

UNDERLYING CAUSES AND LONG-TERM SURVIVAL IN PATIENTS WITH INITIALLY UNEXPLAINED CARDIOMYOPATHY

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ABSTRACT

Background Previous studies of the prognosis of patients with heart failure due to cardiomyopathy categorized patients according to whether they had ischemic or nonischemic disease. The prognostic value of identifying more specific underlying causes of cardiomyopathy is unknown.

Methods We evaluated the outcomes of 1230 patients with cardiomyopathy. The patients were grouped into the following categories according to underlying cause: idiopathic cardiomyopathy (616 patients); peripartum cardiomyopathy (51); and cardiomyopathy due to myocarditis (111), ischemic heart disease (91), infiltrative myocardial disease (59), hypertension (49), human immunodeficiency virus (HIV) infection (45), connective-tissue disease (39), substance abuse (37), therapy with doxorubicin (15), and other causes (117). Cox proportional-hazards analysis was used to assess the association between the underlying cause of cardiomyopathy and survival.

Results During a mean follow-up of 4.4 years, 417 patients died and 57 underwent cardiac transplantation. As compared with the patients with idiopathic cardiomyopathy, the patients with peripartum cardiomyopathy had better survival (adjusted hazard ratio for death, 0.31; 95 percent confidence interval, 0.09 to 0.98), and survival was significantly worse among the patients with cardiomyopathy due to infiltrative myocardial disease (adjusted hazard ratio, 4.40; 95 percent confidence interval, 3.04 to 6.39), HIV infection (adjusted hazard ratio, 5.86; 95 percent confidence interval, 3.92 to 8.77), therapy with doxorubicin (adjusted hazard ratio, 3.46; 95 percent confidence interval, 1.67 to 7.18), and ischemic heart disease (adjusted hazard ratio, 1.52; 95 percent confidence interval, 1.07 to 2.17).

Conclusions The underlying cause of heart failure has prognostic value in patients with unexplained cardiomyopathy. Patients with peripartum cardiomyopathy appear to have a better prognosis than those with other forms of cardiomyopathy. Patients with cardiomyopathy due to infiltrative myocardial diseases, HIV infection, or doxorubicin therapy have an especially poor prognosis. (N Engl J Med 2000;342:1077-84.)

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DESPITE advances in drug therapy, the prognosis of patients with heart failure remains poor.¹ The accurate assessment of prognosis in patients with this disorder is critical, to ensure that patients with the most severe disease receive appropriate consideration for the limited number of hearts available for transplantation. Although substantial research has demonstrated the prognostic value of a variety of clinical characteristics in patients with heart failure,²⁻⁵ few data are available on the association between the cause of cardiomyopathy and the long-term prognosis.^{6,7} Previous studies addressing the influence of the underlying cause on prognosis have generally compared patients with ischemic heart disease and those with nonischemic causes of heart failure. Although it is possible to identify a more specific cause in a substantial percentage of patients with nonischemic cardiomyopathy,⁸ consensus recommendations suggest that the underlying cause is clinically important in only a few cases.^{9,10} Definitive data on the long-term prognosis of many uncommon forms of cardiomyopathy are limited. We undertook this study to determine the prognosis associated with cardiomyopathy of different causes, as defined by an exhaustive diagnostic evaluation performed at a tertiary care center with expertise in the diagnosis and treatment of cardiomyopathy.

METHODS

Selection of Patients

Between December 1982 and December 1997, 1230 patients underwent endomyocardial biopsy as part of an evaluation for heart failure due to unexplained cardiomyopathy. The majority of these patients were referred by other physicians, and thus some common but easily identified causes of heart failure, such as ischemic heart disease, hypertension, and valvular heart disease, were underrepresented. In addition to endomyocardial biopsy, all the patients underwent a careful history taking and physical examination; selected laboratory studies, including thyroid-function testing and measurement of antinuclear antibodies; and right-heart catheterization. All patients with a history suggestive of ischemic heart disease or at least two standard risk factors for atherosclerosis underwent coronary angiography. We recently reported detailed clinical characteristics of this cohort of patients and the safety of endomyocardial biopsy in this cohort.¹¹ The study was

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approved by the Joint Committee on Clinical Investigation at Johns Hopkins Hospital. Oral informed consent to include their data in the study was obtained from the patients.

Endomyocardial Biopsy

All the patients underwent endomyocardial biopsy and right-heart catheterization in a standardized manner, as previously described.¹¹ Specimens were examined at a minimum of four section levels by an experienced cardiac pathologist. Staining with Congo red to identify amyloidosis and with Prussian blue to identify hemochromatosis was performed when appropriate.

Cause of Cardiomyopathy

All patients were prospectively assigned an underlying cause of cardiomyopathy at the completion of the clinical evaluation, according to previously published definitions.^{8,11} The diagnostic classification was based on the recommendations of the World Health Organization–International Society and Federation of Cardiology Task Force for the classification of cardiomyopathy, as originally defined in 1980 and as modified in 1996.^{12,13} In patients for whom there was more than one potential cause of heart failure, the single most likely cause was chosen. Final diagnoses were assigned without knowledge of the patients’ status with respect to long-term survival or cardiac transplantation. For the purposes of analysis, patients were assigned to one of the following categories according to the underlying cause of the cardiomyopathy: idiopathic cardiomyopathy; peripartum cardiomyopathy; or cardiomyopathy due to ischemic heart disease, infiltrative myocardial disease (i.e., amyloidosis, hemochromatosis, or sarcoidosis), myocarditis, substance abuse (i.e., cocaine or alcohol abuse), connective-tissue disease, infection with the human immunodeficiency virus (HIV), hypertension, therapy with doxorubicin, or other causes.

Follow-up

Information on the vital status of the patients was obtained from clinical records and through a search of the National Death Index.¹⁴ The status of the patients with respect to cardiac transplantation was obtained from their clinical records.

Statistical Analysis

Comparisons among groups were made with the use of Student’s t-test for continuous variables and the chi-square test for categorical variables. Since many of the patients in this study would have been classified as having idiopathic cardiomyopathy if they had not undergone a rigorous diagnostic evaluation, each diagnostic group was compared with the group of patients with idiopathic cardiomyopathy (the reference group). The primary end point was death from all causes. Data on patients who underwent cardiac transplantation were censored at the time of transplantation. Survival curves were constructed according to the method of Kaplan and Meier. Multivariate Cox proportional-hazards modeling was used to adjust for demographic and hemodynamic variables. The following prespecified variables were tested in the multivariate model: cause of cardiomyopathy, age, sex, race, heart rate, pulse pressure, cardiac index, pulmonary-artery systolic blood pressure, and pulmonary-capillary wedge pressure. A two-sided P value of less than 0.05 was considered to indicate statistical significance.

RESULTS

Causes of Cardiomyopathy

A specific cause of cardiomyopathy was identified in 614 of the 1230 patients (50 percent). The remaining 616 patients were classified as having idiopathic cardiomyopathy despite having undergone a comprehensive clinical evaluation. Endomyocardial biopsy provided a specific histologic diagnosis in 188 patients (15 percent). Specific diagnoses for all 1230

patients are shown in Table 1. The complication rate of endomyocardial biopsy was 8 percent, and there were two procedure-related deaths (0.2 percent).

Characteristics of the Patients

The clinical and hemodynamic characteristics of the patients, according to the cause of cardiomyopathy, are shown in Table 2. There was substantial heterogeneity among the groups with regard to age,

TABLE 1. FINAL DIAGNOSES IN 1230 PATIENTS WITH INITIALLY UNEXPLAINED CARDIOMYOPATHY.

DIAGNOSIS	NUMBER (%)
Idiopathic cardiomyopathy	616 (50)
Myocarditis	111 (9)
Ischemic heart disease	91 (7)
Cardiomyopathy due to infiltrative myocardial disease	59 (5)
Amyloidosis	36
Sarcoidosis	14
Hemochromatosis	9
Peripartum cardiomyopathy	51 (4)
Cardiomyopathy due to hypertension	49 (4)
Cardiomyopathy due to infection with the human immunodeficiency virus	45 (4)
Cardiomyopathy due to connective-tissue disease	39 (3)
Scleroderma	12
Systemic lupus erythematosus	9
Marfan’s syndrome	3
Polyarteritis nodosum	3
Dermatomyositis or polymyositis	3
Nonspecific connective-tissue disease	3
Ankylosing spondylitis	2
Rheumatoid arthritis	1
Relapsing polychondritis	1
Wegener’s granulomatosis	1
Mixed connective-tissue disease	1
Cardiomyopathy due to substance abuse	37 (3)
Chronic alcohol abuse	28
Cocaine abuse	9
Cardiomyopathy due to doxorubicin therapy	15 (1)
Cardiomyopathy due to other causes	117 (10)
Restrictive cardiomyopathy	28
Familial cardiomyopathy	25
Valvular heart disease	19
Endocrine dysfunction	
Thyroid disease	7
Carcinoid	2
Pheochromocytoma	1
Acromegaly	1
Neuromuscular disease	7
Neoplastic heart disease	6
Congenital heart disease	4
Complication of coronary-artery bypass surgery	4
Radiation	3
Critical illness	3
Endomyocardial fibroelastosis	1
Thrombotic thrombocytopenic purpura	1
Rheumatic carditis	1
Drug therapy (not including doxorubicin)	
Leukotrienes	2
Lithium	1
Prednisone	1
Total	1230 (100)

TABLE 2. CLINICAL AND HEMODYNAMIC CHARACTERISTICS ACCORDING TO CAUSE OF CARDIOMYOPATHY.*

CHARACTERISTIC	ALL CAUSES (N=1230)	IDIOPATHIC CARDIOMYOPATHY (N=616)	PERIPARTUM CARDIOMYOPATHY (N=51)	INFILTRATIVE MYOCARDIAL DISEASE (N=59)	DOXORUBICIN THERAPY (N=15)	HIV INFECTION (N=45)	ISCHEMIC HEART DISEASE (N=91)	MYOCARDITIS (N=111)	HYPERTENSION (N=49)	CTD (N=39)	SUBSTANCE ABUSE (N=37)	OTHER (N=117)
Sex (%)												
Male	60	62	NA	68	13†	83†	77†	59	58	31†	81†	59
Female	40	38	100	32	87	17	23	41	42	69	19	41
Race (%)												
White	63	65	53	68	60	22†	82	70	36	49	32	72
Nonwhite	37	35	47	32	40	78	18	30	64	51	68	28
Age (yr)	48±15	49±14	29±7†	56±12†	52±10	38±9†	56±13†	41±15†	49±13	46±16	41±10†	49±15
Heart rate (beats/min)	89±20	89±20	89±23	82±16†	89±32	100±22†	89±17	89±23	89±15	87±16	93±24	85±18
Pulse pressure (mm Hg)	48±20	48±19	42±14†	42±15†	37±12†	43±12†	45±19	47±19	61±20†	50±32	42±20	51±22
Cardiac index (liters/min/m ²)	2.3±0.7	2.3±0.7	2.4±0.7	2.1±0.8	1.8±0.6†	2.9±0.9†	2.0±0.5†	2.4±0.6	2.5±0.7†	2.2±0.6	2.2±0.7	2.2±0.6
Left ventricular stroke-work index (g/m/m ²)	28±13	28±13	30±12	25±14	19±10†	34±16†	23±8†	30±15	35±12†	29±13	25±10	29±12
Pulmonary-capillary wedge pressure (mm Hg)	17±9	17±9	14±9†	18±8	16±9	12±8†	19±10†	15±9	17±9	16±9	20±8†	18±10
Pulmonary-artery systolic blood pressure (mm Hg)	39±16	39±16	34±14†	44±15†	39±12	31±14†	43±17†	35±14†	42±17	38±13	43±14	42±18

*Plus-minus values are means ±SD. HIV denotes human immunodeficiency virus, CTD connective-tissue disease, and NA not applicable.

†P<0.05 for the comparison with idiopathic cardiomyopathy.

sex, and severity of hemodynamic compromise. The mean age of the study cohort at the time of diagnosis was 48 years. The patients with cardiomyopathy due to ischemic heart disease and those with cardiomyopathy due to infiltrative myocardial disease were significantly older than those with idiopathic cardiomyopathy, whereas the patients with HIV infection, myocarditis, substance abuse, or peripartum cardiomyopathy were younger.

Association between Cause and Outcome

During a mean follow-up period of 4.4 years, 417 patients died and 57 underwent cardiac transplantation. Unadjusted and adjusted hazard ratios for each etiologic group, as compared with the group with idiopathic cardiomyopathy (in which the hazard ratio for death was 1.0, by definition), are provided in Table 3. In the unadjusted analysis, survival was substantially better among the patients with peripartum cardiomyopathy than among those with idiopathic cardiomyopathy (hazard ratio for death, 0.14; 95 percent confidence interval, 0.05 to 0.44; P=0.001). In contrast, survival was significantly worse among the patients with cardiomyopathy due to infiltrative myocardial diseases (hazard ratio, 4.79; 95 percent confidence interval, 3.36 to 6.81; P<0.001), HIV infection (hazard ratio, 4.00; 95 percent confidence interval,

2.80 to 5.74; P<0.001), therapy with doxorubicin (hazard ratio, 2.64; 95 percent confidence interval, 1.35 to 5.17; P=0.005), and ischemic heart disease (hazard ratio, 2.01; 95 percent confidence interval, 1.46 to 2.77; P<0.001). Survival among the patients with cardiomyopathy due to myocarditis, substance abuse, hypertension, connective-tissue disease, or other causes did not differ significantly from that among patients with idiopathic cardiomyopathy.

To adjust for differences between groups, we performed multiple Cox proportional-hazards analyses. The inclusion of age, sex, race, and hemodynamic variables with underlying cause in a multivariate model did not substantively alter the association between cause and prognosis. Adjusted estimates of survival for the groups that were significantly different from the group with idiopathic cardiomyopathy are shown in Figure 1. Older age (hazard ratio for death associated with each additional decade of life, 1.20; 95 percent confidence interval, 1.10 to 1.30; P<0.001) and male sex (hazard ratio, 1.26; 95 percent confidence interval, 1.00 to 1.60; P=0.05) were associated with worse survival than younger age and female sex (Table 3). After the inclusion of prespecified hemodynamic variables in the multivariate model, a previous trend toward worse survival in patients with cardiomyopathy due to connective-tissue disease reached

TABLE 3. ASSOCIATION BETWEEN CLINICAL VARIABLES AND SURVIVAL.*

VARIABLE	UNADJUSTED ANALYSIS		MULTIVARIATE ANALYSIS	
	HAZARD RATIO FOR DEATH (95% CI)	P VALUE	HAZARD RATIO FOR DEATH (95% CI)	P VALUE
Cause				
Idiopathic cardiomyopathy†	1.00		1.00	
Peripartum cardiomyopathy	0.14 (0.05–0.44)	0.001	0.31 (0.09–0.98)	0.05
Cardiomyopathy due to hypertension	0.69 (0.35–1.35)	0.28	0.74 (0.36–1.52)	0.42
Cardiomyopathy due to myocarditis	0.74 (0.49–1.10)	0.13	1.05 (0.67–1.61)	0.82
Cardiomyopathy due to other causes	1.21 (0.85–1.72)	0.28	1.30 (0.89–1.91)	0.18
Cardiomyopathy due to connective-tissue disease	1.44 (0.85–2.43)	0.18	1.75 (1.02–3.01)	0.04
Cardiomyopathy due to substance abuse	1.45 (0.88–2.38)	0.15	1.41 (0.79–2.53)	0.25
Cardiomyopathy due to ischemic heart disease	2.01 (1.46–2.77)	<0.001	1.52 (1.07–2.17)	0.02
Cardiomyopathy due to doxorubicin therapy	2.64 (1.35–5.17)	0.005	3.46 (1.67–7.18)	0.001
Cardiomyopathy due to HIV infection	4.00 (2.80–5.74)	<0.001	5.86 (3.92–8.77)	<0.001
Cardiomyopathy due to infiltrative myocardial disease	4.79 (3.36–6.81)	<0.001	4.40 (3.04–6.39)	<0.001
Demographic characteristics				
Age (each additional decade of life)			1.20 (1.10–1.30)	<0.001
Male sex			1.26 (1.00–1.60)	0.05
White race			0.98 (0.78–1.23)	0.88
Hemodynamic characteristics				
Pulse pressure (each increment of 5 mm Hg)			0.97 (0.94–1.00)	0.04
Heart rate (each increment of 10 beats/min)			1.05 (0.99–1.11)	0.13
Pulmonary-artery systolic blood pressure (each increment of 5 mm Hg)			1.11 (1.04–1.17)	0.001
Pulmonary-capillary wedge pressure (each increment of 5 mm Hg)			1.00 (0.91–1.11)	0.93
Cardiac index (each increment of 1 liter/min/m ²)			0.94 (0.78–1.13)	0.53

*In multivariate analysis, survival was adjusted for demographic and hemodynamic characteristics. CI denotes confidence interval, and HIV human immunodeficiency virus.

†Idiopathic cardiomyopathy served as the reference category.

statistical significance (adjusted hazard ratio for death, 1.75; 95 percent confidence interval, 1.02 to 3.01; $P=0.04$). As shown in Table 3, the following variables were independently associated with survival in a multivariate model: cause (with the exception of hypertension, myocarditis, other causes, and substance abuse), age, sex, pulse pressure, and pulmonary-artery systolic pressure.

Several alternative analyses were performed to test the validity of these results. To confirm the results in the group with peripartum cardiomyopathy, we repeated the multivariate analysis with age considered as a categorical variable in 10-year increments rather than as a continuous variable. In this analysis, the improved survival in the group with peripartum cardiomyopathy persisted (adjusted hazard ratio, 0.28; 95 percent confidence interval, 0.08 to 0.91; $P=0.04$). To evaluate the potential effect of improvements in medical therapy for heart failure over time, the multivariate analysis was repeated with the inclusion of the calendar year of diagnosis, in five-year increments. This analysis revealed a trend toward improved survival over time (adjusted hazard ratio as compared with diagnosis in 1983 to 1987: diagnosis in 1988 to 1992,

0.88; and diagnosis in 1993 to 1997, 0.81) that did not reach statistical significance.

To assess the effect of cardiac transplantation, we reanalyzed the data using the combined end point of death or cardiac transplantation. In this alternative analysis, the associations between specific causes of cardiomyopathy and prognosis were unchanged, with the exception that cardiomyopathy due to connective-tissue disease was no longer significant (adjusted hazard ratio for death or transplantation, 1.44; 95 percent confidence interval, 0.84 to 2.27; $P=0.18$). Multivariate modeling in which transplantation-free survival was used as an end point produced results that were similar to those of the analysis of absolute survival, with cause (with the exception of hypertension, myocarditis, ischemic heart disease, other causes, and substance abuse), age, sex, pulse pressure, and pulmonary-artery systolic blood pressure remaining as independent predictors of survival.

Analysis of Cardiomyopathy Due to Infiltrative Myocardial Disease

Because the group with cardiomyopathy due to infiltrative myocardial disease was composed of pa-

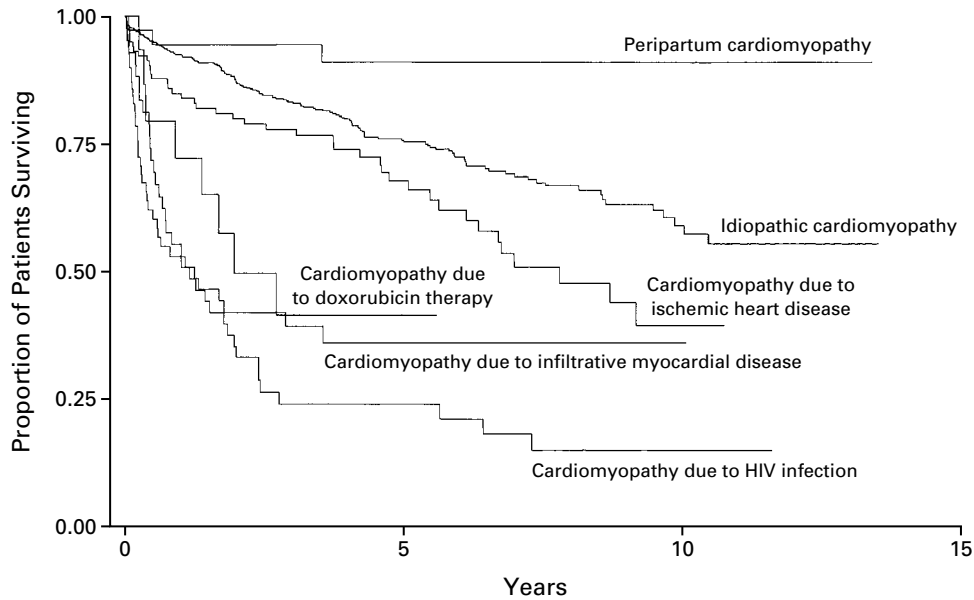


Figure 1. Adjusted Kaplan–Meier Estimates of Survival According to the Underlying Cause of Cardiomyopathy. Only idiopathic cardiomyopathy and cardiomyopathy due to causes for which survival was significantly different from that in patients with idiopathic cardiomyopathy are shown.

tients with three distinct histologic diagnoses (amyloidosis, hemochromatosis, and sarcoidosis), each of these causes was analyzed separately. After adjustments were made for demographic and hemodynamic variables, survival was found to be markedly worse among the patients with amyloidosis (adjusted hazard ratio for death, 7.41; 95 percent confidence interval, 4.45 to 12.33; $P < 0.001$) or hemochromatosis (adjusted hazard ratio, 8.88; 95 percent confidence interval, 3.64 to 21.65; $P < 0.001$) than among those with idiopathic cardiomyopathy. The prognosis in patients with sarcoidosis was not significantly different from that in the patients with idiopathic cardiomyopathy (adjusted hazard ratio, 1.72; 95 percent confidence interval, 0.69 to 4.27; $P = 0.24$). The adjusted survival curves for the patients with cardiomyopathy due to infiltrative myocardial disease are shown in Figure 2.

DISCUSSION

This study examined the association between the specific cause of cardiomyopathy and long-term survival in a large group of patients evaluated at a single tertiary care center with expertise in the diagnosis and treatment of cardiomyopathy. The patients with peripartum cardiomyopathy had the best prognosis of any subgroup and were the only group to have a significantly better rate of survival than the patients with idiopathic cardiomyopathy. As compared with the patients with idiopathic cardiomyopathy, the pa-

tients with cardiomyopathy due to infiltrative myocardial disease, HIV infection, therapy with doxorubicin, or ischemic heart disease had significantly worse survival in the unadjusted analysis. After multivariate adjustment, the patients with cardiomyopathy due to connective-tissue disease also had significantly worse survival. We did not find a significant difference in survival between the patients with idiopathic cardiomyopathy and those with cardiomyopathy due to myocarditis, hypertension, substance abuse, or other causes.

In our study, the patients with peripartum cardiomyopathy had a substantially better prognosis than those with other causes of heart failure, with a 94 percent survival rate at five years. Peripartum cardiomyopathy is, by definition, a disease that affects young women, and the mean age of the patients with this diagnosis was substantially younger than that of the patients with idiopathic cardiomyopathy (29 years as compared with 49 years). Even after adjustments were made for differences in age and sex, however, the prognosis among the patients with peripartum cardiomyopathy remained better than that of the other groups. In addition, a substantial portion of the patients with peripartum cardiomyopathy (26 of 51 patients) had histologic evidence of myocarditis on endomyocardial biopsy. These findings are in contrast to those of previous studies, which generally described poor outcomes and a low incidence of myocarditis in patients with peripartum cardiomyopathy.^{15,16} The stricter diagnostic definition of peripar-

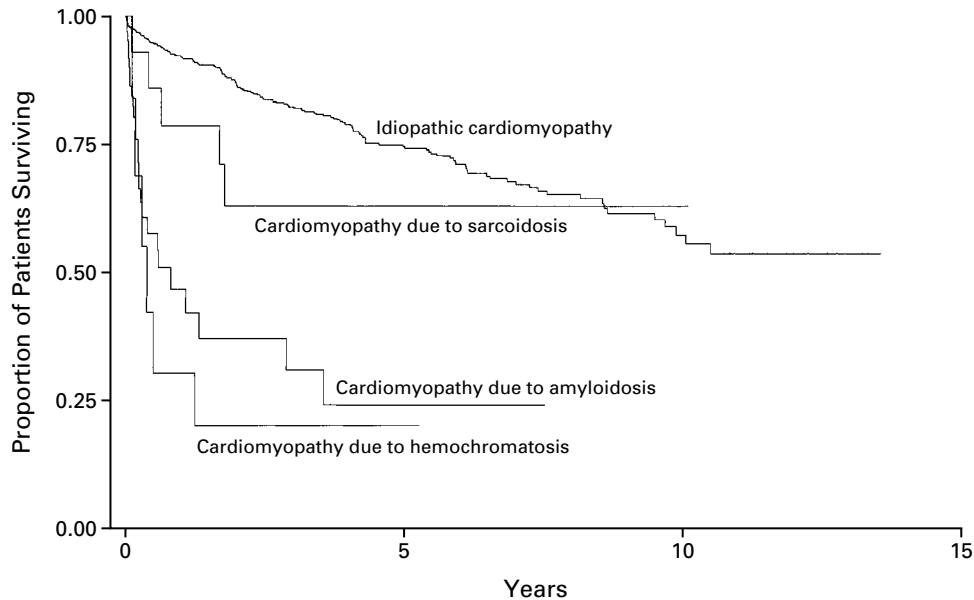


Figure 2. Adjusted Kaplan–Meier Estimates of Survival among Patients with Cardiomyopathy Due to Amyloidosis, Sarcoidosis, or Hemochromatosis, as Compared with That among Patients with Idiopathic Cardiomyopathy.

tum cardiomyopathy used in our study may account for the difference in results.

The worst prognosis was in the group with cardiomyopathy due to infiltrative myocardial disease, which included patients with cardiac amyloidosis, sarcoidosis, or hemochromatosis. Further analysis of this subgroup indicated extremely poor long-term survival among the patients with amyloidosis and hemochromatosis, with one-year survival rates of 29 percent and 44 percent, respectively. Poor survival in patients with cardiac amyloidosis has been reported previously.¹⁷ In contrast, the patients in our study who had cardiac sarcoidosis had a prognosis similar to that of the patients with idiopathic cardiomyopathy, with a one-year survival rate of 77 percent. The natural history of cardiac sarcoidosis thus appears to be markedly different from that of giant-cell myocarditis, a rare disorder that may be confused with sarcoidosis on histologic examination. Recently published data confirm the extremely poor prognosis of patients with giant-cell myocarditis, who have a one-year survival rate of less than 40 percent.¹⁸

High mortality among patients with amyloidosis, hemochromatosis, HIV infection, or doxorubicin cardiotoxicity can be partially attributed to noncardiac causes, since each of these disorders may be associated with decreased long-term survival independently of the diagnosis of cardiomyopathy. Improvements in specific therapies for both HIV infection and cancer, however, may make the cardiomyopathy that is associated with these conditions more prevalent as patients survive longer with their primary illness. Re-

gardless of the cause of death, these data demonstrate the extremely poor prognosis associated with cardiomyopathy due to these disorders and the potential prognostic value of identifying a specific cause of heart failure in patients who present with unexplained cardiomyopathy.

Ischemic as Compared with Nonischemic Cardiomyopathy

In this study, survival was worse among the patients with cardiomyopathy due to ischemic heart disease than among those with idiopathic cardiomyopathy. This finding is consistent with the results of most previous studies, which have demonstrated a worse prognosis in patients with ischemic cardiomyopathy than in those with other causes of heart failure.^{2,7,19,20} In addition, in the placebo groups of several large trials of therapy for heart failure, higher mortality has been found among patients with an ischemic cause of heart failure than among patients with a nonischemic cause.^{21–23} These findings contrast, however, with those of the community-based Framingham Heart Study, which found worse long-term survival among patients with nonischemic causes of heart failure.⁶ In our study, hemodynamic compromise was greater in the patients with cardiomyopathy due to ischemic heart disease than in those with idiopathic cardiomyopathy, suggesting that the patients with ischemic heart disease may have had more advanced heart failure at the time of evaluation.

Even after adjustments were made for demographic and hemodynamic variables, however, survival was worse among patients with cardiomyopathy due to

ischemic heart disease. Because so many of the patients with easily identifiable causes of heart failure, such as ischemic disease and hypertension, were not referred to our study, patients with such causes were underrepresented in our cohort, as compared with a general population of patients with heart failure. The patients in our study with cardiomyopathy due to ischemic heart disease may therefore have differed from those seen in a community setting. Still, our findings support the general conclusion that patients with cardiomyopathy due to ischemic heart disease have a worse prognosis than do patients with nonischemic causes of cardiomyopathy.

Previous Studies of Cause and Prognosis

Previous studies that have addressed the prognostic importance of the underlying cause of cardiomyopathy have generally categorized patients according to whether they had ischemic or nonischemic causes of heart failure. The lack of specific information about the cause of heart failure in patients with cardiomyopathy due to nonischemic causes is a limitation of such studies. Our study differs from others in that we performed an exhaustive clinical evaluation of each patient, including endomyocardial biopsy, in order to identify the cause of cardiomyopathy as precisely as possible. Our study also included a much more heterogeneous population of patients with regard to cause of cardiomyopathy than did either the Framingham Study⁶ or the Studies of Left Ventricular Dysfunction (SOLVD) registry.¹⁹ Because of the large size of the study cohort and the fact that all the patients had been referred to our center, we were able to provide data on long-term survival in patients with cardiomyopathy due to many relatively rare nonischemic causes; such patients are often excluded from randomized trials of therapy for heart failure.

The proportions of both women and members of minority groups were higher in our series than in many previous studies of heart failure. Forty percent of the patients in our study were women, and 34 percent were black, as compared with 26 percent and 12 percent, respectively, in the SOLVD registry.¹⁹ When considered along with cause, age, and race, sex was an independent predictor of prognosis in this cohort, with men having worse survival than women. This trend persisted ($P=0.05$) after additional adjustment for hemodynamic variables. These findings are in general agreement with epidemiologic data from the Framingham Study and the first National Health and Nutrition Examination Survey (NHANES I), which demonstrated better prognosis among women with heart failure than among men.^{1,6} Work by Adams and colleagues suggested that these sex differences are most pronounced among patients with nonischemic causes of heart failure.^{7,24} The results of our study in a cohort of patients with primarily nonischemic cardiomyopathy lend further support to this finding.

Limitations of the Study

The applicability of our results to the general population of patients with heart failure is limited by the referral nature of this cohort. Patients with some common causes of cardiomyopathy were not referred for an exhaustive evaluation, including endomyocardial biopsy, and thus were underrepresented in our cohort. In addition, data on the cause of death of the patients were not obtained, and we were therefore unable to differentiate between deaths due to cardiac causes and other deaths. Clearly, survival among patients with cardiomyopathy due to HIV infection, infiltrative myocardial disease, or doxorubicin therapy may be limited by the primary illness. Drug therapy for heart failure was not controlled for during this study, so we are unable to speculate on the extent to which differences in therapy for heart failure may have affected our results, although a trend toward improved survival was seen in patients who received a diagnosis more recently, as compared with those who received a diagnosis earlier. Because of the methods used to establish vital status, it is possible that some patients who were lost to clinical follow-up may have been classified incorrectly as long-term survivors if they were not identified during a search of the National Death Index. The accuracy of the National Death Index has been externally validated, but up to 5 percent of persons who have died may be missing, particularly women and members of minority groups.²⁵

Conclusions

Our study demonstrates that the underlying cause of heart failure is independently associated with survival among patients with certain types of cardiomyopathy. Whereas peripartum cardiomyopathy had a better long-term prognosis than idiopathic cardiomyopathy, cardiomyopathy due to infiltrative diseases of the myocardium, HIV infection, doxorubicin therapy, ischemic heart disease, and connective-tissue disease were associated with worse survival. Among patients with cardiomyopathy due to infiltrative myocardial disease, those with amyloidosis or hemochromatosis had the worst prognosis, whereas patients with sarcoidosis had a prognosis similar to that of patients with idiopathic cardiomyopathy. As in previous studies, older age and male sex were associated with a worse prognosis than younger age and female sex.

We conclude that the identification of the underlying cause of heart failure, beyond the differentiation between ischemic and nonischemic causes, has prognostic importance, primarily for patients with peripartum cardiomyopathy and those with cardiomyopathy due to infiltrative myocardial disease, doxorubicin therapy, or HIV infection. The evaluation of patients with unexplained cardiomyopathy should include a careful search for a specific cause, and the referral of patients to a tertiary care center may facilitate the accurate assessment of prognosis. Further under-

standing of the prognostic and therapeutic importance of the specific cause of cardiomyopathy may aid in tailoring available therapies to individual patients.

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