

## LONG-TERM OUTCOME OF FULMINANT MYOCARDITIS AS COMPARED WITH ACUTE (NONFULMINANT) MYOCARDITIS

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**ABSTRACT**

**Background** Lymphocytic myocarditis causes left ventricular dysfunction that may be persistent or reversible. There are no clinical criteria that predict which patients will recover ventricular function and which cases will progress to dilated cardiomyopathy. We hypothesized that patients with fulminant myocarditis may have a better long-term prognosis than those with acute (nonfulminant) myocarditis.

**Methods** We identified 147 patients considered to have myocarditis according to the findings on endomyocardial biopsy and the Dallas histopathological criteria. Fulminant myocarditis was diagnosed on the basis of clinical features at presentation, including the presence of severe hemodynamic compromise, rapid onset of symptoms, and fever. Patients with acute myocarditis did not have these features. The incidence of the end point of this study, death or heart transplantation, was ascertained by contact with the patient or the patient's family or by a search of the National Death Index. The average period of follow-up was 5.6 years.

**Results** A total of 15 patients met the criteria for fulminant myocarditis, and 132 met the criteria for acute myocarditis. Among the patients with fulminant myocarditis, 93 percent were alive without having received a heart transplant 11 years after biopsy (95 percent confidence interval, 59 to 99 percent), as compared with only 45 percent of those with acute myocarditis (95 percent confidence interval, 30 to 58 percent;  $P=0.05$  by the log-rank test). Fulminant myocarditis was an independent predictor of survival after adjustments were made for age, histopathological findings, and hemodynamic variables. The rate of transplantation-free survival did not differ significantly between the patients considered to have borderline myocarditis and those considered to have active myocarditis according to the Dallas histopathological criteria.

**Conclusions** Fulminant myocarditis is a distinct clinical entity with an excellent long-term prognosis. Aggressive hemodynamic support is warranted for patients with this condition. (N Engl J Med 2000;342:690-5.)

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**L**YMPHOCYTIC myocarditis remains a poorly characterized disorder. Approximately 10 percent of patients with cardiomyopathy of recent onset who undergo endomyocardial biopsy have this condition, which is presumed to be caused by viral infection.<sup>1,2</sup> The clinical course of patients with lymphocytic myocarditis varies; some patients have subclinical disease,<sup>3</sup> some

present with fulminant disease, which is frequently fatal,<sup>4-6</sup> and others have indolent disease that progresses to dilated cardiomyopathy.<sup>7,8</sup>

Although a histopathological classification system, referred to as the Dallas criteria, has been widely applied in the diagnosis of myocarditis since 1987,<sup>9</sup> whether these criteria alone can be used to predict outcome in patients with lymphocytic myocarditis has been controversial.<sup>10</sup> Currently, there are no clinical criteria that reliably predict which patients with myocarditis are likely to recover.

In a study of 35 patients, Lieberman et al. classified myocarditis as either fulminant or acute (nonfulminant) on the basis of clinicopathological criteria, including the severity of illness at presentation.<sup>11</sup> Paradoxically, the patients with fulminant myocarditis, though more severely ill at presentation, were more likely to recover left ventricular function than were those with acute myocarditis. Supporting this observation are several case reports of patients with fulminant myocarditis whose ventricular dysfunction resolved after aggressive pharmacologic support, mechanical circulatory support, or both.<sup>12-15</sup> Despite these observations, the long-term outcome of patients with fulminant myocarditis has not been determined. In a prospective study, we used clinical features to classify patients with myocarditis diagnosed by biopsy in order to test the hypothesis that patients with fulminant myocarditis have better long-term survival than patients with acute myocarditis.

**METHODS****Patients**

The study was approved by the Joint Committee on Clinical Investigation of Johns Hopkins Hospital. Patients with cardiomyopathy of recent onset (those who had had symptoms for less than 12 months) or unexplained ventricular arrhythmia who underwent endomyocardial biopsy at Johns Hopkins Hospital between July 1, 1984, and June 30, 1997, were eligible to participate. Patients were identified through a search of the Johns Hopkins pathology data base for all cases of myocarditis diagnosed by endomyocardial biopsy. To be included in this study, patients had to meet the following criteria: evidence of "borderline" myocarditis (indicated by lymphocytic infiltration without myocyte necrosis) or "active" myocarditis (indicated by lymphocytic infiltration with myocyte necrosis) on biopsy, according to the Dallas histopathological criteria;

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absence of any underlying disorder known to be associated with myocarditis; and left ventricular dysfunction (defined as an ejection fraction of  $\leq 40$  percent) documented by echocardiography, radionuclide ventriculography, or contrast ventriculography. All the patients were seen by a member of the cardiomyopathy service at Johns Hopkins Hospital. It has been a universal policy of this hospital to perform endomyocardial biopsy in all patients with cardiomyopathy of recent onset that is not due to ischemia. Because of concern about the heterogeneity of myocarditis in children, we excluded patients younger than 15 years of age from the study. Likewise, we excluded eight patients with chronic active myocarditis, a syndrome that is characterized by the presence of replacement fibrosis or giant cells in histopathological specimens, which may be a different entity from lymphocytic myocarditis.<sup>11</sup>

### Clinical Classification

The patients were classified as having fulminant myocarditis or acute myocarditis according to the criteria of Lieberman and colleagues.<sup>11</sup> Clinical classification, based on data from the medical record, was undertaken by investigators who had no knowledge of the patients' follow-up status. All patients with fulminant myocarditis had severe hemodynamic compromise requiring high doses of vasopressors ( $\geq 5 \mu\text{g}$  of dopamine or dobutamine per kilogram of body weight per minute) or a left ventricular assist device. In addition, at least two of the following clinical features had to be present for histopathologically borderline or active myocarditis to be classified as fulminant: fever, distinct onset of symptoms of heart failure (fatigue, dyspnea on exertion or at rest, or edema that could be dated specifically to a one-to-two-day period), and a history consistent with the presence of a viral illness within the two weeks before hospitalization. The patients with borderline or active myocarditis were classified as having an acute presentation if they had an indistinct onset of symptoms of heart failure (symptoms that could be dated to a period of weeks to months), were hemodynamically stable or required only low doses of vasopressors ( $< 5 \mu\text{g}$  of dopamine or dobutamine per kilogram per minute) to improve renal perfusion, and had no fever.

### Endomyocardial Biopsy and Right-Heart Catheterization

Biopsy specimens were taken from the right ventricular septum, with the use of either a modified Stanford-Caves bioptome (Scholten Surgical, Redwood City, Calif.) or a disposable bioptome (Maxxim Medical, Athens, Tex.), by way of the right internal jugular vein. At least five specimens were obtained from each patient, immediately fixed in 10 percent formalin, embedded in paraffin, sectioned, stained with hematoxylin and eosin, and reviewed at a minimum of four section levels by one of two cardiac pathologists who used the Dallas criteria to determine whether myocarditis was present. The reviewing pathologists were not aware of the clinical characteristics of the patients.

After the biopsy specimens were obtained, the patients underwent right-heart catheterization. A thermodilution Swan-Ganz catheter (Baxter Healthcare, Irvine, Calif.) was placed with the use of fluoroscopy, and right atrial, right ventricular, pulmonary arterial, and pulmonary-capillary wedge pressures were recorded. Cardiac output, calculated with the use of the thermodilution technique (the average of three measures with less than 10 percent variability), was recorded.

### End Point and Follow-up

The end point of this study was death or cardiac transplantation. The occurrence of death or cardiac transplantation was determined through direct contact with the patient or the family of the patient, review of the patient's medical record, search of the National Death Index, or all three. The National Death Index is a central computerized index of records of death compiled from data submitted by the vital-statistics offices of every state to the National Center for Health Statistics. The reliability of the National Death Index as a means of establishing vital status has been validated.<sup>16</sup> The negative predictive value of a search of the National Death

Index is higher than 99 percent.<sup>17</sup> Consequently, patients whom we could not contact and who were not matched through the search of the National Death Index (7 patients with fulminant myocarditis and 41 with acute myocarditis,  $P=0.25$  by Fisher's exact test) were presumed to be alive as of December 31, 1996 (the last date for which data were available in the index); data on these patients were censored after this date.

### Statistical Analysis

Between-group analysis of categorical variables was performed with the two-tailed Fisher's exact test. Student's t-test was used to analyze continuous variables. Survival curves were generated according to the Kaplan-Meier method and were compared with use of the log-rank statistic. Multivariate analysis was performed with the use of the Cox proportional-hazards model for censored data. Mean pulmonary-artery pressure and cardiac output were analyzed as continuous variables. All analyses were two-tailed. All analyses were performed with the use of Stata statistical software (version 4.0, Stata, College Station, Tex.).

## RESULTS

Between July 1, 1984, and June 30, 1997, a total of 1757 patients with cardiomyopathy of recent onset or unexplained ventricular arrhythmia underwent endomyocardial biopsy at the study hospital; 252 of these patients had histopathological evidence of myocarditis. Of these 252 patients, 147 had no other condition known to be associated with myocardial inflammation and thus made up the study population. The base-line characteristics of the patients are shown in Table 1. Table 2 presents the conditions associated with myocardial inflammation in the 90 patients at least 15 years of age who were excluded from the study (15 patients younger than 15 years of age were also excluded).

Fifteen patients (10 percent) had fulminant myocarditis, and the remaining 132 had acute myocarditis. Two patients with fulminant myocarditis required circulatory assistance with a mechanical device; the remainder were receiving high-dose vasopressors. Pa-

TABLE 1. BASE-LINE CHARACTERISTICS OF THE PATIENTS.\*

CHARACTERISTIC	FULMINANT MYOCARDITIS (N=15)	ACUTE MYOCARDITIS (N=132)	P VALUE
Age (yr)	35±16	43±13	0.05
Male sex (%)	73	64	0.58
White race (%)	73	74	1.0
Borderline myocarditis (%)	13	48	0.01
Heart rate at rest (beats/min)	100±20	88±21	0.04
Mean arterial pressure (mm Hg)	80±18	92±16	0.005
Right atrial pressure (mm Hg)	9.5±8	6.2±5	0.02
Mean pulmonary-artery pressure (mm Hg)	23±12	23±10	0.87
Mean pulmonary-capillary wedge pressure (mm Hg)	16±10	16±9	0.10
Cardiac output (liters/min)	5.0±1.8	4.6±1.3	0.23

\*Plus-minus values are means  $\pm$ SD.

**TABLE 2.** CLINICAL REASONS FOR EXCLUSION FROM THE STUDY.\*

REASON	NO. OF PATIENTS (%)
Peripartum cardiomyopathy	22 (24)
Human immunodeficiency virus infection	19 (21)
Ischemic injury	12 (13)
Chronic active myocarditis	8 (9)
Sarcoidosis	6 (7)
Systemic lupus erythematosus	5 (6)
Myocarditis with normal left ventricular function (chronic persistent myocarditis)	4 (4)
Eosinophilic myocarditis	4 (4)
Giant-cell myocarditis	3 (3)
Amyloidosis with myocardial inflammation	3 (3)
Doxorubicin-induced injury	2 (2)
Hemochromatosis with myocardial inflammation	1 (1)
Inflammatory bowel disease	1 (1)
Total	90

\*Only reasons for excluding patients 15 years of age or older are shown. An additional 15 patients who were younger than 15 years old were excluded according to the study design.

tients with fulminant myocarditis were younger, were less likely to have borderline myocarditis on biopsy, and had a higher heart rate at rest, a lower mean arterial pressure, and a higher right atrial pressure than those with acute myocarditis. There were no other significant differences in hemodynamic or demographic characteristics between the two groups.

During an average follow-up of 5.6 years (5.7 years for the patients with acute myocarditis [range, 4 days to 12 years]; 5.3 years for those with fulminant myocarditis [range, 15 days to 11 years]), 48 patients died and 7 received a heart transplant. The five-year rate of transplantation-free survival for all the patients with myocarditis was 70 percent (95 percent confidence interval, 61 to 77 percent). Only one patient with fulminant myocarditis died, and this death occurred during the index hospitalization. No patient with fulminant myocarditis received a heart transplant.

Figure 1 shows unadjusted transplantation-free survival according to the clinicopathological classification. Among the patients with fulminant myocarditis, 93 percent were alive without having received a transplant at one year (95 percent confidence interval, 59 to 99 percent). In contrast, 85 percent of the patients with acute myocarditis were alive without having received a transplant at one year (95 percent confidence interval, 78 to 90 percent). Furthermore, whereas 93 percent of the patients with fulminant myocarditis remained alive without having received a transplant at the end of 11 years (95 percent confidence interval, 59 to 99 percent), only 45 percent

of those with acute myocarditis (95 percent confidence interval, 30 to 58 percent) were still living without having received a transplant 11 years after the initial biopsy. The long-term transplantation-free survival of the patients with fulminant myocarditis was significantly better than that of the patients with acute myocarditis ( $P=0.05$  by the log-rank test).

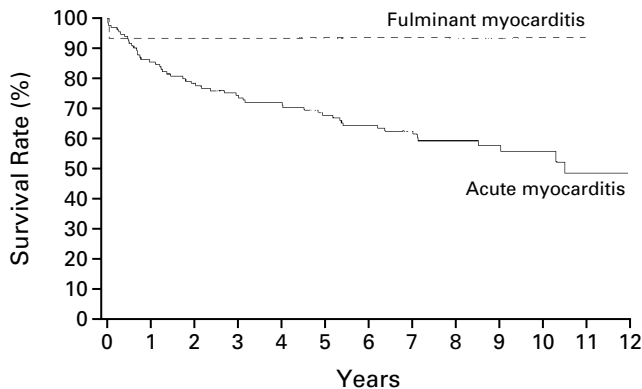
Figure 2 shows unadjusted transplantation-free survival according to histopathological classification (borderline myocarditis vs. active myocarditis). Among the patients with borderline myocarditis, 87 percent survived one year (95 percent confidence interval, 76 to 93 percent), as compared with 85 percent of those with active myocarditis (95 percent confidence interval, 75 to 91 percent). At five years, 69 percent of the patients who had borderline myocarditis on initial biopsy were alive (95 percent confidence interval, 55 to 79 percent), as were 71 percent of those who had active myocarditis on initial biopsy (95 percent confidence interval, 59 to 79 percent). There was no significant difference in survival between the patients with borderline myocarditis on biopsy and those with active myocarditis ( $P=0.38$  by the log-rank test).

To determine whether fulminant myocarditis was an independent predictor of long-term transplantation-free survival, we performed a multivariate analysis using the Cox proportional-hazards model. We included variables that were either distributed differently between the fulminant-myocarditis and acute-myocarditis groups (histopathological status, age, heart rate, mean arterial pressure, and right atrial pressure) or that are clinically relevant to patients with heart failure (cardiac output, mean pulmonary pressure, and pulmonary-capillary wedge pressure). The presence of fulminant myocarditis was an independent predictor of long-term transplantation-free survival (hazard ratio for death or transplantation, 0.10; 95 percent confidence interval, 0.01 to 0.88) after adjustments were made for age, severity of inflammation, and hemodynamic variables (Table 3). Long-term transplantation-free survival also correlated with higher cardiac output and lower mean pulmonary-artery pressure.

Figure 3 shows cases of fulminant myocarditis and cases of acute myocarditis as a proportion of the total number of patients with recent onset of heart failure who underwent endomyocardial biopsy per fiscal year. The number of cases of acute myocarditis has declined since the 1980s ( $P<0.001$  for annual trend). In contrast, the number of cases of fulminant myocarditis has been relatively stable and has averaged one case per year.

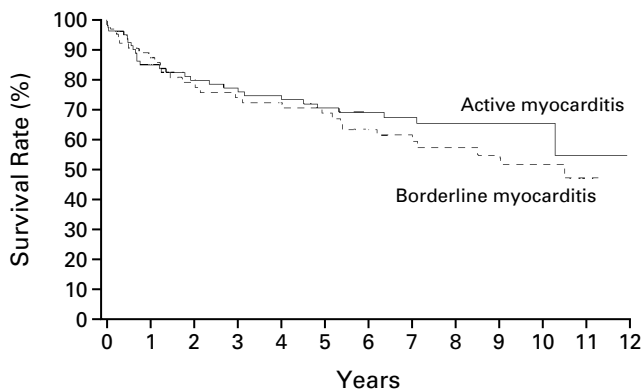
## DISCUSSION

The purpose of this study was to determine whether a clinicopathological classification scheme provides useful prognostic information about patients with myocarditis. We have shown that patients with fulmi-



NO. AT RISK	0	1	2	3	4	5	6	7	8	9	10	11	12
Acute myocarditis	132	110	98	91	84	79	73	59	41	28	18	3	0
Fulminant myocarditis	15	12	12	10	10	9	7	5	4	3	2	0	0

**Figure 1.** Unadjusted Transplantation-free Survival According to Clinicopathological Classification. Patients with fulminant myocarditis were significantly less likely to die or require heart transplantation during follow-up than were patients with acute myocarditis (P=0.05 by the log-rank test).



NO. AT RISK	0	1	2	3	4	5	6	7	8	9	10	11	12
Borderline myocarditis	82	68	61	58	53	50	47	34	22	13	6	1	0
Active myocarditis	65	54	47	43	40	38	33	30	23	18	14	2	0

**Figure 2.** Unadjusted Transplantation-free Survival According to the Dallas Histopathological Criteria. Long-term survival did not differ significantly according to the degree of inflammation on biopsy (P=0.38 by the log-rank test).

nant myocarditis have a clinical course that is distinct from that of patients with acute myocarditis. Fulminant myocarditis is characterized by critical illness at presentation but excellent long-term survival. In contrast, patients with acute myocarditis are less ill initially but have a progressive course that leads to death or the need for cardiac transplantation. Having fulminant myocarditis was an independent predictor of transplantation-free survival even after adjustments were made for the severity of inflammation, age, and clinically relevant hemodynamic variables.

Our data agree with previous reports from the Myocarditis Treatment Trial<sup>2</sup> and Grogan et al.<sup>10</sup> that my-

ocarditis causes substantial mortality. The mortality rate one year after presentation with myocarditis in these studies was about 20 percent. The one-year mortality rate among the patients with acute myocarditis in our study (15 percent) does not differ appreciably from earlier estimates.

We observed a decline in the incidence of acute myocarditis over time. Non-poliovirus enteroviruses are considered to be the predominant cause of myocarditis.<sup>18</sup> These agents are known to produce endemic as well as epidemic patterns of infection.<sup>19</sup> Interestingly, the decline in the incidence of acute myocarditis that we observed mirrors the decline in the number

**TABLE 3.** INDEPENDENT PREDICTORS OF LONG-TERM TRANSPLANTATION-FREE SURVIVAL IN PATIENTS WITH HISTOPATHOLOGICALLY DEFINED ACTIVE MYOCARDITIS OR BORDERLINE MYOCARDITIS.

VARIABLE*	ADJUSTED HAZARD RATIO FOR DEATH OR TRANSPLANTATION (95% CI)	P VALUE
Fulminant myocarditis at presentation	0.10 (0.01–0.88)	0.04
Increased mean pulmonary-artery pressure (for each increment of 5 mm Hg)	1.5 (1.1–2.1)	0.01
Increased cardiac output (for each increment of 1 liter/min)	0.75 (0.59–0.96)	0.02

\*Nonsignificant predictors were age, histopathological findings (borderline myocarditis or active myocarditis), heart rate, mean arterial pressure, mean right atrial pressure, and mean pulmonary-capillary wedge pressure. Mean pulmonary-artery pressure and cardiac output were evaluated as continuous variables. CI denotes confidence interval.

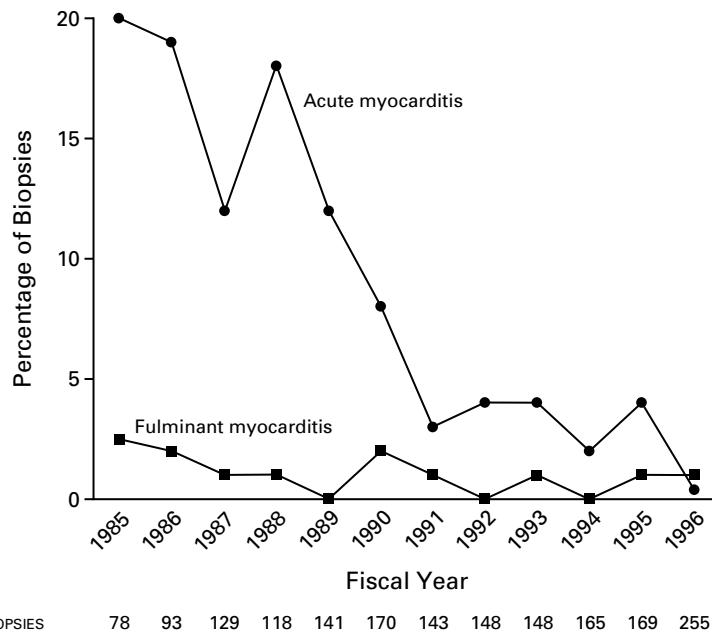
of isolates of non-poliovirus enteroviruses reported by the Centers for Disease Control and Prevention,<sup>20</sup> suggesting that the decline in the incidence of acute myocarditis that we observed may be explained by patterns of enteroviral infection.<sup>21</sup>

In contrast with the incidence of acute myocardi-

tis, the incidence of fulminant myocarditis remained stable over time. The reason for this stability is not clear. It may be that fulminant myocarditis is caused by an enterovirus, such as coxsackievirus B4, that is associated predominantly with endemic patterns of infection.<sup>22</sup> In mice, coxsackievirus B4 produces a disease similar to fulminant myocarditis.<sup>23</sup> Alternatively, fulminant myocarditis may be due to infection by another type of virus. There is mounting evidence that adenoviruses may have a greater role in virus-related heart disease than previously thought.<sup>24,25</sup> Finally, it is possible that fulminant myocarditis is not due to viral infection at all but, rather, is an autoimmune disorder.<sup>26</sup>

Despite the fact that endomyocardial biopsy has been shown to have a low negative predictive value in the diagnosis of myocarditis,<sup>27,28</sup> it has a high positive predictive value. We included only patients with histopathologically defined borderline or active myocarditis in this study so as to reduce the likelihood of bias due to misclassification. Consequently, our findings may not be applicable to patients who do not undergo biopsy or who do not have histopathological evidence of inflammation. However, we would be inclined to begin aggressive treatment if a patient had a clinical picture that suggested fulminant myocarditis, regardless of the histopathological findings.

During the period of our study, the pharmacologic treatment of heart failure has improved. Our data



**Figure 3.** Cases of Acute Myocarditis and Fulminant Myocarditis as a Percentage of Biopsies Performed, 1985 through 1996.

Both the absolute number and the proportion of cases classified as acute myocarditis declined over time ( $P < 0.001$  for annual trend). In contrast, the number and proportion of cases classified as fulminant myocarditis remained relatively stable.

do not include all the various therapies patients may have received over the 13-year period of this study. Given that patients with fulminant myocarditis recover early, improvements in long-term medical therapy are unlikely to account for the observed survival benefit in this group of patients in our study. Other potential confounding factors, such as heavy alcohol use, could also contribute to a survival effect. However, Herskowitz et al. have previously reported that the prevalence of heavy alcohol use in a subgroup of the patients with myocarditis whom we studied is low.<sup>1</sup>

Patients with fulminant myocarditis are critically ill at presentation. Although most of the patients in this study could be treated adequately with high-dose vasopressors, two patients required temporary circulatory support with a left ventricular assist device. Given that patients with fulminant myocarditis have excellent long-term survival, an aggressive approach that may include mechanical circulatory assistance is warranted.

In conclusion, clinical characteristics can be used to identify patients with histopathological features of primary myocarditis whose ventricular function is likely to improve; such patients would not be well served by cardiac transplantation. Fulminant myocarditis is a distinct entity, characterized by severe hemodynamic compromise at presentation but an excellent long-term prognosis. These findings have important implications for the management of acute heart failure.

Supported in part by a grant (KO8-HL03238) from the National Institutes of Health (to Dr. Hare). Dr. McCarthy was an American College of Cardiology–Merck Cardiology Fellow and also received support from Hoechst Marion Roussel.

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