Survival analysis of patients with idiopathic dilated cardiomyopathy in Oman

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ABSTRACT

Objective: To study the 10-year survival of adults with idiopathic dilated cardiomyopathy (IDC) in Oman.

Methods: Ninety-seven patients aged >13 years with IDC attending the Cardiology Unit, Sultan Qaboos University Hospital, Muscat, Oman from 1992-1995 were prospectively studied, in order to identify the outcome and factors contributing to death.

Results: Among 97 patients, 2 died from acute heart failure at presentation. The remaining 95 patients were followed up for periods ranging from 1-10 years (median 7 years). Twenty-four out of 95 patients exhibited clinical deterioration with reduced left ventricular ejection fraction (LVEF), by 5-11%, and 17 of them expired due to resistant heart failure. The remaining 71 patients remained stable and did not show deterioration in LVEF; however, 7 of them died suddenly at home possibly from ventricular arrhythmia. The survival rates were 94% at one year (95% confidence interval [CI] 88% to 99%), 86% at 3 years (95% CI 79% to 93%), and 64% at 10 years (95% CI 51% to 78%). Mean survival was 6.5 years (95% CI 6 to 7 years). Multivariate regression analysis revealed that factors related to death were LVEF <30% (p<0.001) and presence of severe mitral regurgitation (p=0.01).

Conclusion: Outcome of dilated cardiomyopathy has improved due to greater understanding of this condition leading to better therapeutic approach. Resistant heart failure and cardiac arrhythmias remain the main causes of mortality. Poor outcome was related to low LVEF and presence of severe mitral regurgitation.

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Despite many years of research, idiopathic dilated cardiomyopathy (IDC) continues to be a serious and challenging problem for physicians around the world. The course of the disease is usually steadily downhill but can be rapid and death has been reported to occur within 6 months to 5 years after the onset of the symptoms. Although previous reports had placed the 5-year mortality at approximately 40%,[1-4] this has improved considerably in recent years.[5,6] Ninety-seven patients with IDC from the Sultanate of Oman were studied. We have earlier published a prevalence study with a complete clinical profile and natural history of these well-characterized patients.[7] This report is a 10-year follow up with survival analysis of patients.

Methods. All patients with IDC, during a 3-year period from 1992 to 1995 were included in the study. Idiopathic dilated cardiomyopathy was defined using World Health Organization Criteria.[8] All known causes of myocardial dysfunction, particularly patients with history of alcohol intake, hypertension, diabetes mellitus, thyroid disease or other systemic diseases, and acute myocarditis were excluded. Myocardial biopsy was not part of the study protocol. Echocardiographic demonstration of

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dilated ventricles with depressed myocardial function as assessed by left ventricular ejection fraction (LVEF) of <50% was used as inclusion criteria. Exercise testing and coronary angiography excluded coronary artery disease. All patients had 24-hour Holter electrocardiogram at the commencement of the study and again during follow up on suspicion of new arrhythmias. Regular clinical follow up was arranged with echocardiogram repeated once a year or earlier if acute heart failure occurred. Variables recorded during follow up included the class of heart failure as per New York Heart Association (NYHA) functional classification,[9] arrhythmia, systemic or pulmonary embolic events and death. Treatment of heart failure included a combination of diuretics, angiotensin converting enzyme inhibitor (ACEI), and digoxin. Anticoagulation was considered in the presence of atrial fibrillation, thromboembolism or when an intracardiac thrombus was demonstrated on echocardiography. Beta-blocker therapy using carvedilol was commenced during the course of the illness in selected patients.

Statistical Package for Social Sciences (SPSS) 9.0 for Windows 2000 was used for data entry and analysis. Unpaired t-test for continuous variables and Chi square test for discrete variables were used to identify significant differences in the factors related to outcome (alive or dead). Kaplan-Meier method was used to construct survival curves and the log rank method applied to compare the influence of possible risk factors on the survival.

Results. Ninety-seven patients (56 males and 41 females) aged 15-69 years (median age 50 years) with a male to female ratio of 1.4:1 were included in this study. Parental consanguinity, a common occurrence in Arab culture was seen in 31 patients. Only 3 patients had another affected member in the family, and none of them had consanguineous parents. Duration of symptoms at entry ranged from one month to 7 years (median 1 year, mean±SD 1.3±1.4 years). Majorities (69/97) were symptomatic from at least a year. Shortness of breath was the main symptom (100%), and 37/97 (38%) patients could be categorized as NYHA Functional Class III-IV. Palpitation, syncope and chest pain were less frequent. Cardiac rhythm at entry was sinus in 87 (89.6%) patients, atrial fibrillation in 8 and atrial flutter and junctional rhythm in one each. The major conduction abnormalities were left bundle branch block (16%) and intraventricular conduction delay (25%). Electrocardiogram evidence of left or biventricular hypertrophy was the predominant feature (78.4%) and isolated right ventricular hypertrophy was seen only in one patient. Although 74% of patients showed ventricular tachycardia on 24-hour ambulatory ECG, majority (62%) were short (<10 beats) and self-limiting. Echo-Doppler studies revealed global hypokinesia of left ventricle (LVEF <50%) in all patients. Severe left ventricular dysfunction (LVEF <30%) was seen in 33 (34%) patients, of whom only 18 had class III or IV symptoms. Mitral regurgitation (MR) was a common finding present in majority (88/97) but was severe only in 27 (27.8%). But all these 27 with severe MR had dilated left ventricle cavity (≥ 6.1 cm) and a significantly reduced LVEF (18-40%). Approximately one half of patients also had tricuspid regurgitation and few had a mild aortic and pulmonary regurgitations. Within its diagnostic limitations, diastolic dysfunction, as assessed by mitral diastolic Doppler flow pattern was found in 40.2% patients. Although global systolic hypokinesia was the major contractile abnormality, disproportionately impaired septal motion was seen in 50% (51/97) of patients. Right ventricular ejection fraction was reduced in only 12 patients (<30% in 8 and 30-49% in 4). Left ventricle thrombus formation was detected in 10 patients.

Table 1 shows the clinical course and outcome of 97 patients with IDC. Two patients died from end stage heart failure at first admission. The rest were followed up for 1-10 years (median 7 years). Patients with stable clinical course with no deterioration in functional class were placed in Group A, and those with clinical deterioration in Group B. Their clinical course and mortality variables were analyzed. Patients in Group A did not require modifications in anti-heart failure therapy, and did not show any deterioration in LVEF. However, Group B patients exhibited clinical deterioration with reduced LVEF by 5-11%,

Table 1 - Outcome of 97 patients with idiopathic dilated cardiomyopathy (N=97).

Clinical course	Group A*	Group B†	Total
Outcome			
Alive	62	9	**71**
Dead	7	≥19‡	**26**
Total	**69**	**28**	**97**
Causes of death			
Resistant heart failure	0/7	15/19	
Cardiac arrhythmia	5/7	0/19	
Pulmonary embolism	1/7	3/19	
Malignancy	1/7	0/19	
Septicemia	0/7	1/19	

*LVEF 26-45% (mean 42%), stable course,
†LVEF 18-30% (mean 24%), deteriorating course,
‡includes 2 patients, who died during first admission,
LVEF - left ventricular ejection fraction.

Table 2 - Analysis of variables related to outcome in idiopathic dilated cardiomyopathy (N=97).

Variables	Live	Dead	*p* value
Age (years) (mean +SD)*	47 ± 13	49 ± 12	0.55‡
Sex			0.58‡
Male	42	14	
Female	29	12	
Duration of symptoms (years) (mean+SD)*	1.5 ± 1.3	1 ± 1.2	0.17‡
LVEF (%) (mean+SD)*	42 ± 8.6	24 ± 6.2	0.01§
Severity of symptoms*			0.12‡
A	50	10	
B	21	16	
Severe MR*			0.01§
Yes	7	20	
No	64	6	
***Significant VT**†*			0.07‡
Yes	6	6	
No	65	20	

*at entry into study, †during follow up,
‡not significant, §significant, LVEF - left ventricular ejection fraction, MR - mitral regurgitation, VT - ventricular tachycardia,
A - NYHA Functional Class I and II,
B - NYHA Functional Class III and IV

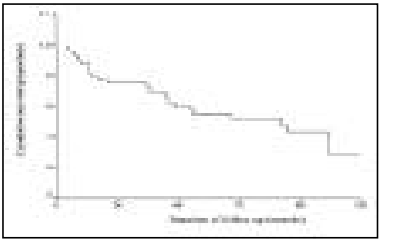

Figure 1 - Cumulative survival during a 10-year follow up of 97 patients with idiopathic dilated cardiomyopathy.

and required major adjustments in their drug therapy. Death occurred in 26 of the 97 (26.8%) patients during the study period. Besides the 2 who died at initial presentation, there were 17 deaths in group B and 7 in group A. Deaths in group A occurred in patients whose heart failure was under control and could be attributed to fatal ventricular arrhythmias in 5 (3 of which were at home), pulmonary embolism in one and disseminated malignancy (non-cardiac) in one. The remaining 19 deaths occurring in group B were due to resistant heart failure. Additional contributing factors in this group included pulmonary embolism in 3 and *Pseudomonas septicemia* in one.

Dead and live patients were compared with regard to possible outcome variables (**Table 2**). On multivariate regression analysis, LVEF was <30% (p<0.001) and the presence of severe MR (p=0.01) were identified as independent predictors of poor outcome. Survival curves were drawn using Kaplan-Meier method (**Figure 1**) and the calculated survival rates were 94% at one year (95% confidence interval [CI] 88-99%), 86% at 3 years (95% CI 79-93%), 76% at 5 years (95% CI 67-86%), 68% at 8 years (95% CI 54-82%), and 64% at 10 years (95% CI 51-78%). Mean survival was 6.5 years (95% CI 6-7 years). Median survival time at which 50% of the patients died could not be computed as >50% of patients were alive at the conclusion of the study. Patients with LVEF of <30% had a mean survival of 6.3 years (95% CI 5-7.4 years) while for those with LVEF of >30% it was 12.5 years (95% CI 11.4-13.8 years). The difference was highly significant (p<0.001). Shortened survival was also related to the presence of severe MR (4.7 years versus 13.6 years; p<0.001), and NYHA class III and IV at presentation (8.8 years versus 12 years; p=0.04).

Discussion. The mortality of 27% over a 10-year period shows improved survival over previous years. Maximum number of deaths occurred in the first year of follow up and the rest were distributed mostly over the 1-10 years. Similar pattern has been reported by other studies.[5,10-13] This observation of high mortality in the first year and reduced mortality in later years is likely to be due to specialist care approach of patients once they enter the study period which provide close monitoring and optimal treatment. Sugrue et al[14] also showed that survival at one year differed dramatically between population based cohort and referral cases (95% compared with 69%) and at 5 years (80% compared with 36%) (p<0.001). The improvement in survival from IDC worldwide has largely been due to early diagnosis, introduction of ACEI and beta-blockers in the therapy, and prevention of complications such as embolic events and arrhythmias. Better survival in our patients reflects improved health care facilities in Oman and can also be due to the fact that nearly all the patients were referred cases for specialist care.

A number of studies have investigated the predictors of death in IDC.[10,15-19] The following parameters have been reported as independent predictors of mortality: first symptom, pulmonary edema, peripheral edema, syncope, duration of symptoms at the time of inclusion, end systolic LV

volume, end diastolic LV diameter, pulmonary artery systolic pressure; and their combination had the most accurate predictive value for death. Romeo et al[20] found similar factors but added lower ejection fraction (p=0.0001) and severe MR (p=0.0095) in their patients. The severity of heart failure at the time of initiating therapy is a significant factor affecting mortality due to resistant heart failure.[14] Nineteen out of 26 deaths (73%) in our series occurred in patients who were in severe heart failure with an LVEF of <30%. There was a positive correlation between the LVEF at presentation and mortality (p=0.01), and this was the main predictive variable identified by multivariate analysis. Over 50% (19/28) mortality in group B with resistant heart failure and 10% (7/69) in group A with stable patients strongly favor worsening myocardial function as the most important factor in the mortality from IDC. Severe MR was also a significant predictor (p<0.001). However, the presence of severe MR could be related to the LV end-diastolic dimensions and to LVEF itself and therefore it may not be an independent predictor if allowance is given to the low LVEF. New York Heart Association Functional class III-IV was related to poor outcome (p=0.04) on univariate analysis, but this factor did not reach statistical significance on multivariate analysis (p=0.12). However, survival analysis shows a significant difference between patients who presented with NYHA Functional Class III and IV from those in Class I and II, emphasizing the importance of severe symptomatology at the time of presentation.

The occurrence of cardiac arrhythmias both tachycardias and bradycardias in IDC is well established.[18,21-23] Ventricular arrhythmias in particular are important with their potential to cause sudden death.[24] Ventricular ectopics and non-sustained ventricular tachycardia, although more common, have not been associated with increased morbidity or mortality. Besides precipitating heart failure, all types of arrhythmias cause additional myocardial insult worsening the functional class of heart failure even after the acute episode is controlled. Five patients died despite control of heart failure reflect the other important factor relevant to death in IDC - malignant ventricular arrhythmias. These patients had a stable hemodynamic state in NYHA II/III and LV ejection fraction of >30%. It is also relevant to note that all these 5 patients were already on amiodarone for documented ventricular tachycardia. As high as 30% of deaths among patients with IDC are reported to be sudden deaths.[25] Fruhwald et al[15] however, found 13.8% cases of sudden deaths in their long-term follow-up of 167 patients. Similarly Romeo et al[20] had reported sudden death in 13% and resistant heart failure in 20%. In Hofmann et al study[26] 36% died of heart failure but there was a high percentage (64%) of sudden deaths. Depressed LV systolic function and presence of frequent complex ventricular arrhythmias was identified in patients who were at high risk of sudden deaths. Interestingly in this study, presence of atrial fibrillation significantly increased the risk of sudden deaths and death from heart failure.

The correlation between ventricular arrhythmia and sudden death in IDC is debatable. The development of new sustained ventricular tachycardia in our study patients nearly reached the statistical significant (p=0.07) and in our 3 patients who died suddenly at home due to malignant ventricular arrhythmia is most likely the cause. The role of arrhythmia is also interesting and it is more relevant in stable patients since none of the deaths in group B was due to arrhythmia. Therefore, the role of arrhythmia appears to be independent in the severity of myocardial impairment. Fatal arrhythmias attributed to 5 sudden deaths in this study is however, somewhat presumptive. Since these patient's heart failure was under good control with stable hemodynamics; ventricular arrhythmia was considered as prime suspect. It is further relevant that all these 5 patients were taking amiodarone as part of their antiarrhythmic therapy. Pro-arrhythmia would also need to be suspected. Post-mortem examination would have helped to elucidate the cause of death but this could not be performed due to cultural restrictions. Strictly speaking, at least 3 deaths at home thus can be argued to be of unknown cause.

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