

Profile of nonischemic dilated cardiomyopathy patients with long-term survival ≥ 10 years on medical therapy alone

Inderjeet S. Monga, Parminder Singh, Ajay Bahl

Department of Cardiology, Postgraduate Institute of Medical Education and Research, Chandigarh, India

ABSTRACT

Background: Most studies have focussed on short and medium-term survival in dilated cardiomyopathy (DCM) patients. We aimed to study the profile and changes in left ventricular ejection fraction (LVEF) of nonischemic DCM patients who survived more than 10 years on medical management alone. **Methods:** This was a retrospective analysis of patients in the nonischemic DCM cohort recruited from April 2003 to January 2007 with LVEF $\leq 40\%$. All patients who survived at least 10 years from the initial DCM diagnosis and were on medical therapy alone were included in the study. **Results:** Forty of 127 (31.5%) patients survived over 10 years. Mean follow-up duration was 145.48 ± 16.8 months. Baseline left ventricular (LVEF) was $30.01 \pm 7.89\%$. Of these, 26 (65%) patients showed recovery of LVEF. Eight (30.8%) of these had a relapse following initial recovery. 14 patients (35%) did not show improvement in LVEF. Multivariate analysis showed that only variable associated with sustained recovery of LVEF was shorter QRS duration with a mean QRS duration of 95.2 ± 11.3 ms versus 117.4 ± 22.6 ms in the two groups ($P < 0.001$). **Conclusions:** 31.5% of patients with nonischemic DCM survived more than 10 years with medical therapy alone. Almost two-thirds of these long-term survivors showed recovery of LVEF. Narrow QRS duration predicted sustained recovery of LVEF.

Keywords: Dilated cardiomyopathy, left ventricular ejection fraction, survival

Introduction

Outcomes of dilated cardiomyopathy (DCM) have improved over the past few decades due to advances in medical and device therapies. The 1-year mortality in the placebo arm was a dismal 50% in the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS) conducted in the 1980s.^[1] The death rate has progressively dropped in subsequent trials and the 1-year mortality was around 10% in the PARADIGM-HF study.^[2-6] Drugs such as angiotensin-converting enzyme

inhibitors, beta-blockers, and aldosterone antagonists have largely contributed to the improved survival.

Most of these randomized trials have reported on only short and medium-term survivals and there is a lack of data on long-term survival. We have followed up a large cohort of patients with nonischemic DCM who have largely been only on medical management. We aimed to study the profile of non-ischemic DCM patients who survive ≥ 10 years on guideline-directed medical management. We also aimed to look at the changes in left ventricular ejection fraction (LVEF) in these long-term survivors on follow-up.

Methods

This was a retrospective, single-center, observational study that comprised of all adult patients in nonischemic DCM cohort

Address for correspondence: Prof. Ajay Bahl,

Department of Cardiology, Post Graduate Institute of Medical Education and Research, Sector 12, Chandigarh - 160 012, India.

E-mail: drajaybahl@hotmail.com

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presenting to the department of cardiology of a tertiary care hospital who entered the cohort from June 2003 to January 2007 and who had survived for at least 10 years after initial diagnosis of dilated cardiomyopathy and were on medical management alone. The study protocol conforms to the ethical guidelines of the 1975 declaration of Helsinki and was approved by the institute's ethics committee. Written informed consent was obtained from all patients.

Inclusion criteria were age ≥ 18 years, absence of history of coronary artery disease or myocardial infarction, and LVEF on echocardiography $\leq 40\%$ by modified Simpsons method. All patients ≥ 35 years of age underwent coronary angiography at diagnosis and had either normal coronaries or insignificant coronary artery disease ($< 50\%$ stenosis in any major coronary artery). Patients with peripartum cardiomyopathy were included if their LVEF was $\leq 40\%$ at least 1 year after delivery. Patients with history of less than 1 year were excluded.

Exclusion criteria were patients with coronary artery disease on coronary angiography or myocardial infarction in the past, reversible cause of DCM like thyrotoxicosis, heavy alcohol intake, significant primary valvular heart disease, or use of devices like biventricular pacing device and implantable cardioverter defibrillator for heart failure management. However, patients on single or dual-chamber pacing for bradyarrhythmia pacing were included in the study.

We also aimed to look at the changes in LVEF on follow-up. Patients were considered to in the recovered group if there was an increase in LVEF of $\geq 10\%$ to a level $> 40\%$ from baseline till the end of follow-up. The relapsed group included patients with a fall in the LVEF $\geq 10\%$ by the end of follow-up after an initial improvement in LVEF to $> 40\%$ with a net increase of $\geq 10\%$ from baseline. The not improved group included patients with no change or decline in LVEF or increase in LVEF $< 10\%$ compared to baseline.

The information collected was history and physical examination findings, routine laboratory investigations, baseline electrocardiogram, baseline and serial echocardiographic parameters, and the treatment offered during the baseline and follow-up, which were compared among these three groups.

Statistical analysis was performed using SPSS version 17. Continuous data was expressed as mean \pm SD. Categorical variables were expressed as a percentage. Comparison among the three groups was done using a one-way analysis of variance for continuous variables. Differences within the group, from baseline to follow-up parameters, were compared using a *t*-test for paired data. Categorical variables were compared by Chi-square or Fisher's exact test. To study the role of various variables in predicting improvement in LVEF or recurrence of left ventricular systolic dysfunction, a univariate logistic regression analysis was performed. A multivariate logistic regression analysis using the block method was performed on variables reaching a significance

of $P < 0.10$ on univariate analysis. A value of $P < 0.05$ was considered significant.

Results

There were 127 patients with nonischemic DCM cohort and LVEF $\leq 40\%$ who entered the cohort from April 2003 to January 2007 and were only on medical management alone. Of these, 40 (31.5%) patients survived more than 10 years. The mean age of the patients is 39.6 ± 2.2 years and the follow-up duration is 145.38 ± 16.78 months. The baseline characteristics of the patients are mentioned in Table 1. All patients were on angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, beta-blockers, and either spironolactone or eplerenone. Thirty-four (85%) patients received digoxin at some period during their illness.

Twenty-six (65%) patients showed recovery of LVEF. The sustained recovery of LVEF was observed in 18 (45%), while eight (20%) patients relapsed following initial recovery. Fourteen (35%) patients were in the not-improved group. Baseline characteristics of the 3 groups are mentioned in Table 2. The LVEF increased significantly from mean of $28.1 \pm 7.6\%$ to $52.9 \pm 1.0\%$ in the improved group ($P = < 0.001$). The mean LVEF increased from $36.9 \pm 5.7\%$ to a peak of $50.6 \pm 6.4\%$ and then declined to $35.4 \pm 8.4\%$ in relapsed group, with no significant change compared to baseline ($P = 0.682$). In the not improved group, the LVEF had shown no significant change. It was $28.5 \pm 9.5\%$ at baseline and $27.2 \pm 7.4\%$ at end of study ($P = 0.704$).

Significant differences in the recovered group on univariate analysis were younger age, narrow QRS, lower left ventricular end-diastolic dimension, lower left atrial size, and lesser incidence of mitral regurgitation, while only narrow QRS was significant on multivariate analysis. There was no significant difference in their initial NYHA class, gender, body mass index, presence of diabetes mellitus, blood pressure levels, serum creatinine, and hemoglobin levels as well as baseline LVEF.

Discussion

Survival of DCM has improved over the past decades due to drugs and devices. We have a large cohort of nonischemic

Table 1: Baseline characteristics of patients

	Number (%) n=40
Age (Mean \pm SD)	39.6 \pm 12.2
Males	21 (52.5%)
NYHA class	2.8 \pm 0.9
Hypertension (%)	17 (42.5%)
Diabetes mellitus	10 (25%)
Smoking	5 (12.5%)
Heavy alcohol intake	0
Chronic kidney disease	0
Hypothyroidism	5 (12.5%)
Left bundle branch block	4 (10%)

Table 2: Baseline characteristics of the three groups

	Recovered Group (n=18)	Relapsed Group (n=8)	Nonrecovered Group (n=14)	P
Age at entry	35.67±10.91	48.5±10.21	39.5±12.69	0.041
Males n (%)	10 (47.6%)	5 (23.8%)	6 (28.6%)	0.910
NYHA class (baseline)	3.0±0.84	2.0±0.54	3.0±0.88	0.041
Hypertension n (%)	5 (29.4%)	5 (29.4%)	7 (41.2%)	0.199
Diabetes mellitus n (%)	3 (30.0%)	3 (30.0%)	4 (40.0%)	0.489
Body mass index (kg/m ²)	26.19±7.56	25.12±3.87	24.65±5.68	0.785
Systolic blood pressure mmHg	117.0±23.85	129.25±16.0	124.43±28.89	0.461
Diastolic blood pressure mmHg	73.33±15.7	81.25±9.91	79.29±12.69	0.348
Hemoglobin (g/dL)	12.12±2.14	13.12±3.65	12.6±1.79	0.616
Serum creatinine (mg/dL)	0.96±0.23	0.71±0.21	0.95±0.16	0.768
Smoking n (%)	4 (80.0%)	0 (0%)	1 (20.0%)	-
Hypothyroidism n (%)	1 (20.0%)	1 (20.0%)	3 (60.0%)	0.403
QRS duration (milliseconds)	95.17±11.27	98.7±16.04	117.36±22.63	0.002
Left bundle branch block n (%)	1 (5.6%)	0	3 (21.4%)	-
Baseline LVEF (%)	28.11±7.62	36.88±5.69	28.5±9.48	0.085
Left atrial dimension (mm)	37.22±6.78	41.88±3.56	46.36±7.62	0.02
LVEDD (mm)	48.83±9.12	51.88±8.58	62.57±10.59	0.01
TAPSE (mm)	20.61±3.22	17.13±3.90	17.79±4.53	0.052
At least moderate mitral regurgitation	2 (22.2%)	3 (25%)	9 (64.2%)	0.015
Pulmonary arterial hypertension n (%)	1 (5.6%)	0 (0%)	2 (14.3%)	-

LVEDD - Left ventricular end-diastolic dimension; LVEF - Left ventricular ejection fraction; TAPSE - Tricuspid annular plane systolic excursion.

DCM patients in whom devices were not used largely due to personal or financial reasons. Such a cohort may not be possible today due to the increased use of devices in recent years. Even though the cohort is small, it provides insights into the profile of long-term DCM survivors on medical therapy. Large drug trials do not provide this data due to shorter follow-up periods. In addition, drug trials do not reflect a real-world setting.

Since patients entered the cohort till 2007, the medical therapy was as per the contemporary guidelines. All patients received angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, beta-blockers, and either spironolactone or eplerenone. This is likely due to dedicated follow-up. In addition, this indicates that these long-term survivors did not have contraindications or side effects that could have prevented the use of some drugs in some of the patients. Neprilysin inhibitors were not used since the follow-up period was largely prior to their availability. With the use of neprilysin inhibitors, sodium-glucose co-transporter-2 inhibitors, and cardiac resynchronization therapy, the survival may be better.^[7,8]

Is it possible to predict which nonischemic DCM patients will be long-term survivors? A comparison with nonsurvivors was not carried out. However, some features stand out. Over two-thirds of long-term survivors had recovery of LVEF of 10% to at least ≥ 40 , which is consistent with the current definition of DCM with recovered LVEF.^[9] Such a high prevalence of patients with recovered LVEF indicates that they have markedly improved survivals. Previous studies have also shown improved outcomes for these patients.^[10,11] Of the 26 patients who showed improvement in LVEF, the improvement occurred within 1 year in 13 (50%) and within 3 years in 21 (80.8%) patients. This

indicates that LVEF can improve even a few years after starting therapy.^[12] Keeping patients with recovered LVEF under close follow-up is important since 8 (30.8%) relapsed. This study also highlights the high risk of relapse, which was reported in earlier studies as well.^[12,13] In the TRED-HF trial, 44% of DCM patients who withdrew from drug therapy relapsed, whereas none of those who continued their medications had a relapse.^[13] Thus, the current opinion recommends that drug therapy should be continued indefinitely in recovered DCM patients.^[9] 35% of long-term survivors did not improve their LVEF. Thus, medical therapy may also result in long-term stabilization of patients who continue to have severe left ventricular systolic dysfunction.

Previous studies have shown several factors like younger age, female sex, absence of left bundle branch block, narrower QRS complex, and history of hypertension were predictors of recovery of LVEF.^[10,12,14-16] However, left ventricular size was not a predictor of recovery.^[17] In our study, though several parameters were significant predictors of improvements in LVEF on univariate analysis, only a narrower QRS duration predicted LVEF recovery on multivariate analysis.

One limitation is the small sample size. We also did not study biomarkers like brain natriuretic peptides in this study.

Dilated cardiomyopathy is a common cause of heart failure with reduced ejection fraction encountered in primary practice. This study highlights that adherence to low-cost medical therapy alone can result in long-term survival even in patients with severe left ventricular systolic dysfunction. Thus, it is important to ensure that all patients receive guideline-directed medical therapy. Addition of newer drugs like neprilysin inhibitors and

sodium-glucose co-transporter-2 inhibitors, and devices like cardiac resynchronization therapy and implantable cardioverter defibrillators increase the cost of treatment but may result in even better long-term survival.^[18,19]

To conclude, 31.5% of patients with nonischemic DCM survived more than 10 years with low-cost medical therapy alone. Almost two-thirds of these showed recovery of LVEF. Narrow QRS duration predicted sustained recovery of LVEF.

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Nil

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. The patients understand that their names and initials will not be published and due efforts has been made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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