failure due to systolic dysfunction.

Methods

Subjects

We studied 20 consecutive patients with the dilated phase of HCM (D-HCM; 11 were familial HCM) and 115 consecutive patients with DCM. All patients were evaluated at the Kochi Medical School Hospital for confirmation of diagnosis, risk assessment, and symptom management between 1990 and 2005. The diagnosis of HCM was based on echocardiographic demonstration of an unexplained left ventricular hypertrophy (LVH), that is, maximum left ventricular wall thickness (MLVWT) $\geq$15 mm. D-HCM was defined as LV systolic dysfunction of global ejection fraction (EF) $<50\%$ at study entry or during follow-up in the presence of (1) unexplained hypertrophied LV (MLVWT $\geq$15 mm), or (2) previous documentation of unexplained LVH on echocardiography (MLVWT $\geq$15 mm), or (3) proven familial HCM with at least 1 relative who had an unequivocal diagnosis. Concomitant coronary artery

Clin. Cardiol. 33, 7, E24–E28 (2010)
Published online in Wiley InterScience. (www.interscience.wiley.com)
DOI:10.1002/clc.20533 © 2010 Wiley Periodicals, Inc.

Received: July 17, 2008
Accepted with revision: September 25, 2008

disease was excluded either by coronary angiography and/or myocardial scintigraphy. The diagnostic criteria of DCM were: (1) a dilated left ventricle (left ventricular end-diastolic diameter [LVEDD]>55 mm) with EF <50%, and (2) exclusion of patients with acute myocarditis, specific heart muscle disease, general systemic disease, significant coronary artery stenosis, valvular disease, sensitivity/toxic reactions, and history of excessive alcohol intake. The study was approved by the Ethics Committee on Medical Research of the Kochi Medical School.

Clinical Evaluation

Evaluation of patients included history, clinical examination, 12-lead electrocardiography, M-mode, 2-dimensional (2D) and Doppler echocardiography, and ambulatory 24-hour Holter ECG analysis. The severity and distribution of LVH were assessed in the parasternal short axis plane at mitral valve and papilliary muscle levels. Left ventricular end-diastolic diameter (LVEDD) and end-systolic diameter (LVESD) were measured from M-mode and 2D images obtained from parasternal long axis views. Global EF was determined from apical 2-chamber and 4-chamber views.

For survival analysis, 3 modes of cardiovascular death were defined: (1) sudden and unexpected death (including resuscitated 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; (2) heart failure-related death, which was in the context of progressive cardiac decompensation ≥1 year before death (including patients who had undergone heart transplantation); and (3) stroke-related death, which occurred as a result of probable or proven embolic stroke.

Data Analysis

Statistical analysis was performed using SPSS (version 14.0J) statistical software (SPSS Inc., Chicago, IL). All data are expressed as mean ± SD (range) or frequencies (percentage). Differences in continuous variables were assessed using a Student t test. Pearson's χ^2 test was used for comparisons between noncontinuous variables, and Fisher's exact test was used when expected frequency was lower than 5. Survival estimates were calculated by the Kaplan-Meier method and log-rank test. The 5-year survival values are expressed together with their 95% confidence intervals (CI) defined as survival $\pm 1.96 \times$ SE. Statistical significance was defined by $P \leq .05$.

Results

Baseline Evaluation

The baseline data of clinical and echocardiographic characteristics of the 2 groups (D-HCM and DCM) are summarized in Table 1. This baseline data is at the time when LV systolic dysfunction was first documented, that is, the time of diagnosis of D-HCM and DCM. Nine of the 20 patients with D-HCM were already in the dilated phase at initial evaluation and the other 11 patients progressed to D-HCM during follow-up. The ages of the patients with D-HCM and DCM at diagnosis were 61 and 59 years, respectively. At presentation, all patients with D-HCM

Table 1. Clinical Characteristics of Patients With D-HCM and DCM at Initial Evaluation

	Patients with D-HCM (n = 20)	Patients with DCM (n = 115)	P
Age at diagnosis, years	61 ± 12	59 ± 12	.702
Gender: male, n (%)	11 (55%)	89 (77%)	.035
NYHA functional class, n (%)			
I	0 (0%)	24 (21%)	.024
II	12 (60%)	66 (57%)	1.000
III and IV	8 (40%)	25 (22%)	.079
AF (chronic/paroxysmal), n (%)	10 (50%)	31 (27%)	.039
Medication, n (%)			
ACEI/ARB	16 (80%)	106 (92%)	.103
β-Blocker	7 (35%)	64 (56%)	.096
Diuretics	18 (90%)	99 (86%)	1.000
Spironolactone	8 (40%)	36 (31%)	.444
Digitalis	8 (40%)	78 (68%)	.017
Calcium antagonist	4 (20%)	9 (8%)	.088
Amiodarone	2 (10%)	0 (0%)	.021
Warfarin	13 (65%)	31 (27%)	.001
Echocardiographic findings			
LV end-diastolic diameter, mm	55 ± 7	63 ± 7	<.0001
LV end-systolic diameter, mm	43 ± 7	53 ± 8	<.0001
IVS thickness, mm	15 ± 3	10 ± 2	<.0001
PW thickness, mm	11 ± 2	10 ± 1	.004
Left atrial diameter, mm	50 ± 7	43 ± 7	.0004
LV ejection fraction, %	43 ± 6	32 ± 10	<.0001

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin II type1 receptor blocker; DCM, dilated cardiomyopathy; D-HCM, dilated phase of hypertrophic cardiomyopathy; IVS, interventricular septum; LV, left ventricular; NYHA functional class, New York Heart Association functional class; PW, posterior wall.
Data shown as mean ± SD or number (%).

Published online in Wiley InterScience. (www.interscience.wiley.com)
DOI:10.1002/clc.20533 © 2010 Wiley Periodicals, Inc.

reported dyspnea (New York Heart Association [NYHA] class ≥ II) and 8 (40%) of them showed severe symptoms (NYHA class III/IV). Half of the D-HCM patients had chronic or paroxysmal atrial fibrillation.

Results of echocardiography showed that LVEDD and LVESD were larger and EF was lower in patients with DCM than in patients with D-HCM. On the other hand, the left atrial diameter was larger in the D-HCM group.

Baseline medical treatment of the patients in the 2 groups is shown in Table 1. The use of ACEI and/or ARB, β-blockers, diuretics, and spironolactone was not statistically different between the 2 groups. The majority (over 80%) of patients in both groups were treated with ACEI and/or ARB and diuretics. Warfarin was more frequently used in patients with D-HCM than in patients with DCM. Two of the patients with D-HCM had been taking amiodarone because of ventricular tachycardia.

Clinical Course

The mean follow-up periods in the D-HCM and DCM groups were 4.0±3.1 and 7.3±4.2 years, respectively. In invasive treatment, 3 patients in each group underwent implantable cardioverter defibrillator (ICD) implantation (1 patient in each group experienced appropriate ICD discharge), and 3 patients with D-HCM and 2 patients with DCM underwent cardiac resynchronization therapy (CRT) for medically-refractory heart failure (Table 2). Furthermore, 1 patient with D-HCM underwent mitral valve replacement, 1 DCM patient received mitral valve annuloplasty, and 1 DCM patient underwent heart transplantation.

During the follow-up period, 11 (55%) of the patients with D-HCM died (sudden death in 2 patients, heart failure-related death in 6 patients, stroke in 2 patients, and noncardiovascular death in 1 patient) and 37 (32%) of the DCM patients died. The 5-year event-free survival from any cause of death and cardiac transplantation was 45.6% (95% confidence interval [CI]: 47.6–89.1) in patients with D-HCM vs 81.6% (95% CI: 126.7–155.4; log-rank $P = .0001$) in patients with DCM (Figure 1). The 5-year event-free survival from cardiovascular death including cardiac transplantation was 48.7% (95% CI: 50.8–92.8) in D-HCM patients vs 87.9% (95% CI: 146.3–173.4; log-rank $P \leq .0001$) in DCM patients (Figure 2).

Discussion

Hypertrophic cardiomyopathy is a heterogeneous myocardial disorder with a broad spectrum of clinical presentation and morphologic features.[1–3] Although LV systolic function is supernormal or preserved in most cases of HCM, progression to systolic impairment occurs in about 5% to 10% of patients when they are followed long enough.[4,5,9] It is usually associated with LV remodeling with wall thinning and cavity dilatation, resembling the morphologic features of DCM.[4–7] Although this subtype of HCM, so-called dilated phase of HCM, has been reported to have a poor prognosis, this is in contrast to the improved prognosis of DCM in the era of advancements in heart failure management.[8] To the best of our knowledge this is the first report on the clinical features of D-HCM in comparison with those of DCM treated in a single institute.

Table 2. Clinical Outcome of Patients With D-HCM and DCM

	Patients with D-HCM (n = 20)	Patients with DCM (n = 115)
Follow-up duration, years	4.0±3.1	7.3±4.2
All-cause death, n (%)	11(55%)	37 (32%)
Cardiovascular death, n (%)	10 (50%)	23 (20%)
Sudden cardiac death, n (%)	2 (10%)	10 (9%)
Heart failure-related death, n (%)	6 (30%)	12 (10%)
Stroke-related death, n (%)	2 (10%)	1 (1%)
Others, n (%)	1 (5%)	9 (8%)
Unknown, n (%)	0 (0%)	5 (4%)
VT (nonsustained/sustained), n (%)	14 (70%)	27 (23%)
Appropriate ICD discharge, n (%)	1 (5%)	1 (1%)
Procedures		
ICD, n (%)	3 (15%)	3 (3%)
CRT, n (%)	3 (15%)	2 (2%)
Surgical treatment, n (%)	1 (5%)	1 (1%)
Heart transplantation, n (%)	0 (0%)	1 (1%)

Abbreviations: CRT, cardiac resynchronization therapy; DCM, dilated cardiomyopathy; D-HCM, dilated phase of hypertrophic cardiomyopathy; ICD, implantable cardioverter defibrillator; VT, ventricular tachycardia.
Data shown as number (percent).

Clinical Manifestation at Presentation

In the present study, the ages of patients with D-HCM and DCM at diagnosis were about 60 years. Ejection fraction was significantly higher in the D-HCM group than in the DCM group. Furthermore, LV dimension was larger in the DCM group. At the diagnosis of LV systolic impairment, patients with D-HCM were more symptomatic than those with DCM. Left atrial size was significantly larger and the prevalence of atrial fibrillation (AF) was higher in the D-HCM group. Combined systolic and diastolic dysfunction in patients with D-HCM is probably related to these clinical manifestations.

Patients with D-HCM generally receive medical treatment including administration of standard therapeutic agents

Published online in Wiley InterScience. (www.interscience.wiley.com)
DOI:10.1002/clc.20533 © 2010 Wiley Periodicals, Inc.

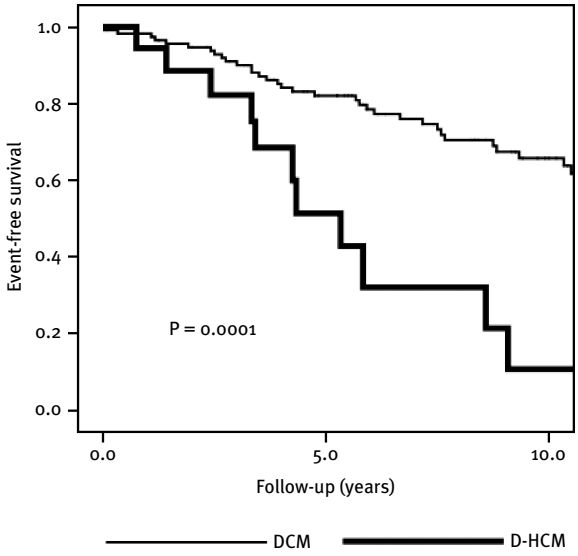

Figure 1. Kaplan-Meier curves for D-HCM vs DCM. Occurrence of all-cause mortality or cardiac transplantation during follow-up. Log-rank for trend $P = .0001$.

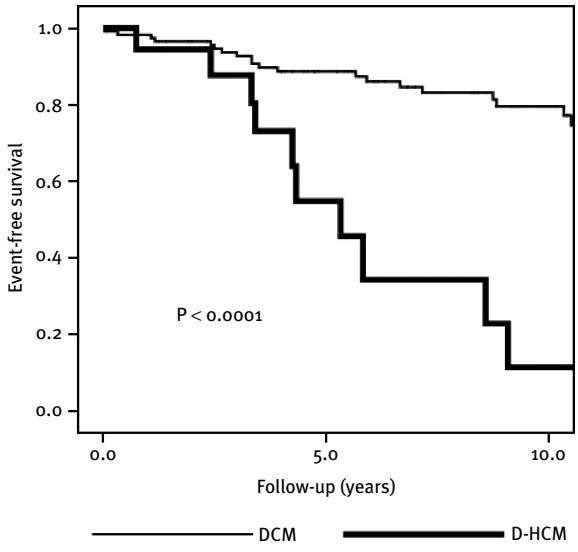

Figure 2. Kaplan-Meier curves for D-HCM vs DCM. Occurrence of cardiovascular death, including death from cardiac transplantation during follow-up. Log-rank for trend $P < .0001$.

for heart failure with systolic dysfunction, that is, mainly afterload-reduction agents such as ACEI or ARB, or diuretics, digitalis, β-blockers, or spironolactone. In the present study, ACEI and/or ARB and diuretics were basically used in both groups. On the other hand, the percentage of patients with D-HCM who received β-blockers was basically not high. One of the reasons for this is that it has not been established whether β-blocker therapy has a benefit similar to that for patients with DCM. In our experience, significant LV reverse remodeling such as reported in DCM patients is rare in patients with D-HCM. Warfarin was used more frequently in patients with D-HCM than in the DCM group because of the high prevalence of AF.

Clinical Course and Prognosis

During follow-up, invasive treatment, including ICD implantation and CRT, was needed more frequently in the D-HCM group. Although HCM is generally associated with mild disability and normal life expectancy, patients with D-HCM had an extremely poor prognosis with an overall survival rate of 46% at 5 years from diagnosis of the dilated phase. This prognosis was significantly worse than that of the patients with DCM despite similar or even more intensive treatment for heart failure.

In patients with D-HCM, the poor clinical course with refractory heart failure is thought to be related to the pathological findings. Walter et al compared explanted hearts from patients with D-HCM and patients with DCM at the time of cardiac transplantation and they reported that 9 of the 10 patients with D-HCM had ventricular wall scarring, whereas only 23% of the patients with DCM had grossly visible small scars.[10] Consequently, more increased LV stiffness seems to lead to more elevated left atrial and LV end-diastolic pressures in patients with D-HCM than in patients with DCM.

Clinical Implications

Considering the rapid clinical deterioration once end-stage is reached, early identification of HCM patients in transition to the dilated phase might enable specific therapies aimed at restraining cardiac fibrosis and delaying the progressive LV remodeling, although it remains to be clarified whether early intervention with specific agents for heart failure associated with systolic dysfunction is effective. Early intervention with ACEI and/or ARB therapy, which has been reported to have an antifibrous effect, might prevent progression of systolic dysfunction although attention should be paid to LV outflow tract obstruction.[11,12] Furthermore, CRT and ICD implantation should be considered for patients with D-HCM. Recently, Rogers et al reported that CRT therapy might be useful in a subset of D-HCM patients with wide QRS prolongation.[13] They showed that an improvement of at least 1 NYHA class was seen in 8 of 20 patients (40%) and symptomatic improvement was associated with reverse remodeling of the left atrium and ventricle. ICD implantation is effective for primary and secondary prevention of HCM.[14] This therapy is thought to be particularly beneficial for patients with D-HCM because sustained or nonsustained ventricular tachycardia is often seen in these patients and sudden death occurs frequently in the presence of severe heart failure. The least we can do is to recognize that though

Published online in Wiley InterScience. (www.interscience.wiley.com)
DOI:10.1002/clc.20533 © 2010 Wiley Periodicals, Inc.

slightly reduced global LV systolic function and tendency of LV dilatation appear subtle, it is indeed an important sign of evolution to D-HCM, since LV cavity size is small and LV systolic function is supernormal in most of patients with HCM.

Limitations

In the present study, we could not compare pathological findings such as degree of fibrosis in D-HCM and DCM. As indicated by Moon et al, gadolinium-enhanced cardiac magnetic resonance might be useful for evaluation of the location and degree of interstitial and replacement fibrosis.[15]

In this study, we could not compare the effects of therapies in the D-HCM patients because of the small number of patients. Further studies on the effects of treatment, particularly early intervention with medical treatment, ICD implantation, and CRT are needed.

Conclusions

Although D-HCM, which is characterized by LV systolic impairment associated with LV remodeling with wall thinning and cavity dilatation, resembles DCM in morphologic features, patients with D-HCM were more symptomatic and showed higher rates of atrial fibrillation already at the first documentation of systolic dysfunction in comparison with DCM patients. After the dilated phase was established, the prognosis for those patients was markedly worse than that for patients with DCM despite similar or even more intensive treatment for heart failure.

Acknowledgment

The study was supported by a grant from St Luke's Life Science Institute.

References

1. Maron BJ. Hypertrophic cardiomyopathy. A systematic review. *JAMA*. 2002;287:1308–1320.
2. Maron BJ, Olivotto I, Spirito P, et al. Epidemiology of hypertrophic cardiomyopathy-related death: revisited in a large non-referral-based patient population. *Circulation*. 2000;102:858–864.
3. Spirito P, Chiarella F, Carratino L, Berisso MZ, Bellotti P, Vecchio C. Clinical course and prognosis of hypertrophic cardiomyopathy in an outpatient population. *N Engl J Med*. 1989;320:749–755.
4. Biagini E, Coccolo F, Ferlito M, et al. Dilated-hypokinesis evolution of hypertrophic cardiomyopathy. Prevalence, incidence, risk factors, and prognostic implications in pediatrics and adult patients. *J Am Coll Cardiol*. 2005;46:1543–1550.
5. Thaman R, Gimeno JR, Mutphy RT, et al. Prevalence and clinical significance of systolic impairment in hypertrophic cardiomyopathy. *Heart*. 2005;91:920–925.
6. Harris KM, Spirito P, Maron MS, et al. Prevalence, clinical profile, and significance of left ventricular remodeling in the end-stage phase of hypertrophic cardiomyopathy. *Circulation*. 2006;114:216–225.
7. Kubo T, Kitaoka H, Okawa M, et al. Lifelong left ventricular remodeling of hypertrophic cardiomyopathy caused by a founder frameshift deletion mutation in the cardiac Myosin-binding protein C gene among Japanese. *J Am Coll Cardiol*. 2005;46:1737–1743.
8. Matsumura Y, Takata J, Kitaoka H, et al. Long-term prognosis of dilated cardiomyopathy revisited: an improvement in survival over the past 20 years. *Circ J*. 2006;70:376–383.
9. Kitaoka H, Kubo T, Okawa M, Hitomi N, Furuno T, Doi YL. Left ventricular remodeling of hypertrophic cardiomyopathy: longitudinal observation in a rural community. *Circ J*. 2006;70:1543–1549.
10. Walter TA, Hister WL, Capehart JE, Roberts WC. Comparison of clinical and morphologic cardiac findings in patients having cardiac transplantation for ischemic cardiomyopathy, idiopathic dilated cardiomyopathy, and dilated hypertrophic cardiomyopathy. *Am J Cardiol*. 1998;81:884–894.
11. Lim D, Lutucuta S, Bachireddy P, et al. Angiotensin II blockade reverses myocardial fibrosis in a transgenic mouse model of human hypertrophic cardiomyopathy. *Circulation*. 2001;103:789–791.
12. Kim S, Yoshiyama M, Izumi Y, et al. Effects of combination of ACE inhibitor and angiotensin receptor blocker on cardiac remodeling, cardiac function, survival in rat heart failure. *Circulation*. 2001;103:148–154.
13. Rogers DPS, Marazia S, Chow AW, et al. Effect of biventricular pacing on symptoms and cardiac remodeling in patients with end-stage hypertrophic cardiomyopathy. *Eur J Heart Fail*. 2008;10:507–513.
14. Maron BJ, Shen W, Link MS, et al. Efficacy of implantable cardioverter-defibrillators for the prevention of sudden death in patients with hypertrophic cardiomyopathy. *N Engl J Med*. 2000;342:365–373.
15. Moon JC, Reed E, Sheppard MN, et al. The histological basis of late gadolinium enhancement cardiovascular magnetic resonance in hypertrophic cardiomyopathy. *J Am Coll Cardiol*. 2004;43:2260–2264.

Published online in Wiley InterScience. (www.interscience.wiley.com)
DOI:10.1002/clc.20533 © 2010 Wiley Periodicals, Inc.