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Determinants of End-Stage Idiopathic Dilated Cardiomyopathy: A Multivariate Analysis of 104 Patients

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Summary: Our purpose in this study was to investigate the correlation of clinical, electrocardiographic, hemodynamic, and histopathologic features at diagnosis with the long-term prognosis in 104 patients with idiopathic dilated cardiomyopathy to determine which factors are the independent determinants of the end-stage disease. During a mean follow-up of 3.8 ± 3.5 years, 35 patients (33%) died, 14 (13%) suddenly and 21 (20%) from congestive heart failure. Univariate analysis of survival curves disclosed that clinical and electrocardiographic variables at diagnosis were similar in survivors and nonsurvivors. On the contrary, patients who subsequently died had higher mean right atrial pressure ($p=0.0001$), right ventricular end-diastolic pressure ($p=0.0061$), mean pulmonary artery pressure ($p=0.0001$), and left ventricular systolic ($p=0.0049$) and end-diastolic ($p=0.0021$) pressure than survivors. They also exhibited larger left ventricular end-diastolic ($p=0.0046$) and end-systolic ($p=0.0027$) volumes, lower ejection fraction ($p=0.0001$), and a greater proportion had severe mitral regurgitation ($p=0.0095$). Univariate analysis of histologic findings collected in a subgroup of patients referred since 1984 revealed a mild degree of myocellular hypertrophy to be associated with a poor prognosis ($p=0.0217$). Multivariate analysis selected only mean right atrial pressure ($p=0.0022$), ejection fraction ($p=0.0089$), and end-systolic volume ($p=0.0265$) as independent determinants of cardiac death. Our results suggest that cardiac catheterization is mandatory for risk stratification of patients with idiopathic dilated cardiomyopathy, since it allows the assessment of hemodynamic, angiographic, and histopathologic features helpful in identifying patients with a poor prognosis.

Key words: idiopathic dilated cardiomyopathy, cardiac catheterization, endomyocardial biopsy, myocellular hypertrophy

Introduction

Idiopathic dilated cardiomyopathy is commonly thought to be the heart muscle disease that carries the poorest prognosis,[1] since 5-year mortality after presentation has been reported to vary from 50 to 75%.[2,3] Patients with idiopathic dilated cardiomyopathy are, therefore, admitted increasingly to current heart transplantation programs,[4] but selection of patients for surgery as well as the timing of the procedure remain controversial. Although several variables have been suggested as predictors of outcome in idiopathic dilated cardiomyopathy, the clinical course of the disease is commonly thought to be still unpredictable.[5,6]

The purpose of this study was to investigate the relation between clinical, electrocardiographic, hemodynamic, and histopathologic features at diagnosis and the long-term prognosis of patients with idiopathic dilated cardiomyopathy to determine which factors are the independent hallmarks of reduced survival.

Methods

Study Patients

We retrospectively analyzed data on 104 patients with idiopathic dilated cardiomyopathy who were consecutively admitted to our hospital from January 1977 to June 1987.

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There were 78 men and 26 women, aged 21-64 years (mean 45 ± 14). The diagnosis was made on the basis of left ventricular dilatation and systolic contraction dysfunction as shown by ejection fraction < 50% and left ventricular end-diastolic pressure > 12 mmHg, in the absence of coronary artery disease, valvular heart disease, systemic hypertension, cor pulmonale, history of previous infective disease, or chronic systemic disease involving the heart muscle or increased alcohol intake.

Noninvasive Studies

The medical history of each patient was reviewed to determine age at onset of symptoms, clinical findings, and clinical course.

The functional status classification of patients was according to the New York Heart Association. All patients had a baseline 12-lead electrocardiogram at admission. Ventricular arrhythmias were graded according to the Lown classification.[7] Echocardiographic and radionuclide findings were not considered in the present study because records were not available for the whole study population.

Cardiac Catheterization

Right- and left-sided heart catheterization were performed off medications without premedication in the fasting state. Cardiac output was determined by means of thermodilution and cardiac index was then derived. All patients also underwent left ventriculography. Left ventricular end-diastolic, end-systolic, and stroke volumes as well as ejection fraction were calculated from the 30° right anterior oblique projection of the left ventriculogram by Kennedy's area length method.[8] Mitral regurgitation was assessed angiographically according to Bjork *et al.*[9] Coronary arteriography (Seldinger technique) was performed in all patients with significant angina, and in those aged 40 years or more: none had significant stenoses of epicardial coronary vessels.

Endomyocardial Biopsy

The 32 patients (31%) referred to us since January 1984 underwent percutaneous endomyocardial biopsy to exclude myocarditis and specific heart muscle diseases.[10] Endomyocardial biopsy specimens were taken from the left ventricle (septum, anterior free wall, and apex) with the King's College bioptome by the retrograde transarterial route.[11] Tissue samples were fixed in 10% formalin and embedded in paraffin. Sections 4 μm thick were cut, stained with hematoxylin-eosin, Heidenhain-azan, and elastic-Van Gieson stain, and examined under a light microscope. The following histopathologic features were blindly and independently analyzed by three pathologists: hypertrophy, hydropic degeneration, and attenuation of myocytes (in myocardium); fibrosis and smooth muscle cell hyperplasia (in endocardium); fibrosis and inflammatory cells infiltration (in interstitium). Each of these histologic features was semiquantitatively scored from 0 to 3, 0 being normal or not present, 1 (mild), 2 (moderate), or 3 (marked) characterizing increasing degree of change or frequency.

Medications

Treatment of patients at time of discharge included digoxin (91 patients, 88%), diuretics (99 patients, 95%), nitrates (68 patients, 65%), and anticoagulants (54 patients, 52%). No patient received antiarrhythmic drugs or beta blockers either during recovery or follow-up.

Follow-Up

The end-point of follow-up was death or survival at December 31, 1987. We were unable to obtain information on the influence of treatment because most patients received nearly the same therapy.

Statistical Analysis

Results are expressed as mean ± standard deviation. Cumulative survival rates from entry in the study (at time of catheterization) were calculated by standard life table methods. Survival curves were univariately compared by Log-rank test. Variables significant by univariate analysis were jointly analyzed by multivariate Cox's proportional hazards model. Computations were performed on an IBM 3081 computer using the SAS software.[12] A $p < 0.05$ was considered significant.

Results

The length of follow-up from diagnosis was 1 to 11 years (mean: 3.8 ± 3.5 years). No patient was lost to follow-up. During the follow-up period, 35 patients (33%) died from cardiac causes, 14 (13%) suddenly and 21 (20%) from congestive heart failure. The cumulative survival rate was 82% at 2 years, 56% at 5 years, and 44% at 10 years.

Each of the clinical, electrocardiographic, and hemodynamic variables at diagnosis was considered individually by a univariate analysis to determine its association with death. Clinical and electrocardiographic features were not significantly different in survivors and nonsurvivors (Table I). On the contrary, most hemodynamic and angiographic findings demonstrated a significant univariate association with death or survival (Table II): at time of diagnosis, patients who subsequently died had higher mean right atrial pressure, mean pulmonary artery pressure, left ventricular systolic pressure, and right and left ventricular filling pressures than survivors; they also showed larger left ventricular end-diastolic and end-systolic volumes and lower ejection frac-

TABLE I Clinical and electrocardiographic findings at diagnosis in survivors and nonsurvivors with idiopathic dilated cardiomyopathy

	Survivors (n=69)	Nonsurvivors (n=35)	p[a]
Age at diagnosis (yrs)	45±14	43±12	NS
Time-interval onset of symptoms–referral (yrs)	2.9±1.1	2.8±1.2	NS
Follow-up (yrs)	5.4±3.6	2.8±2.4	0.0345
Exertional chest pain	21 (30%)	8 (23%)	NS
Palpitations	27 (39%)	19 (54%)	NS
Functional class ≥III-IV NYHA	30 (43%)	21 (60%)	NS
Atrial fibrillation	8 (11%)	7 (20%)	NS
Atrioventricular conduction disturbances	5 (7%)	5 (14%)	NS
Right bundle-branch block	3 (4%)	—	NS
Left bundle-branch block	18 (26%)	17 (48%)	NS
Ventricular arrhythmias ≥4 Lown class	8 (12%)	11 (31%)	NS

[a]p value as a result of comparison of actuarial survival curves by univariate analysis.
Abbreviations: NS=not significant; NYHA=New York Heart Association.

TABLE II Cardiac catheterization findings in survivors and nonsurvivors with idiopathic dilated cardiomyopathy

	Survivors (n=69)	Nonsurvivors (n=35)	p[a]
Mean right atrial pressure (mmHg)	5±3	10±5	0.0001
Right ventricular end-diastolic pressure (mmHg)	7±4	11±5	0.0061
Mean pulmonary artery pressure (mmHg)	21±10	33±12	0.0001
Left ventricular systolic pressure (mmHg)	120±20	114±14	0.0049
Left ventricular end-diastolic pressure (mmHg)	17±7	22±8	0.0021
Left ventricular end-diastolic volume (ml/m²)	176±69	209±96	0.0046
Left ventricular end-systolic volume (ml/m²)	115±56	151±79	0.0027
Ejection fraction (%)	35±10	29±10	0.0001
Significant mitral regurgitation	15 (22%)	16 (46%)	0.0095

[a]p value as a result of comparison of actuarial survival curves by univariate analysis.

tion; moreover, a greater proportion had severe mitral regurgitation. As shown in Table III, most histologic features were similar in survivors and nonsurvivors. Interestingly enough, the extension of interstitial fibrosis did not appear to be a predictor of poor outcome. On the contrary, the finding of only a mild degree of myocellular hypertrophy (Fig. 1A) correlated with a worse prognosis, whereas a moderate to marked hypertrophy (Fig. 1B) was associated with a 92% survival rate. Multivariate analysis of variables significant by univariate analysis selected only mean right atrial pressure (p=0.0022, Fig. 2), ejection fraction (p=0.0089, Fig. 3), and left ventricular end-systolic volume (p=0.0265, Fig. 4) as independent determinants of cardiac death.

Discussion

Although medical treatment has improved survival, the prognosis in idiopathic dilated cardiomyopathy remains poor.[1-3] At the present time, heart transplantation seems to be the therapeutic approach with the best survival rate for patients with severely impaired function.[4] It is, therefore, important for the rationalization of the timing of the procedure to define the natural history of idiopathic dilated cardiomyopathy in order to correctly differentiate short-term survivors from nonsurvivors.

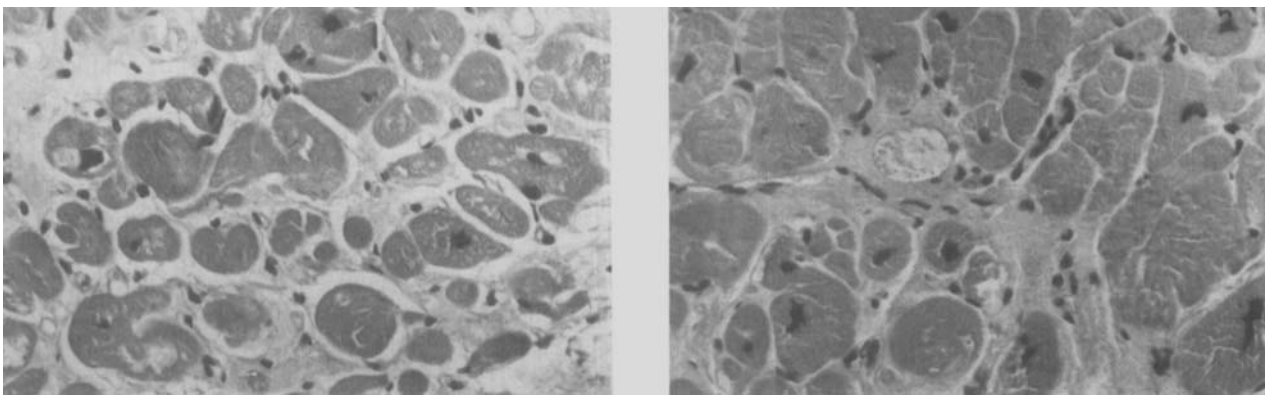
In the present study survivors and nonsurvivors had similar clinical and electrocardiographic features at diagnosis. Although several electrocardiographic findings have been previously stated to correlate with a poor outcome,[13,14] our data agree with most recent reports which showed that electrocardiographic abnormalities at rest do not enable a patient's clinical course to be adequately predicted.[1-3]

The results of our study, on the contrary, show that most hemodynamic and angiographic variables were univariately correlated with cardiac death. However, multivariate analysis selected a raised mean right atrial pressure, a low ejection fraction, and an increased left ventricular

TABLE III Histopathologic findings in survivors and nonsurvivors as graded semiquantitatively (see Methods) in a subgroup of 32 patients

	Survivors (n=23)	Nonsurvivors (n=9)	p[a]
Myocardium			
Hypertrophy			
mild	11 (48%)	8 (89%)	0.0217
moderate or marked	12 (52%)	1 (11%)	
Hydropic degeneration			
not present	15 (65%)	7 (78%)	NS
present	8 (35%)	2 (22%)	
Attenuated myocytes			
not present	13 (56%)	7 (78%)	NS
present	10 (44%)	2 (22%)	
Endocardium			
Fibrosis			
not present or mild	14 (61%)	6 (67%)	NS
moderate or marked	9 (39%)	3 (33%)	
Smooth muscle cell hyperplasia			
not present	19 (83%)	8 (89%)	
present	4 (17%)	1 (11%)	
Interstitium			
Fibrosis			
not present or mild	14 (61%)	5 (56%)	NS
moderate or marked	9 (39%)	4 (44%)	
Inflammatory cells			
not present or rare	22 (96%)	9 (100%)	NS
frequent	1 (4%)	0 —	

[a]p value as a result of comparison of actuarial survival curves by univariate analysis.
Abbreviations: NS=not significant.



A B

FIG. 1 Mild vs. marked degrees of myocellular hypertrophy in endomyocardial biopsy specimens in two patients with idiopathic dilated cardiomyopathy. (A) Slightly hypertrophic myocytes alternate with attenuated fibers. The patient underwent heart transplantation during the follow-up period. (B) Markedly hypertrophic myocytes with irregularly shaped, hyperchromatic nuclei. At the end-point of follow-up, the patient was still alive and was in NYHA functional class III.

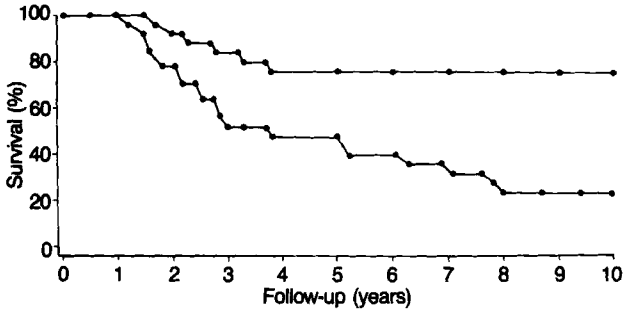


FIG. 2 Actuarial survival curves of patients dichotomized according to mean right atrial pressure. Univariate analysis disclosed a significant difference between the two subgroups (○—○, ≤9 mmHg; •—•, ≥ 10 mmHg) (p=0.0001) and Cox's analysis showed mean right atrial pressure as the most powerful independent predictor of death (p=0.0022).

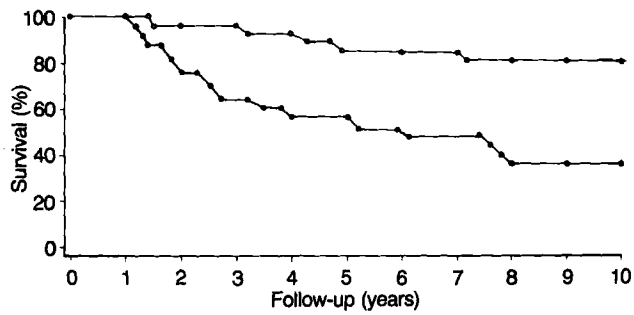


FIG. 3 Actuarial survival curves of patients with idiopathic dilated cardiomyopathy dichotomized according to ejection fraction. Univariate analysis showed a significant difference between the two subgroups (○—○, ≥25%; •—•, <25%) (p=0.0001) and Cox's analysis ranked ejection fraction second (p=0.0089) as independent determinant of death.

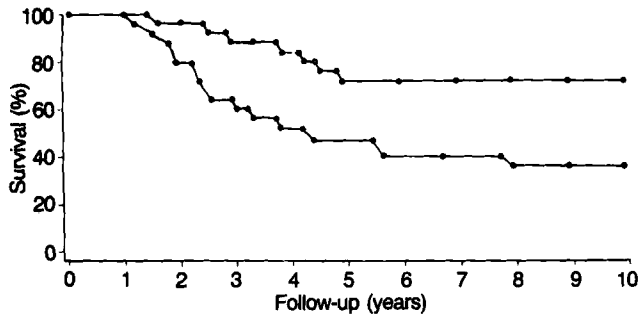


FIG. 4 Actuarial survival curves of patients dichotomized according to left ventricular end-systolic volume. Univariate analysis revealed a significant difference between the two subgroups (○—○, ≤149 ml/m²; •—•, ≥150 ml/m²) (p=0.0027) and Cox's analysis ranked left ventricular end-systolic volume third (p=0.0265) as independent predictor of death.

end-systolic volume as independent predictors of poor prognosis, thus suggesting that only the combination of these variables may accurately predict the outcome of patients with idiopathic dilated cardiomyopathy. These findings are consistent with several studies which have previously shown the predictive value of ejection fraction[2,3,15] as well as of a markedly dilated left ventricle.[3,16,17] Furthermore, our data agree with Unverferth *et al.*,[18] who considered a raised mean right atrial pressure of independent prognostic revelance. In idiopathic dilated cardiomyopathy, the right heart may be involved either primarily by the myocardial pathologic process or secondarily by the increased afterload on the right ventricle of patients with left ventricular dysfunction.[19] Irrespective of the etiology of right heart function impairment, our results suggest that right-sided heart hemodynamic measurements may have an additive prognostic value to left ventricular morphological and functional parameters, as previously shown in patients with coronary artery disease.[20]

With respect to histopathologic features, there is general agreement that light and electron-microscopic examinations of myocardial biopsies in idiopathic dilated cardiomyopathy are useful for diagnostic purposes,[10] even though they do not reveal pathognomic changes.[21] On the contrary, controversy persists as to whether or not prognosis of the disease might be assessed from histological changes.[22-29] A previous report from Kuhn *et al.*[22] showed that alterations of the myocardium were closely linked to the outcome of patients with idiopathic dilated cardiomyopathy and these findings were later confirmed by others.[23,24] Recent investigations, however, failed to show any relation between morphologic changes and the natural history of the disease,[25,26] whereas some authors have suggested that only myocardial fibrosis is an index of a poor prognosis.[27] In the present study, univariate analysis of the survival curves constructed with different degrees of histologic abnormalities showed only mild hypertrophy to be a dependent factor of prognostic significance, though multivariate analysis failed to reveal any independent value. Our results are in contrast with previous observations,[26-28] while they agree with Figulla *et al.*,[29] who have recently demonstrated that a reduced myofibril volume fraction (<60%) had prognostic significance for death. Thus, myocellular hypertrophy seems to have a compensatory role in idiopathic dilated cardiomyopathy. According to Goodwin,[19] the end-stage disease might be due to the failure of the DNA/RNA interaction that is needed for hypertrophy.

Conclusions

In conclusion, although several noninvasive variables have recently been proposed as prognostic determinants in idiopathic dilated cardiomyopathy, our results suggest that cardiac catheterization is still mandatory for risk stratification of patients with idiopathic dilated cardi-

omyopathy, since it allows assessment of hemodynamic, angiographic, and histopathologic features helpful in identifying patients with a poor prognosis.

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