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ORIGINAL ARTICLE

Very long-term follow-up data of non-ischemic idiopathic dilated cardiomyopathy after beta-blocker therapy: recurrence of left ventricular dysfunction and predictive value of ^{123}I-metaiodobenzylguanidine scintigraphy

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Abstract
The management of idiopathic dilated cardiomyopathy (DCM) is well established. However, a subset of patients do not have recovery from or have recurrences of left ventricular (LV) dysfunction despite receiving optimal medical therapy. There are limited long-term follow-up data about LV function and the predictive value of iodine-123-metaiodobenzylguanidine (^{123}I-MIBG) scintigraphy, especially among the Japanese population. We retrospectively investigated 81 consecutive patients with DCM (mean LV ejection fraction (EF) 28 ± 7.5%) who had undergone ^{123}I-MIBG scintigraphy before starting β-blockers. According to chronological changes in LVEF, study patients were classified into three subgroups: sustained recovery group, recurrence group, and non-recovery group. The outcome measure was cardiac death. Mean age was 59 ± 11 years and median follow-up was 11.5 (5.8–15.0) years. Thirty-six patients had recovery, 11 had recurrences, and 34 did not have recovery. The sustained recovery group had the best cardiac death-free survival, followed by the recurrence and non-recovery groups. Prolonged time to initial recovery was associated with recurrence of LV dysfunction. Large LV end-diastolic diameter and reduced heart to mediastinum ratio were associated with poor prognosis. In conclusion, with β-blocker therapy, 14% of patients showed recurrences of LV dysfunction. Thus, careful follow-up is needed, keeping in mind the possibility of recurrence, even if LVEF once improved, especially in patients whose time to initial recovery was long. ^{123}I-MIBG scintigraphy provides clinicians with additional prognostic information.

Keywords ^{123}I-MIBG scintigraphy · Dilated cardiomyopathy · β-Blocker · Prognosis

Introduction

Non-ischemic dilated cardiomyopathy (DCM), a relatively common disorder, is characterized by left ventricular (LV) dilation and impaired systolic function leading to heart failure [1, 2]. Its management is well established, β-blockers being considered the first-line drug [3, 4]. The sympathetic nervous system is activated in patients with DCM and β-blockers are thought to reduce the detrimental effects of catecholamine stimulation [5, 6]. However, despite optimal medical therapy, a subset of patients do not show improvement or have recurrence of LV dysfunction [7–9].

Iodine-123-metaiodobenzylguanidine (^{123}I-MIBG), an analogue of the adrenergic neuron blocking agent guanethidine, is thought to use the same myocardial uptake and release mechanism as norepinephrine [10]. ^{123}I-MIBG scintigraphic findings reflect the status of myocardial sympathetic innervation and may be related to severity of myocardial damage [11]. Previous studies have reported that such findings can predict the prognosis of patients with DCM [12, 13]. However, the duration of follow-up in these previous studies was relatively short and long-term follow-up data are limited, especially among Japanese population. The

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purpose of this study was to investigate long-term chronological changes in LV function after β-blocker therapy and long-term prognosis in patients with DCM and to clarify the predictive value of ^{123}I-MIBG scintigraphic findings.

Patients and methods

Study population

Relevant data of 81 consecutive patients (mean age 59 ± 11 years) with DCM who had undergone ^{123}I-MIBG scintigraphy before starting β-blockers (carvedilol or bisoprolol fumarate) from 1993 to 2005 in Tenri Hospital were retrospectively investigated. DCM was defined by the following criteria: (1) LV dysfunction with left ventricular ejection fraction (LVEF) < 40% according to transthoracic echocardiography (TTE) and (2) no significant coronary artery disease according to coronary angiography or coronary multidetector computed tomography. Patients whose LV dysfunction was caused by acute myocarditis, stress-induced cardiomyopathy, cardiac amyloidosis, sarcoidosis, valvular heart disease, or sepsis were also excluded. To distinguish the patients with DCM from those with tachycardia-induced cardiomyopathy, we also excluded patients with atrial fibrillation which may become the cause of tachyarrhythmia. The study protocol was approved by the institutional ethics committee of Tenri Hospital (Nara, Japan).

TTE variables and classification of study patients

During the acute phase of heart failure, patients were treated with standard therapy such as diuretics. After control of heart failure had been achieved and before starting β-blocker therapy, baseline TTE was performed. Follow-up TTE was routinely performed 6 months, and 1, 2 and 3 years after initiating β-blocker therapy. TTE variables included left atrial dimensions, left ventricular end-diastolic diameter (LVDd), left ventricular end-systolic diameter and thickness of left interventricular septum and posterior wall measured by M-mode echocardiography. LVEF was measured using a modified Simpson's method. These comprehensive echocardiographic assessments were conducted by experienced sonographers using commercially available ultrasound systems. TTE performed during long-term follow-up [10.4 (IQR 6.3–13.6) years after initiating β-blocker therapy] was also evaluated.

Study patients were classified according to chronological changes in LVEF as in a previous study [8]. First, study patients were divided into initial recovery and non-recovery groups by comparing LVEF before and early after (from 6 months to 3 years) initiating β-blocker therapy. Initial recovery was defined as recovery of LVEF to > 40% with a net increase in LVEF of ≥ 10% from baseline. Non-recovery was defined as not meeting the above criteria. Patients who died within 3 years without recovery of LVEF were classified into the non-recovery group. The time to achieve initial recovery was also evaluated in the initial recovery group, time to initial recovery being defined as time from baseline TTE to first TTE showing initial recovery.

Next, patients with initial recovery were divided into two subgroups: namely, sustained recovery and recurrence groups, by comparing LVEF early and long-term after initiating β-blocker therapy. Recurrence was defined as showing a decrease in LVEF ≥ 10% at long-term follow-up TTE compared with early after initiating β-blocker therapy, whereas sustained recovery was defined as showing sustained improvement in LVEF from early after initiating β-blocker therapy to long-term follow-up TTE.

^{123}I-MIBG scintigraphy

^{123}I-MIBG scintigraphy was performed at rest in the fasting state after stabilization of heart failure and before starting β-blockers. A large-field gamma camera (Toshiba GCA9300A/HG; Toshiba, Tokyo, Japan) was used to acquire anterior planar images of the chest 15 min and 4 h after intravenous injection of 111 MBq of ^{123}I-MIBG. The heart to mediastinum ratio (HMR) was determined by measuring the average counts in each region of interest after a nuclear cardiologist, who was blinded to the patient's data, had manually outlined regions of interest in the heart, upper mediastinum and right lung. The ^{123}I-MIBG washout rate (WR) from the heart was calculated as the difference between early and delayed images.

Clinical outcomes and their predictors

Clinical follow-up data were obtained from the patients' medical records. The outcome measure was cardiac death, which was defined as sudden death or death from congestive heart failure (CHF). To identify predictors of clinical outcomes, the patients' clinical characteristics, laboratory and cardiac catheterization data and TTE and ^{123}I-MIBG scintigraphic findings at diagnosis were investigated. Clinical characteristics and cardiac catheterization data were collected from the medical records. Clinical characteristics included age, sex, underlying disorders, and medications. Underlying disorders included hypertension, dyslipidaemia and diabetes mellitus. Hypertension was defined as systolic blood pressure of ≥ 140 mmHg and/or a diastolic pressure of ≥ 90 mmHg or use of antihypertensive medications. Dyslipidaemia was defined as serum cholesterol concentration ≥ 220 mg/dL or use of cholesterol-lowering medications. Diabetes mellitus was defined as hyperglycaemia requiring medication. Medications included angiotensin-converting

enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), aldosterone antagonists, diuretics and amiodarone. Laboratory data included estimated glomerular filtration rate, and serum concentrations of haemoglobin, creatinine, sodium and brain natriuretic peptide (BNP), the last being available only for 65 patients (80%). All study patients had undergone cardiac catheterization at diagnosis. Cardiac catheterization data included resting heart rate, systolic and diastolic arterial pressure, mean pulmonary arterial pressure, mean pulmonary capillary wedge pressure and cardiac output. TTE and ^{123}I-MIBG scintigraphic findings are shown above.

Furthermore, to determine predictors of recurrence of LV dysfunction for patients in the initial recovery group, clinical characteristics, laboratory data, TTE findings at both baseline and initial recovery and ^{123}I-MIBG scintigraphic findings were evaluated.

Statistical analysis

Statistical analysis was performed using JMP version 8. Categorical variables are presented as numbers and percentages, and were compared using Fisher's exact test. Continuous variables are presented as mean (standard deviation) or median [interquartile range (IQR)]. Continuous variables were compared using unpaired *t* test or the Wilcoxon rank-sum test between two groups. Event-free survival rates from cardiac death are presented in Kaplan–Meier curves and were compared by a log-rank test. Relative risks and 95% confidence intervals were calculated using Cox proportional-hazards analysis. A p value of < 0.05 was considered to denote statistical significance.

Results

Baseline patient characteristics and initial recovery

The study cohort comprised 59 men and 22 women with a mean age of 59 ± 11 years. LVDd and LVEF at diagnosis were 66 ± 7.4 mm and 28 ± 7.5%, respectively. Median duration of follow-up was 11.5 (IQR 5.8–15.0) years. The baseline characteristics of all 81 patients are shown in Tables 1 and 2. Early after initiating β-blocker therapy, 47 patients (58%) showed initial recovery (initial recovery group), and 34 patients (42%) did not (non-recovery group). LVDd and LVEF at early follow-up TTE were 56 ± 5.6 mm and 54 ± 9.0% in the initial recovery group, and 66 ± 9.9 mm

Table 1 Clinical characteristics of all patients (comparison between non-recovery and initial recovery)

Characteristics	All patients ($n=81$)	Non-recovery ($n=34$)	Initial recovery ($n=47$)	p value
Age (years)	59 ± 11	61 ± 9.0	57 ± 12	0.09
Male sex	59 (73)	25 (74)	34 (72)	1.0
Comorbidities				
Hypertension	19 (23)	8 (24)	11 (23)	1.0
Dyslipidaemia	16 (20)	7 (21)	9 (19)	1.0
Diabetes	16 (20)	8 (24)	8 (17)	0.57
CLBBB	10 (12)	4 (12)	6 (13)	1.0
Implantable cardioverter-defibrillator	7 (8.6)	6 (18)	1 (2.1)	0.038
Medication				
β-Blocker	81 (100)	34 (100)	47 (100)	1.0
ACEIs or ARBs	49 (60)	21 (62)	28 (60)	1.0
Aldosterone antagonist	33 (41)	15 (44)	18 (38)	0.65
Diuretics	57 (70)	23 (68)	34 (72)	0.81
Amiodarone	9 (11)	7 (21)	2 (4.3)	0.031
Laboratory data				
Haemoglobin (g/dL)	14 ± 2.1	14 ± 2.3	14 ± 2.0	0.49
Creatinine (mg/dL)	1.1 ± 0.4	1.0 ± 0.4	1.1 ± 0.4	0.45
eGFR (mL/min/1.73 m^2)	58 ± 15	60 ± 16	56 ± 15	0.30
≤ 60	42 (52)	15 (44)	27 (57)	0.27
Na (mEq/L)	141 ± 3.3	141 ± 3.5	141 ± 3.3	0.52
BNP (pg/mL)	333 ± 329 ($n=65$)	290 ± 218 ($n=24$)	358 ± 380 ($n=41$)	0.42

Data are presented as *n* (%) or mean ± standard deviation

CLBBB complete left bundle branch block, *ACEIs* angiotensin-converting enzyme inhibitors, *ARBs* angiotensin receptor blockers, *eGFR* estimated glomerular filtration rate, *BNP* brain natriuretic peptide

Table 2 Echocardiographic, cardiac catheter and scintigraphic parameters of all patients (comparison between non-recovery and initial recovery)

Characteristics	All patients ($n=81$)	Non-recovery ($n=34$)	Initial recovery ($n=47$)	p value
Echocardiographic variables				
Baseline				
LVDd (mm)	66 ± 7.4	68 ± 8.0	65 ± 6.9	0.15
LVDs (mm)	57 ± 8.2	58 ± 9.0	56 ± 7.6	0.31
LVEF (%)	28 ± 7.5	29 ± 8.1	26 ± 6.8	0.07
IVS (mm)	8.5 ± 1.4	8.3 ± 1.3	8.7 ± 1.5	0.13
LVPW (mm)	8.8 ± 1.5	8.3 ± 1.6	9.1 ± 1.4	0.03
LAD (mm)	42 ± 7.5	41 ± 7.5	43 ± 7.5	0.51
At early follow-up				
LVDd (mm)	60 ± 8.8	66 ± 9.9	56 ± 5.6	< 0.001
LVEF (%)	44 ± 15	30 ± 9.1	54 ± 9.0	< 0.001
Cardiac catheter data				
Systolic BP (mmHg)	122 ± 24	122 ± 22	122 ± 26	0.96
Diastolic BP (mmHg)	75 ± 13	75 ± 14	75 ± 13	0.88
Mean PAP (mmHg)	22 ± 9.8	23 ± 11	21 ± 9.4	0.55
Mean PCWP (mmHg)	13 ± 8.5	13 ± 7.8	14 ± 9.0	0.67
Cardiac output (L/min)	4.0 ± 1.1	4.2 ± 1.3	3.8 ± 1.0	0.17
Heart rate (bpm)	82 ± 14	81 ± 13	83 ± 16	0.59
Scintigraphic findings				
HMR at 15 min	1.80 ± 0.25	1.77 ± 0.24	1.82 ± 0.25	0.37
At 4 h	1.62 ± 0.23	1.61 ± 0.26	1.63 ± 0.21	0.75
Washout rate	43 ± 13	45 ± 12	42 ± 13	0.33

Data are presented as n (%) or mean ± standard deviation

LVDd left ventricular end-diastolic dimension, *LVDs* left ventricular end-systolic dimension, *LVEF* left ventricular ejection fraction, *IVS* interventricular septum, *LVPW* left ventricular posterior wall, *LAD* left atrial dimension, *BP* blood pressure, *PAP* pulmonary arterial pressure, *PCWP* pulmonary capillary wedge pressure, *HMR* heart to mediastinum ratio

and 30 ± 9.1% in the non-recovery group. The non-recovery group tended to be older and had a larger LVDd at diagnosis than the initial recovery group, but these were not statistically significant. The non-recovery group more often received amiodarone and implantable cardioverter-defibrillator than the initial recovery group. All patients had received β-blocker. ACEIs or ARBs had been administered to 60% of the initial recovery and 62% of the non-recovery group. There were no significant differences in treatment strategy at diagnosis between the initial recovery and non-recovery groups.

Chronological changes in LVEF during long-term follow-up

Long-term follow-up TTE was performed 10.4 (IQR 6.3–13.6) years after initiating β-blocker therapy. Four of the 34 patients in the non-recovery group showed cardiac death within 3 years of diagnosis without recovery of LVEF. The remaining 30 patients in the non-recovery group did not have recovery of LVEF at long-term follow-up (LVEF 29 ± 8.7%). No patient experienced recovery of LVEF more than 3 years after initiating β-blocker therapy. Sustained recovery of LVEF occurred in 36 of 47 patients (77%) in the initial recovery group (sustained recovery group). However, LV dysfunction recurred in 11 of 47 patients (23%) in the initial recovery group (recurrence group). In the sustained recovery group, LVEF was 27 ± 6.8% at diagnosis, 53 ± 9.0% at early and 57 ± 8.8% at long-term after initiating β-blocker therapy. In the recurrence group, LVEF was 25 ± 8.0% at diagnosis, 57 ± 8.9% at early and 33 ± 9.7% at long-term after initiating β-blocker therapy. Recurrence of LV dysfunction developed 6.0 (IQR 4.1–6.6) years after initiating β-blocker therapy in the recurrence group. Chronological changes in LVEF are shown in Fig. 1.

At the last follow-up, β-blockers and ACEIs or ARBs were being administered to 94% and 61% of the sustained recovery group, 100% and 55% of the recurrence group, and 100% and 62% of the non-recovery group, respectively. There were no significant differences between groups in treatment strategy at the last follow-up.

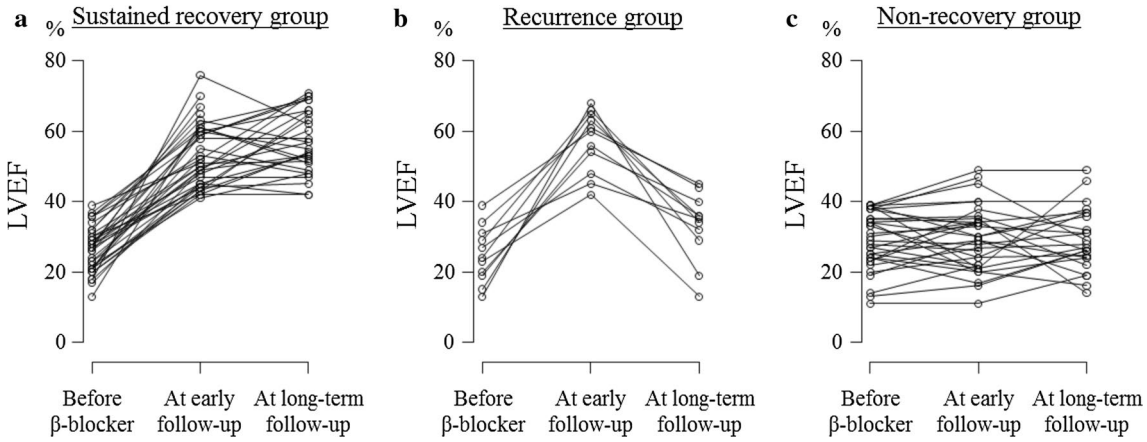


Fig. 1 Chronological changes in LVEF before, at early after and long-term after β-blocker therapy; (**a**) sustained recovery group, (**b**) recurrence group, (**c**) non-recovery group. *LVEF* left ventricular ejection fraction

Predictors of recurrence of LV dysfunction

Clinical characteristics, laboratory data and scintigraphic and TTE variables both before initiating β-blockers and at initial recovery were compared between the sustained recovery and recurrence groups to determine predictors of recurrence of LV dysfunction. The time to initial recovery was longer, mean pulmonary arterial pressure and mean papillary wedge pressure at diagnosis were higher in the recurrence than the sustained recovery group. There were no significant differences in ^{123}I-MIBG scintigraphic findings at diagnosis or other TTE findings at both baseline and initial recovery (Tables 3, 4).

Table 3 Comparison of clinical characteristics between recurrence and sustained recovery

Characteristics	Initial recovery ($n=47$)		p value
	Recurrence ($n=11$)	Sustained recovery ($n=36$)	
Age (years)	61 ± 11	56 ± 12	0.26
Male sex	8 (73)	30 (83)	0.42
Comorbidities			
Hypertension	3 (27)	8 (22)	0.70
Dyslipidaemia	3 (27)	6 (17)	0.42
Diabetes	2 (18)	6 (17)	1.0
CLBBB	3 (27)	3 (8.3)	0.13
Time to initial recovery (days)	582 ± 340	370 ± 60	0.039
Implantable cardioverter-defibrillator	1 (9.1)	0 (0)	0.23
Medication			
β-Blocker	11 (100)	51 (100)	1.0
ACEIs or ARBs	6 (55)	22 (61)	0.74
Aldosterone antagonist	3 (27)	15 (42)	0.49
Diuretics	8 (73)	26 (72)	1.0
Amiodarone	0 (0)	2 (5.6)	1.0
Laboratory data			
Haemoglobin (g/dL)	15 ± 1.3	14 ± 2.2	0.37
Creatinine (mg/dL)	1.0 ± 0.2	1.1 ± 0.5	0.30
eGFR (mL/min/1.73 m^2)	59 ± 14	55 ± 15	0.44
≤ 60	7 (64)	20 (56)	0.74
Na (mEq/L)	140 ± 2.1	141 ± 3.5	0.91
BNP (pg/mL)	499 ± 496 ($n=10$)	313 ± 331 ($n=31$)	0.18

Data are presented as n (%) or mean ± standard deviation. Abbreviations are same as in Table 1

Table 4 Comparison of echocardiographic, cardiac catheter and scintigraphic parameters between recurrence and sustained recovery

Characteristics	Initial recovery ($n=47$)		p value
	Recurrence ($n=11$)	Sustained recovery ($n=36$)	
Echocardiographic variables			
Baseline			
LVDd (mm)	64 ± 6.4	66 ± 7.1	0.41
LVDs (mm)	54 ± 9.4	57 ± 7.0	0.33
LVEF (%)	25 ± 8.0	27 ± 6.8	0.35
IVS (mm)	8.8 ± 1.4	8.7 ± 1.5	0.85
LVPW (mm)	9.7 ± 0.7	8.9 ± 1.5	0.09
LAD (mm)	41 ± 5.9	43 ± 7.9	0.50
At early follow-up			
LVDd (mm)	55 ± 6.3	57 ± 5.4	0.44
LVDs (mm)	39 ± 6.2	41 ± 6.3	0.35
LVEF (%)	57 ± 8.9	53 ± 9.0	0.18
IVS (mm)	9.5 ± 2.1	9.1 ± 1.0	0.55
LVPW (mm)	9.5 ± 1.9	9.4 ± 1.1	0.75
LAD (mm)	39 ± 4.7	38 ± 6.1	0.68
At long-term follow-up			
LVDd (mm)	60 ± 9.3	52 ± 6.3	< 0.001
LVEF (%)	33 ± 9.7	57 ± 8.8	< 0.001
Cardiac catheter data			
Systolic BP (mmHg)	127 ± 23	120 ± 26	0.44
Diastolic BP (mmHg)	76 ± 16	75 ± 12	0.83
Mean PAP (mmHg)	26 ± 10	20 ± 8.7	0.046
Mean PCWP (mmHg)	19 ± 9.7	12 ± 8.3	0.031
Cardiac output (L/min)	3.6 ± 0.7	3.9 ± 1.0	0.31
Heart rate (bpm)	78 ± 15	85 ± 16	0.22
Scintigraphic findings			
HMR at 15 min	1.83 ± 0.22	1.81 ± 0.27	0.85
At 4 h	1.65 ± 0.24	1.62 ± 0.25	0.68
Washout rate	38 ± 12	44 ± 7.9	0.23

Data are presented as n (%) or mean ± standard deviation. Abbreviations are same as in Table 2

Cardiac events and their predictors

Cardiac death-free rates for all the study patients were 85% at 10 years and 73% at 15 years (Fig. 2a). The cardiac death-free rate was significantly better in the sustained recovery group than in the other two groups (cardiac death-free rate at 15 years: 100% vs. 86% vs. 39%, respectively; $p<0.01$) (Fig. 2b). There were no cardiac deaths in the sustained recovery group, whereas there were 14 deaths (sudden death, 10; death due to CHF, 4) in the non-recovery group and 2 deaths (sudden death, 1; death due to CHF, 1) in the recurrence group. Univariate Cox proportional-hazard analysis identified LVDd and HMR as predictors of cardiac death (Table 5). Focusing on sudden death, HMR tended to be lower in 11 patients with sudden death than those without sudden death (HMR at 15 min, 1.68 vs. 1.82, $p=0.08$; HMR at 4 h, 1.53 vs. 1.64, $p=0.15$). Cardiac death-free rates tended to be higher in patients with a HMR at 4 h of ≥ 1.63 ($n=41$) than in those with a HMR at 4 h of < 1.63 ($n=40$) (91% vs. 80% at 10 years, 82% vs. 66% at 15 years; $p=0.17$) (Fig. 3). This cut-off value of HMR at 4 h was determined by the median value.

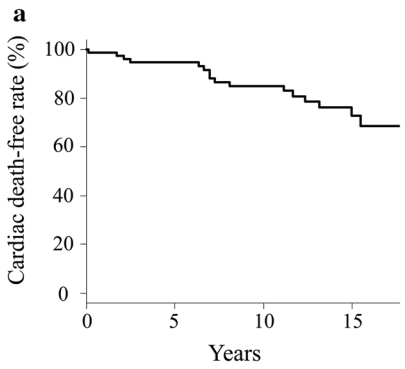
Discussion

In the present study, we examined chronological changes in LV function and responsiveness to β-blocker therapy in patients with DCM and clarified the very long-term clinical outcomes, prognostic factors and predictive value of ^{123}I-MIBG scintigraphy findings.

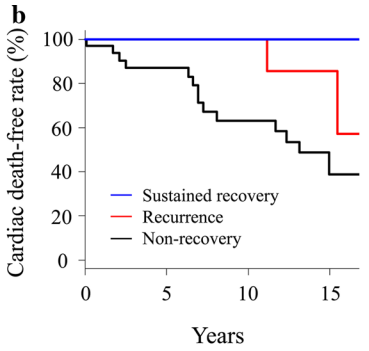
Chronological changes in LV function and prognosis of subgroups

In the present study, 36 patients (44%) had sustained recovery of LVEF, 11 (14%) had recurrence of LV dysfunction, and 34 (42%) had no recovery of LVEF. Previous studies have reported that LVEF recovered in 30–50% of patients with DCM [8, 9, 14, 15] and that there is a 15–39% incidence of recurrence of LV dysfunction after initial recovery [7, 8]. Regarding the timing of recurrence, Gupta et al. [8] reported that 32% of patients had recurrences by 5 years after diagnosis and that 68% had recurrences thereafter. Although the duration of follow-up in our study was much longer than in these previous studies (11.5 years vs. 4.2 years), the incidences of recovery and recurrence, and timing of recurrence in our study are consistent with those of previous studies. Additionally, we documented chronological changes in LV function during very long-term follow-up, and no patients who failed to show recovery of LV function within 3 years after initiating β-blocker therapy experienced improvement in LVEF thereafter. These findings suggest that further treatment, such as cardiac resynchronization therapy or cardiac transplantation, should be considered for patients with no evidence of recovery of LVEF by 3 years after initiating β-blocker therapy.

Regarding prognosis, the event-free rate was significantly greater in the sustained recovery group than in the non-recovery and recurrence groups. Previous studies have also shown that patients who recover LV function have better prognoses; however, there are few data on prognosis of patients with recurrence of LV dysfunction [7–9, 14]. In this study, the prognosis of patients with recurrence of



Interval	0	5 year	10 year	15 year
All patients				
N of patients at risk	81	64	48	21
Event-free rate		94.8	84.9	72.7



Interval	0	5 year	10 year	15 year
Sustained recovery				
N of patients at risk	36	29	25	13
Event-free rate		100	100	100
Recurrence				
N of patients at risk	11	11	7	4
Event-free rate		100	100	85.7
Non-recovery				
N of patients at risk	34	24	16	4
Event-free rate		87.0	63.3	38.9

Fig. 2 Cardiac death-free rate of entire study cohort (**a**) and subgroups (**b**)

LV dysfunction is similar to that of those with sustained recovery up to 10 years; however, once LV dysfunction has recurred, the prognosis became poorer than that of patients with sustained recovery.

Predictors of recurrence

As to predictors of recurrence, time to initial recovery was longer in the recurrence than the sustained recovery group. Both patients with recurrence and sustained recovery showed similar LVEF at initial recovery, but some later developed recurrences whereas others showed sustained recovery. These findings suggest that recovery of LVEF early after initiating β-blocker therapy cannot be regarded as complete recovery. It is possible that ultrastructural damage to the myocardium may persist after initial recovery and be related to recurrence; however, we did not confirm this possibility by endomyocardial biopsy in all patients [16]. The prolonged time to initial recovery in the recurrence group may reflect persistence of ultrastructural damage to the myocardium. Therefore, careful follow-up is needed, keeping in mind the possibility of recurrence, even if LVEF once improved, especially in patients whose time to initial recovery was longer.

Predictive value of ^{123}I-MIBG scintigraphy

Reduced HMR is a predictor of prognosis, and ^{123}I-MIBG scintigraphic findings can predict cardiac death. In the current study, the main cause of cardiac deaths was not CHF (5 patients, 31%), but sudden death (11 patients, 69%), and HMR tended to be lower in patients with sudden death. ^{123}I-MIBG scintigraphic findings may be able to predict sudden death in patients with DCM, as has been shown for those with chronic heart failure [17]. Increased sympathetic activity can modulate arrhythmogenic mechanism of reentry, automaticity, and triggered activity, provoking lethal arrhythmias [18]. However, ^{123}I-MIBG scintigraphic findings did not predict improvement in cardiac function. The explanation for this discrepancy is unknown; however, several studies have reported similar results to ours. Lee et al. have reported that MIBG imaging does not predict increase in LVEF after β-blocker therapy in patients with DCM [19]. Yamazaki et al. have also reported no significant differences in ^{123}I-MIBG scintigraphic findings, including WR and reduced HMR, between responders and non-responders to β-blockers [20].

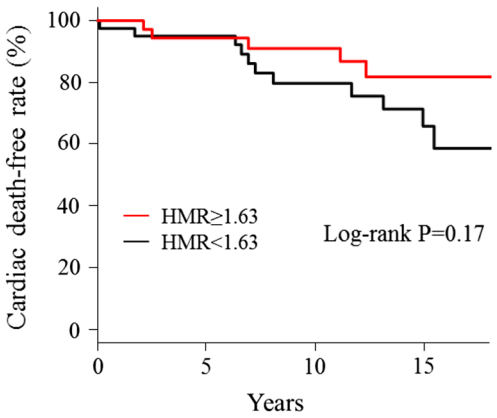
Limitations

The present study has several limitations, mainly because of its retrospective nature. First, not all patients were followed-up systematically during long-term follow-up, and selection bias was inevitable. Second, biomarkers such as BNP were not available for all patients because this study included old data and BNP was unavailable before 1994. Third, a relatively small percentage of patients had received ACEIs or ARBs compared with previous studies. This discrepancy may be attributable to adverse reactions to ACEIs and ARBs, such as cough, hypotension and renal dysfunction. East Asian ethnicity is known to be a risk

Table 5 Univariate analysis for predictors of cardiac death

Characteristics	Univariate predictors	
	HR (95% CI)	*p* value
Clinical factors		
Age (per year)	1.03 (0.98–1.09)	0.20
Female	0.53 (0.15–1.86)	0.32
Hypertension	0.67 (0.19–2.36)	0.53
Dyslipidaemia	2.25 (0.78–6.50)	0.13
Diabetes	1.51 (0.49–4.74)	0.47
CLBBB	1.27 (0.29–5.60)	0.75
Implantable cardioverter-defibrillator	2.38 (0.68–8.35)	0.18
Echocardiographic parameters at baseline		
LVDd (per mm)	1.07 (1.01–1.14)	0.032
LVDs (per mm)	1.07 (1.00–1.13)	0.037
LVEF (%)	0.97 (0.91–1.04)	0.38
IVS (per mm)	0.99 (0.70–1.41)	0.97
LVPW (per mm)	0.79 (0.56–1.11)	0.18
LAD (per mm)	1.02 (0.96–1.09)	0.47
Cardiac catheter parameters		
Systolic BP (per mmHg)	0.99 (0.97–1.01)	0.42
Diastolic BP	0.98 (0.94–1.03)	0.40
Mean PAP	1.04 (0.99–1.09)	0.12
Mean PCWP	1.04 (0.98–1.10)	0.17
Cardiac output	0.91 (0.54–1.56)	0.74
Heart rate	0.98 (0.94–1.01)	0.17
^{123}I-MIBG scintigraphic parameters		
HMR at 4 h (per −1)	17.3 (1.47–204)	0.023
Washout rate	1.03 (1.00–1.07)	0.074
Medications		
ACEIs or ARBs	0.93 (0.34–2.57)	0.89
Aldosterone antagonist	1.82 (0.68–4.90)	0.24
Diuretics	7.11 (0.94–53.9)	0.058
Amiodarone	1.36 (0.39–4.78)	0.63
Laboratory data		
Haemoglobin (per +1 g/dL)	0.94 (0.75–1.18)	0.60
Creatinine (+1 g/dL)	0.99 (0.33–3.00)	0.98
eGFR ≤ 60 mL/min/1.73 m^2	1.00 (0.37–2.69)	1.0
Na (+1 mEq/L)	0.89 (0.71–1.11)	0.30

HR hazard ratio, *CI* confidence interval, *^{123}I-MIBG* iodine-123-meta-iodobenzylguanidine. Other abbreviations are same as in Tables 1 and 2



Interval	0	5 year	10 year	15 year
HMR≥1.63				
N of patients at risk	41	29	24	9
Event-free rate		94.4	90.9	81.8
HMR<1.63				
N of patients at risk	40	35	24	12
Event-free rate		94.9	79.7	65.8

Fig. 3 Comparison of cardiac death-free rate between patients with a delayed HMR of < 1.63 and ≥ 1.63. *HMR* heart to mediastinum ratio

factor for ACEI-induced cough, whereas African–American ethnicity is not [21]. Furthermore, the indication of chronic heart failure for ARBs was first approved in Japan in 2005. Patients enrolled in the present study were treated between 1993 and 2005, at least in part explaining the low rate of administration of ACEIs or ARBs. The same tendency was observed in another study evaluating the clinical characteristics and outcomes of hospitalized patients with CHF that was conducted in Japan between 2001 and 2002, in which 62.5% of participants received ACEIs or ARBs [22]. Although the percentages of patients receiving ACEIs or ARBs were similar in the three subgroups in this study, they may have affected our results. Fourth, the limited number of patients and cardiac events did not allow us to perform multivariable analysis. Finally, we excluded patients with atrial fibrillation but there remains a possibility that our study cannot completely exclude patients with tachycardia-induced cardiomyopathy.

Conclusions

With β-blocker therapy, 42% of patients did not improve and 14% had recurrence of LV dysfunction; both groups of patients had poor prognoses. Careful follow-up is needed, even after restoration of LV dysfunction. Furthermore, ^{123}I-MIBG scintigraphy can provide clinicians with additional information regarding prognosis.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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