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CLINICAL STUDIES

HEART FAILURE

Prediction of Improvement in Recent Onset Cardiomyopathy After Referral for Heart Transplantation

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Objectives. The purpose of this investigation was to determine how often left ventricular function improves in recent onset dilated cardiomyopathy of sufficient severity to cause referral for heart transplantation and how to predict this improvement at the time of evaluation for transplantation.

Background. Improvement has been reported to occur frequently in patients with acute dilated cardiomyopathy but has not been described specifically in these patients referred for transplantation. To avoid potentially needless transplantation, it would be useful to know the frequency of improvement and how to predict it in these patients.

Methods. A consecutive series of 297 patients with primary dilated cardiomyopathy evaluated for heart transplantation was reviewed to identify those with onset of heart failure symptoms within the preceding 6 months and to examine their outcome. The clinical, echocardiographic, hemodynamic and laboratory profiles of patients with improvement in left ventricular function (defined as an increase in left ventricular ejection fraction ≥0.15 to a final ejection fraction of ≥0.30) were compared with those of patients without improvement to assess which variables might predict improvement.

Results. Of 49 patients with recent onset dilated cardiomyopathy, 13 (27%) showed improvement, with an increase in mean left ventricular ejection fraction from 0.22 ± 0.08 to 0.49 ± 0.09. All patients with improvement had survived without heart transplantation at 43 ± 29 months. Survival time was shorter in the remaining 36 patients without improvement with recent onset cardiomyopathy than in the 248 with chronic symptoms ($p = 0.03$) and in younger compared with older patients with recent onset cardiomyopathy ($p = 0.0001$). By multivariate analysis, predictors of improvement were shorter duration of symptoms, lower pulmonary wedge and right atrial pressures and higher serum sodium levels.

Conclusions. A minority of patients with dilated cardiomyopathy and symptoms for ≤6 months will have marked improvement in left ventricular function, after which prognosis is excellent despite previous referral for heart transplantation. Those with symptom duration >3 months and more severe initial decompensation as reflected by higher filling pressures and lower serum sodium levels are unlikely to show improvement and may require earlier consideration for heart transplantation.

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In patients presenting with recent onset dilated cardiomyopathy, subsequent improvement in left ventricular function has been reported in up to 37% (1). However, the frequency of improvement is not known for those with recent onset cardiomyopathy of sufficient severity to require evaluation for cardiac transplantation. Factors associated with improvement, which could be used to identify patients who are likely to regain ventricular function and do well on medical therapy, are also unknown. Avoiding cardiac transplantation in these patients is important to spare them the risks of rejection and immunosuppression and allow better allocation of the limited number of donor hearts. Therefore, the relation among clinical characteristics, hemodynamic variables and outcome were reviewed in patients with recent onset dilated cardiomyopathy referred for transplantation. The purpose of this investigation was to determine how often left ventricular function improves and how to predict that improvement at the time of evaluation.

Methods

Study patients. The registry of all patients undergoing complete evaluation for cardiac transplantation at the University of California, Los Angeles (UCLA) between January 1983 and June 1992 was reviewed to identify patients with recent onset dilated cardiomyopathy. Dilated cardiomyopathy was defined as a left ventricular ejection fraction ≤0.45 in the absence of significant coronary artery disease or

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primary restrictive, hypertrophic, infiltrative, valvular or chemotherapy-induced cardiomyopathy. Patients with antecedent viral syndromes, peripartum cardiomyopathy, history of hypertension, diabetes or heavy alcohol use were included because in an individual patient it is often unclear whether these risk factors cause, exacerbate or have no relation to the development of cardiomyopathy (2). Dilated cardiomyopathy was defined as of recent onset if heart failure symptoms were first noted within the 6 months before evaluation. Patients with known cardiomegaly of >6 months' duration were not considered to have recent onset cardiomyopathy regardless of symptom duration. The original medical records of patients identified as having recent onset cardiomyopathy were reviewed to confirm clinical features, duration of symptoms, absence of excluding diagnoses and endomyocardial biopsy results.

Initial evaluation. Evaluation for heart transplantation included pulmonary artery catheterization with measurement of cardiac output and ventricular filling pressures. Left ventricular ejection fraction and dimensions were determined by two-dimensional echocardiography in all patients, except two who had baseline and follow-up measurements of ejection fraction by radionuclide angiography because echocardiography was technically difficult. Neither of these patients had a significant change in ejection fraction over time. Baseline clinical, echocardiographic, hemodynamic and laboratory data were recorded at the time of transplant evaluation. Endomyocardial biopsy procedures were obtained either at UCLA or by the referring physicians in all patients presenting with recent onset of symptoms, except those believed to be at high risk for complications. The pathologic specimens for biopsies performed elsewhere and reported as positive for myocarditis were reviewed at UCLA and classified by the Dallas criteria (3).

Patients were treated with vasodilators tailored to hemodynamic goals at the time of evaluation and were taught management of low salt diets and self-adjustment of diuretic drugs on the basis of daily weight. Patients had subsequent follow-up at intervals of 1 week to 3 months, depending on severity of illness and involvement of the referring physician. Repeat echocardiograms were performed at intervals of 6 to 12 months when possible.

Outcomes. Outcomes included death, cardiac transplantation, survival without improvement and improvement. All patients were followed up for ≥1 year or to death or cardiac transplantation, except for one patient who showed improvement at 8 months and was then lost to follow-up. Patients who died or underwent transplantation before repeat echocardiography were considered to be without major improvement. In patients who survived without cardiac transplantation, improvement was defined as an increase in left ventricular ejection fraction ≥0.15 to a final ejection fraction ≥0.30.

Data analysis. Analysis included the clinical variables of age, New York Heart Association functional class, symptom duration before evaluation, the baseline echocardiographic variables of left ventricular ejection fraction, left ventricular end-diastolic dimension and mitral regurgitation, the initial hemodynamic variables of heart rate, cardiac output, mean arterial and right atrial and pulmonary capillary wedge pressures and serum sodium levels at presentation. Variables were evaluated for their association with the outcome of improvement in recent onset cardiomyopathy by univariate analysis. Variables with a p value < 0.10 by univariate analysis were entered into a stepwise logistic regression that retained all independent variables with a p value < 0.10 (4). The same variables were assessed for their association with survival. Variables significant with a p value < 0.10 by univariate analysis were entered into a Cox proportional hazards regression model that retained independent variables with a p value < 0.10 (3). The actuarial survival rate was calculated using the Kaplan-Meier product limit estimate with transplant candidates being censored at the time of transplantation; survival between groups was compared by the Mantel-Cox statistic. Proportions were compared using the chi-square test. Group averages are expressed as the mean value ± SD.

Results

During the period reviewed, 49 patients with recent onset dilated cardiomyopathy were evaluated. Criteria for improvement were met in 13 (27%) of these, who had an increase in left ventricular ejection fraction from 0.22 ± 0.08 to 0.49 ± 0.09 (mean increase 0.27 ± 0.08). This increase in ejection fraction was associated with a decrease in left ventricular end-diastolic dimension from 67 ± 8 to 59 ± 6 mm ($p = 0.0005$) and in mitral regurgitation on a 0 to 3 scale from 1.3 ± 0.7 to 0.6 ± 0.7 ($p = 0.03$). All patients with improvement were alive at a follow-up interval of 43 ± 29 months (range 8 to 112). Eight of these patients had serial echocardiograms after their ejection fraction had increased and none showed subsequent deterioration.

Of the 36 patients who did not meet criteria for improvement, 18 died at a mean of 11 ± 14 months after evaluation (nine sudden deaths, eight deaths attributed to hemodynamic decompensation, one unspecified), 13 underwent cardiac transplantation at 11 ± 16 months and 5 (14%) were alive after 27 ± 22 (range 13 to 70) months of follow-up. Patients with recent onset cardiomyopathy surviving 1 year without improvement remained at risk for late deterioration; of the 16 patients alive but without improvement at 1 year, 6 died, 3 underwent cardiac transplantation, 5 remained alive but without improvement and 2 had subsequent improvement (Fig. 1). Among the patients who did not have documented improvement, 12 of 31 patients who died or underwent cardiac transplantation and all 5 who were alive at the end of the follow-up period were followed up for a sufficient period to have a repeat echocardiogram. The largest increase in left ventricular ejection fraction in this unimproved group was from 0.16 to 0.27, whereas the mean change was only +0.02 (Fig. 2). Change in left ventricular ejection fraction did not

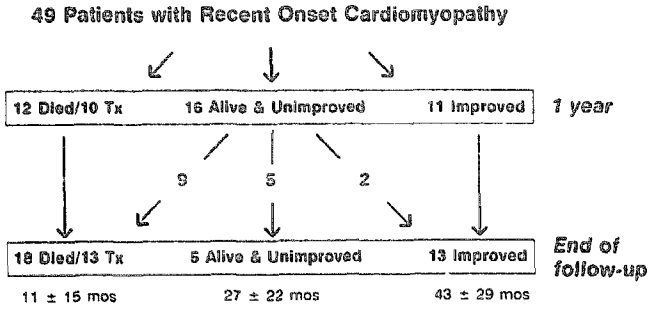


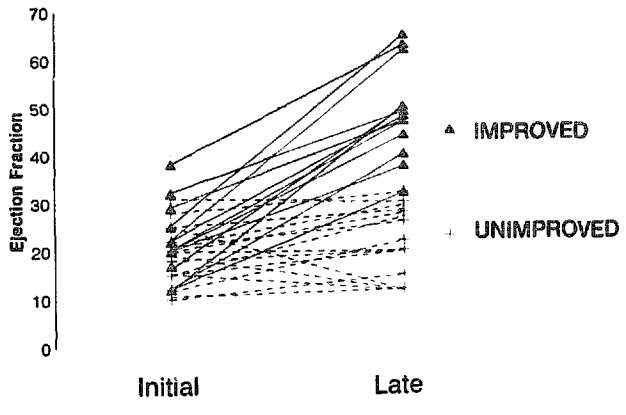
Figure 1. Outcome at 1 year and at the end of follow-up for 49 patients with recent onset dilated cardiomyopathy evaluated for cardiac transplantation (Tx). Of 16 patients alive without improvement at 1 year, 9 patients died or underwent transplantation, 5 remained alive without improvement, and 2 had late improvement.

vary continuously. Those patients who had an increase in ejection fraction tended to have a large increase, whereas those who did not meet the study criteria for improvement tended to have very little change; therefore, the exact definition of improvement did not greatly alter how patients were classified.

In the majority of patients, the ejection fraction had increased by the time of the second echocardiogram (8 ± 6 months). However, in four patients with later improvement, earlier echocardiograms at 5, 7, 15 and 17 months showed little increase in left ventricular ejection fraction, documenting that late improvement could occur.

The clinical and hemodynamic profiles of the 13 patients with improvement and the 36 patients without improvement in recent onset dilated cardiomyopathy are compared in Table 1. Both groups were young and had a similar frequency of viral symptoms, history of heavy alcohol use, peripartum onset, diabetes and hypertension. The initial left ventricular ejection fraction did not differ significantly. Drug therapy during the follow-up period did not differ significantly between the groups with and without improvement; patients in the two groups were treated with vasodilators, nitrates, digoxin, diuretic drugs and type I antiarrhythmic agents with similar frequency. Mitral regurgitation assessed qualitatively by echocardiography tended to be less severe in patients with improvement ($p = 0.06$). Myocarditis according to the Dallas criteria (3) was diagnosed from only 3 (9%) of 35 endomyocardial biopsy specimens in both groups combined.

Figure 2. Initial and late ejection fraction (in %) in 30 patients with recent onset cardiomyopathy, 13 of whom were defined as having improvement (increase in left ventricular ejection fraction ≥15% to a final ejection fraction ≥30%) and 17 of whom had no improvement and survived long enough without death or cardiac transplantation to undergo repeat echocardiography. Improvement was generally either minimal or dramatic. **Solid lines** represent patients defined as improved; **dashed lines** represent patients without improvement.



By univariate analysis, improvement was significantly associated with the presenting profile of shorter duration of symptoms before evaluation, higher cardiac output, lower functional class, smaller initial left ventricular end-diastolic dimension, lower pulmonary capillary wedge and right atrial pressures and higher serum sodium levels (Table 1). By stepwise logistic regression, short symptom duration before evaluation was a strong independent predictor of improvement. Three variables predicted improvement independently of symptom duration: higher serum sodium level and lower right atrial and pulmonary capillary wedge pressures. Neither cardiac output nor functional class was an independent predictor. Right atrial and pulmonary capillary wedge pressure were highly correlated ($r = 0.73$) and were thus not independent of one another. The relations among symptom duration, wedge pressure and improvement is graphically displayed in Figure 3. Of the 13 patients with improvement, 10 had lower than mean values for both symptom duration and pulmonary capillary wedge pressure; both of these variables were less than the mean in only 3 of 36 patients without improvement.

Although shorter duration of symptoms was predictive of improvement, it was not an independent predictor of survival. In contrast, lower pulmonary capillary wedge and right atrial pressures and higher serum sodium levels predicted both improvement and survival by multivariate analysis. Older age was also independently predictive of survival but was not associated with improvement. Patients with recent onset cardiomyopathy who were younger than average (<33 years old) had only a 32% survival rate at 2 years compared with a 90% rate for the older patients ($p = 0.0001$, Fig. 4). Differences in drug therapy did not appear to explain the higher survival rate of older patients, who received heart failure medications with a frequency similar to that of younger patients: angiotensin-converting enzyme inhibitors (61% vs. 46%, old vs. young), hydralazine (35% vs. 35%), nitrates (43% vs. 54%), digoxin (57% vs. 38%), diuretic drugs (100% vs. 96%) and type I antiarrhythmic agents (22% vs. 23%) (p = NS for all five drugs).

For purposes of comparison, the survival was examined for the 248 of 297 patients who met the study criteria for dilated cardiomyopathy but who had symptoms for >6 months. The actuarial survival of these patients with chronic cardiomyopathy and patients with recent onset did not differ significantly at 3 years (49% vs. 57%, Fig. 5). Survival remained similar when cardiac transplantation was equated

Table 1. Profiles of 49 Patients With Recent Onset Dilated Cardiomyopathy Evaluated for Heart Transplantation

	With Improvement (n = 13)	Without Improvement (n = 36)	p Value
Age (yr)	35 ± 10	33 ± 12	NS
Male (%)	54	61	NS
Viral prodrome (%)	54	42	NS
Alcohol (%)	8	14	NS
Peripartum (%)	15	14	NS
Myocarditis on biopsy (%)	17 (2/12)	4 (1/24)	NS
Diabetes (%)	0	6	NS
Hypertension (%)	15	3	NS
Therapy during follow-up (%)			
ACEI	54	53	NS
Hydralazine	31	33	NS
Nitrates	38	55	NS
Digoxin	46	50	NS
Diuretic drug	92	100	NS
Type I antiarrhythmic agent	23	22	NS
NYHA functional class	3.1 ± 0.6	3.7 ± 0.7	0.01
Symptom duration (mo)	1.2 ± 0.9	3.2 ± 1.8	0.0005*
Initial LVEF	[illegible]	0.19 ± 0.07	NS
Initial LVEDD (mm)	[illegible]	74 ± 8	0.01
Mitral regurgitation (0 to 3)	[illegible]	2.0 ± 0.9	0.06
Cardiac output (liters/min)	5.2 ± 2.1	3.6 ± 1.6	0.01
PCWP (mm Hg)	16 ± 6	24 ± 8	0.003*
RA (mm Hg)	6 ± 4	13 ± 7	0.002*
Serum sodium (mmol/liter)	139 ± 2	134 ± 6	0.003*

*Independently associated with improvement by multivariate analysis. Data are expressed as mean ± SD or percent of patients. ACEI = angiotensin-converting enzyme inhibitor; LVEDD = left ventricular end-diastolic dimension; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; PCWP = pulmonary capillary wedge pressure; RA = right atrial pressure.

with death as an end point. Survival was then considered separately for the patients with recent onset cardiomyopathy who showed improvement, all of whom survived (survival compared with chronic cardiomyopathy, p = 0.0075), and for those with recent onset cardiomyopathy without improvement, who had a lower survival at 3 years (34%) than that of either the patients with improvement (p = 0.0009) or the patients with chronic cardiomyopathy (p = 0.03).

Figure 3. Distribution of pulmonary capillary wedge pressures (PCWP) and symptom durations before evaluation for heart transplantation in 13 patients with recent onset cardiomyopathy who had improvement and 36 who did not have improvement. The mean wedge pressure (22 mm Hg) and symptom duration (2.7 months) for all 49 patients with recent onset cardiomyopathy are shown by dashed lines.

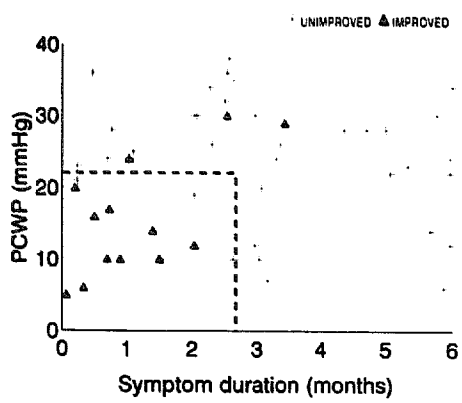
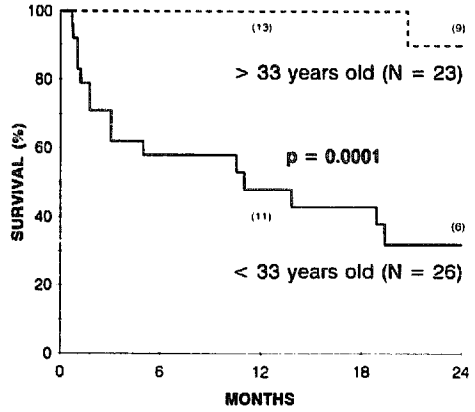


Figure 4. Kaplan-Meier survival curves of patients with recent onset cardiomyopathy who were younger (n = 26) and older (n = 23) than the mean age (33 years).



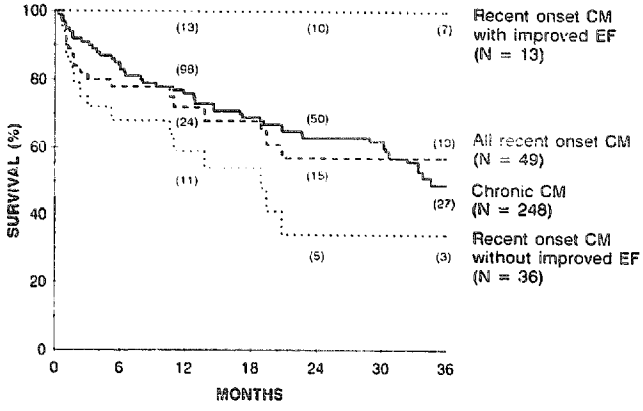


Figure 5. Kaplan-Meier survival curves of 297 patients with primary dilated cardiomyopathy (CM) evaluated for cardiac transplantation. Compared with the survival of patients with chronic cardiomyopathy, the survival of all patients with recent onset cardiomyopathy was not significantly different, whereas the survival was significantly worse for patients who had recent onset cardiomyopathy without later improvement in left ventricular function ($p = 0.03$). Survival for patients with recent onset cardiomyopathy and improvement was better than either survival for patients without improvement ($p = 0.0009$) or survival for patients with chronic cardiomyopathy ($p = 0.0075$, all p values by Mantel-Cox statistic). EF = left ventricular ejection fraction.

Discussion

This study demonstrated that 13 (27%) of 49 patients with recent onset dilated cardiomyopathy had a major improvement in left ventricular function and that all patients with improvement survived despite previous referral for cardiac transplantation. Improvement in left ventricular function was more common in patients with shorter symptom duration before evaluation and less severe clinical decompensation as reflected by hemodynamic values and serum sodium levels. Recent onset cardiomyopathy in younger patients and patients without early improvement was associated with a poorer prognosis than that of chronic cardiomyopathy. The present study is the first to specifically determine improvement and outcome in patients referred for cardiac transplantation with recent onset of cardiomyopathy symptoms.

Frequency of improvement. The potential for left ventricular ejection fraction to improve in dilated cardiomyopathy has been documented in the past (5–12). Most previous reports (8–12) of improvement, however, have been for cardiomyopathy selected for the presence of myocarditis on biopsy rather than for short symptom duration. In these reports, objective improvement in ventricular function has varied in frequency (13,14) but has been noted in >50% (10–12). Because myocarditis has been reported (1) to be more common when heart failure symptoms are acute, the likelihood of improvement in recent onset cardiomyopathy might be expected to be similar to that seen in the presence of myocarditis. However, in the present study, improvement was seen in only 27% of patients with cardiomyopathy for ≤6 months who were referred for cardiac transplantation. Only 9% of patients had myocarditis on biopsy diagnosed by the Dallas criteria (3). This low rate of myocarditis is similar to the rate observed in pooled series of unexplained cardiomyopathy (13) and may have been due to delayed referral. Because patients whose condition improved rapidly may never have been referred for cardiac transplantation, the frequency of improvement observed in this study may be an underestimate of the frequency of improvement in all recent onset cardiomyopathy. Nevertheless, these results indicate that improvement occurs in a minority of patients with recent onset cardiomyopathy evaluated for cardiac transplantation and is less common than is suggested by reports of cardiomyopathy associated with myocarditis. Dec et al. (1) also described improvement in dilated cardiomyopathy selected for recent onset. In 27 patients with unexplained "acute dilated cardiomyopathy" who had symptoms for ≤6 months, improvement was reported in 37% (mean increase in ejection fraction from 0.21 to 0.41). Using equivalent ejection fraction criteria for improvement, the frequency would have been 30%, similar to that in the present study. Although showing a similar rate of improvement, the patients studied by Dec et al. (1) differed in that initial referral was for endomyocardial biopsy rather than for cardiac transplantation and myocarditis was diagnosed in a large proportion (67%). In addition, the prognostic potential of the hemodynamic profile was not explored.

Survival. Although survival with recent onset and chronic cardiomyopathy appeared to be similar, the recent onset group represented a composite of two groups with very different outcomes. The patients with improvement all survived and did not require subsequent cardiac transplantation. In contrast, patients with recent onset cardiomyopathy who did not show improvement were actually less likely to survive than were patients referred after 6 months of symptoms (Fig. 5). Survival without cardiac transplantation, either with or without improvement, could be predicted in patients with recent onset cardiomyopathy by lower cardiac filling pressures (either right atrial or pulmonary capillary wedge pressure), higher serum sodium levels and older age. However, patients with recent onset cardiomyopathy who were alive but without improvement at 1 year remained at high risk for late deterioration; >50% subsequently died or underwent cardiac transplantation (Fig. 1). To safely avoid early cardiac transplantation that later might be unnecessary, it would be important to identify patients with recent onset cardiomyopathy who are likely not only to survive the 1st year but also to have significant recovery of ventricular function that allows long-term survival.

Predictors of improvement. By multivariate analysis, duration of symptoms was a strong independent predictor of improvement; patients with symptoms for >3 months before evaluation were unlikely to regain good ventricular function. This finding suggests that recovery is rare after an extended period of hemodynamic decompensation has caused severe symptoms to persist without clinical improvement, such that referral for cardiac transplantation is still required after 3

months. Nevertheless, recovery of ventricular function could occur late, and a few patients did not increase their ejection fraction until >1 year after referral. In contrast, Dec et al. (1) found no association between symptom duration and improvement and all patients who showed improvement did so within the 1st 6 months. It is important to note that duration of symptoms does not necessarily reflect the actual time since the onset of cardiomyopathy. Asymptomatic ventricular dilation may occur long before the onset of symptoms in some patients, making it more difficult to detect an association between symptom duration and improvement. It is possible that the patients without improvement had a longer period of asymptomatic ventricular dysfunction and therefore their cardiomyopathy was considerably more chronic than suggested by symptom duration. It is not clear whether the results of Dec et al. (1) were related to a greater disparity between overt symptom duration and actual duration of cardiomyopathy, the differing indication for referral, the higher frequency of myocarditis or other intergroup differences. Other investigators (6,7) have found an association between improvement and shorter symptom duration in patients with cardiomyopathy mixed with respect to chronicity.

Either lower pulmonary capillary wedge or lower right atrial pressure predicted improvement independently when combined with symptom duration. Patients were more likely to show improvement if they had remained compensated with low ventricular filling pressures at rest despite depressed ejection fraction, indicating maintenance of more normal diastolic function and systemic volume regulation for a given degree of impairment in systolic function. One factor in the compensation of patients with improvement was that they had smaller mitral regurgitant volumes than those of patients without improvement, allowing higher cardiac outputs despite similar ejection fractions and smaller ventricular dimensions (Table 1). Previously, lower ventricular filling pressures have been correlated with survival in both recent onset and chronic dilated cardiomyopathy (2,15–19), but this study was the first to examine the relation between initial hemodynamic status and subsequent improvement in ventricular function. A lower serum sodium level, which often reflects increasing activation of the renin-angiotensin system, was also an independent predictor of poor outcome, as it has been in chronic heart failure (20). Other more direct measures of neurohormonal activation, such as serum catecholamine or plasma renin levels, were not routinely obtained throughout the study period and could not be analyzed for their association with improvement or survival.

Surprisingly, younger age did not predict improvement and, in fact, was associated with a higher mortality rate (Fig. 4). It is unclear whether the prognosis of younger patients was poor because they had greater prevalence of certain types of cardiac insults or because their immune, hemodynamic and reflex responses to myocardial injury once it had occurred led to more rapid progression. The incidence of previous heavy alcohol use, peripartum onset, diabetes and hypertension did not differ between patients with and without improvement but the number of patients was too small to distinguish the possible effects of these risk factors on outcome.

Limitations. This study was a retrospective analysis of a relatively small number of improvement outcomes and was limited in the number of variables it could accurately screen for predictive value. Therefore, it will be important to validate these suggested predictors prospectively. It is possible that some of the patients without improvement had unappreciated improvement in ventricular function initially and deterioration later. The fact that none of the eight patients with improvement who had serial echocardiograms after their ejection fraction had increased showed subsequent deterioration argues that this was not common. This study was not designed to determine the rate of improvement in patients with chronic cardiomyopathy, in whom serial echocardiograms were not routinely obtained. Nor was the study designed to examine the influence of drugs on improvement. Although there were no significant differences in the use of vasodilators or other agents that could explain greater survival in patients with improvement or in older patients, the study groups were too small to reliably identify the possible effects of these therapies on survival and improvement.

Implications. Patients with dilated cardiomyopathy for ≤6 months can have marked improvement in left ventricular function even after referral for cardiac transplantation and it is reasonable to defer transplantation for some of these patients. The frequency of improvement, however, may be lower than previously reported for other groups of patients with recent onset cardiomyopathy. Patients with longer duration of symptoms or more severe initial decompensation, as reflected by higher ventricular filling pressures and lower serum sodium levels, may stabilize symptomatically but are unlikely to regain good ventricular function. Because these patients, particularly if younger, remain at risk for deterioration and may have a worse prognosis than that of patients with longer-term symptoms, they should be followed up closely and may require earlier consideration for cardiac transplantation.

References

1. Dec GW, Igor FP, Fallon JT, et al. Active myocarditis in the spectrum of acute dilated cardiomyopathies—clinical features, histologic correlates, and clinical outcome. N Engl J Med 1985;312:885–90.
2. Fuster V, Gersh BJ, Giuliani ER, Tajik AJ, Brandenburg RO, Frye RL. The natural history of idiopathic dilated cardiomyopathy. Am J Cardiol 1981;47:525–31.
3. Aretz HT, Billingham ME, Edwards WD, et al. Myocarditis: a histopathologic definition and classification. Am J Cardiovasc Pathol 1987; 1:3–14.
4. Dixon EJ, editor. BMDP Statistical Software. Los Angeles: University of California Press, 1985:557–94.
5. Parillo JE, Cunnion RF, Epstein SE, et al. A prospective, randomized, controlled trial of prednisone for dilated cardiomyopathy. N Engl J Med 1989;321:1061–8.
6. Anguita M, Arizón JM, Bueno G, Concha M, Vallés F. Spontaneous

clinical and hemodynamic improvement in patients on waiting list for heart transplantation. Chest 1992;102:96–9.

7. Figulla HR, Rahlf G, Nieger M, Luig H, Kreuzer H. Spontaneous hemodynamic improvement or stabilization and associated biopsy findings in patients with congestive cardiomyopathy. Circulation 1983;71: 1095–104.
8. Fenoglio JJ, Ursell PC, Collins FK, Drusin RE, Weiss MB. Diagnosis and classification of myocarditis by endomyocardial biopsy. N Engl J Med 1983;308:12–8.
9. Mortensen SA, Baandrup U, Buch J, Bendtzen K, Hvid-Jacobsen K. Immunosuppressive therapy of biopsy proven myocarditis: experiences with corticosteroids and cyclosporine. Int J Immunother 1985;1:35–45.
10. Quigley PJ, Richardson PJ, Meany BT, et al. Long-term follow-up of acute myocarditis: correlation of ventricular function and outcome. Eur Heart J 1987;8 Suppl J:39–42.
11. Daly K, Richardson PJ, Olsen EGJ, et al. Acute myocarditis—role of histological and virological examination in the diagnosis and assessment of immunosuppressive treatment. Br Heart J 1984;51:30–5.
12. Salvi A, Hrovatin E, Dreas L, Silvestri F, Camerini F. Changes in histology and left ventricular ejection fraction during immunosuppressive treatment in active myocarditis. Eur Heart J 1987;8 Suppl J:267–9.
13. O'Connell JB, Mason JW. Diagnosing and treating active myocarditis. West J Med 1989;150:431–5.
14. Hosenpud JD, McAnulty JH, Niles NR. Lack of objective improvement in ventricular systolic function in patients with myocarditis treated with azathioprine and prednisone. J Am Coll Cardiol 1985;6:797–801.
15. Diaz RA, Obasohan A, Oakley C. Prediction of outcome in dilated cardiomyopathy. Br Heart J 1987;58:393–9.
16. Latham RD, Mulrow JP, Virmani R, Robinowitz M, Moody JM. Recently diagnosed idiopathic dilated cardiomyopathy: incidence of myocarditis and efficacy of prednisone therapy. Am Heart J 1989;117:876–82.
17. Keough AM, Baron DW, Hickie JB. Prognostic guides in patients with idiopathic or ischemic dilated cardiomyopathy assessed for cardiac transplantation. Am J Cardiol 1990;65:903–8.
18. Romeo F, Pelliccia F, Cianfrocca C, et al. Determinants of end-stage idiopathic dilated cardiomyopathy: a multivariate analysis of 104 patients. Clin Cardiol 1989;12:387–92.
19. Stevenson LW, Tillisch JH, Hamilton MA, et al. Importance of hemodynamic response to therapy in predicting survival with ejection ≤20% secondary to ischemic or nonischemic dilated cardiomyopathy. Am J Cardiol 1990;66:1348–54.
20. Lee WH, Packer M. Prognostic importance of serum sodium concentration and its modification by converting-enzyme inhibition in patients with severe chronic heart failure. Circulation 1986;73:257–67.