Early spontaneous recovery of left ventricular function in patients with myocarditis

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The natural history of myocarditis is varied. We describe 6 out of a cohort of 15 consecutive patients with histopathologic evidence of myocarditis who showed a remarkable early symptomatic and spontaneous recovery of left ventricular systolic function. The left ventricular ejection fraction increased to ≥ 50% at discharge, and this improvement was maintained at late follow-up. The other 9 patients, despite clinical improvement, were not thought to have spontaneous recovery. Neither clinical severity of the illness (NYHA functional class) nor left ventricular ejection fraction at presentation demonstrated any difference in the two groups. By contrast, a smaller left ventricular internal diameter at end-diastole and a smaller left atrial dimension as determined by transthoracic echocardiography were predictive of spontaneous recovery. Firstly, we confirm that the natural history of myocarditis is indeed varied with the possibility of early spontaneous recovery; secondly we suggest that left ventricular internal diameter at end-diastole and left atrial dimension may have prognostic implications in this disease.

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Introduction

The natural history of human myocarditis is quite variable, ranging from an asymptomatic state to fulminant fatal congestive heart failure[1-5]. Among patients with symptomatic myocarditis, spontaneous recovery (SR) has been suspected to occur and noted occasionally[6-9]. The purpose of this study was to report on 6 patients with biopsy proven myocarditis who showed a remarkable SR of left ventricular function during their initial hospitalization.

Methods

The study population consisted of 15 consecutive patients (9 men, 6 women, mean age 40 ± 14 years, range 19 to 68 years) with histopathologic evidence of myocarditis according to the Dallas criteria[10], evaluated at the University of Michigan Hospital. A transthoracic echocardiogram was obtained in every patient at admission to assess left ventricular function and chamber size. Six patients showed remarkable clinical improvement, becoming asymptomatic (NYHA functional class I) during their hospitalization. To confirm the apparent clinical improvement, predischarge radionuclide gated blood-pool imaging (MUGA) was performed in these patients. The 9 remaining patients were not studied at discharge as they did not recover fully. All patients had follow-up evaluation including MUGA within 6 months of discharge. Based on the improvement in clinical status (NYHA functional class I) and left ventricular ejection fraction ≥ 50% at discharge, and maintenance of improvement at late follow-up, 6 of the 15 (40%) were considered in retrospect to have SR. The remaining 9 out of 15 (60%) were considered not to have spontaneous recovery (NSR). At baseline the following characteristics were recorded: age, gender, heart rate, severity of congestive heart failure based on functional class (NYHA), time from onset of symptoms to hospitalization, prodromal symptoms (upper respiratory infection, fever), presence of chest pain, left ventricular ejection fraction, left ventricular internal diameter at end-diastole, and left atrial dimension as determined by two-dimensional transthoracic echo-Doppler examination. Coronary angiograms were performed in 9 patients (3 SR, 6 NSR) as clinically indicated, including presence or absence of chest pain, ECG changes of ischemia, age, or presence of risk factors raising the suspicion of

ischemic heart disease. Serologic studies for virus etiology were not carried out systematically. The history of cocaine was raised in every patient, with each one of them denying its use. The urine was not examined for cocaine use. All SR patients received supportive therapy, including digitalis, diuretics and ACE-inhibitors, but none received immunosuppressive therapy. Three of 9 NSR patients received immunosuppression in addition to supportive heart failure therapy. Three of the 6 SR and 5 of the 9 NSR patients underwent follow-up endomyocardial biopsy 3 to 6 months after discharge.

Statistical analysis. SR and NSR patients were compared with respect to several baseline variables. Fisher's exact tests were used to compare binary baseline measurements (e.g., presence or absence of chest pain). Continuous measurements (days between symptom onset and hospital admission, heart rate, left ventricular internal diameter at end-diastole, left atrial dimension, and ejection fraction) were examined for group differences using the Mann-Whitney U test. In each group, changes in ejection fraction between baseline and follow-up were examined using the Wilcoxon signed rank test.

Results

Patient outcome was unrelated to sex; 4 of 9 males (44.4%) and 2 of 6 females (33.3%) recovered ($p \cong 1.00$). Younger patients were more likely to recover; the average age of those who recovered was 32 years (range 19 to 51 years), while among those who did not recover the mean age was 45 years (range 22 to 68 years) ($p = 0.088$). There was no statistically significant difference in heart rate between the two groups with only 1 SR patient exhibiting resting sinus tachycardia (Tables I and II). At presentation, all patients were in NYHA functional class III or IV; 3 of the 10 patients (30%) in class III and 3 of the 5 (60%) in class IV had SR. Those with prodromal symptoms prior to the onset

Table I. Clinical characteristics at the time of presentation of spontaneous recovery (SR) vs non-spontaneous recovery (NSR) patients.

Variables	SR (n = 6)	NSR (n = 9)	p
Age (years)	32 ± 11	45 ± 14	0.088
Gender (M/F)	4/2	5/4	1.000
Heart failure (NYHA class III/IV)	3/3	7/2	0.329
Heart rate (b/min)	81.2 ± 27.4	79.2 ± 11.0	1.000
Time from symptom onset to hospitalization (days)	7.8	6.1	0.39
Prodromal symptoms (upper respiratory infection, fever)	5	3	0.119
Chest pain	2	0	0.143
LVEF (%)	39.5 ± 9.0	26.4 ± 12.9	0.088
LVIDd (mm)	49.2 ± 8.5	64.9 ± 6.9	0.005
LAD (mm)	32.7 ± 5.1	42.6 ± 6.2	0.005

Values are expressed as mean ± SD when appropriate. LAD = left atrial dimension; LVEF = left ventricular ejection fraction; LVIDd = left ventricular internal diameter at end-diastole.

Table II. Baseline characteristics of the 6 patients with spontaneous recovery (SR) vs 9 patients with no spontaneous recovery (NSR).

Patient	SR/NSR	Age (years)	Sex	Heart failure (NYHA class)	Prodromal symptoms	Chest pain	Heart rate (b/min)	LVIDd (mm)	LAD (mm)	CA	EF (%)	Biopsy
1	SR	25	M	III	URI, fever	–	50	61	27	0	47	Positive
2	SR	37	F	III	–	+	130	48	33	Negative	43	Positive
3	SR	27	F	IV	URI, fever	–	84	37	31	0	44	Positive
4	SR	19	M	IV	URI, fever	–	82	49	33	0	28	Positive
5	SR	51	M	IV	URI, fever	–	65	56	42	Negative	28	Positive
6	SR	31	M	III	URI, fever	+	72	44	30	Negative	47	Positive
7	NSR	27	F	III	–	–	82	60	36	0	36	Positive
8	NSR	55	M	IV	URI, fever	–	78	69	43	Negative	14	Positive
9	NSR	54	F	IV	URI, fever	–	80	59	34	Negative	37	Positive
10	NSR	39	M	III	URI, fever	–	72	63	52	Negative	34	Positive
11	NSR	45	F	III	–	–	89	68	37	Negative	21	Positive
12	NSR	68	M	III	–	–	84	58	42	Positive	9	Positive
13	NSR	45	F	III	–	–	74	58	42	0	48	Positive
14	NSR	22	M	III	–	–	67	72	50	0	15	Positive
15	NSR	47	M	III	–	–	88	77	47	Negative	24	Positive

CA = coronary angiogram; URI = upper respiratory tract infection. Other abbreviations as in table I.

of cardiac failure seemed more likely to recover: 5 of 8 such patients (62.5%) recovered spontaneously (p = 0.119). The duration in days between the onset of symptoms and admission to the hospital was slightly but not significantly greater among SR patients compared to NSR patients (mean 7.8 vs 6.1 days, p = 0.39) (Tables I and II). Of the 9 patients (3 SR, 6 NSR) who underwent coronary angiogram, only 1 patient, a 68-year-old man with dyslipidemia in the NSR group, had significant coronary artery disease.

SR patients had smaller left ventricular internal diameter at end-diastole and left atrial dimension at presentation (Fig. 1) Among those who recovered, the average left atrial dimension was 32.7 mm (range 27 to 42 mm), while it was 42.6 mm (range 34 to 52 mm) among those who did not recover spontaneously (p = 0.005). The average left ventricular internal diameter at end-diastole was 49.2 mm (range 37 to 61 mm) and 64.9 mm (range 58 to 77 mm) in SR patients vs NSR patients, respectively (p = 0.005). Ejection fraction at baseline was found to be a less strong marker of outcome in these patients. SR patients showed an average ejection fraction of 39.5% (range 28 to 47%), while NSR patients showed a mean ejection fraction of 26.4% (range 9 to 48%); this difference was not statistically significant (p = 0.088) (Tables I and II).

SR patients showed a definite recovery of symptoms and signs of congestive heart failure on supportive medical therapy (digitalis, diuretics, and ACE-inhibitors) during the initial hospital stay, attaining NYHA functional class I status at discharge. They also had significant improvement in ejection fraction at discharge (61.5 ± 8.8%, range 50 to 72%) and they maintained that improvement at late follow-up (61.2 ± 7.6%, range 50 to 70%) (Fig. 2). Furthermore, 3 SR patients had a repeat biopsy 3 to 6 months later, which demonstrated resolution of myocarditis. Five of the 9 NSR patients, 3 on and 2 not on immunosuppressive therapy, had repeat endomyocardial biopsy at follow-up. All showed no residual myocarditis. By contrast, NSR patients

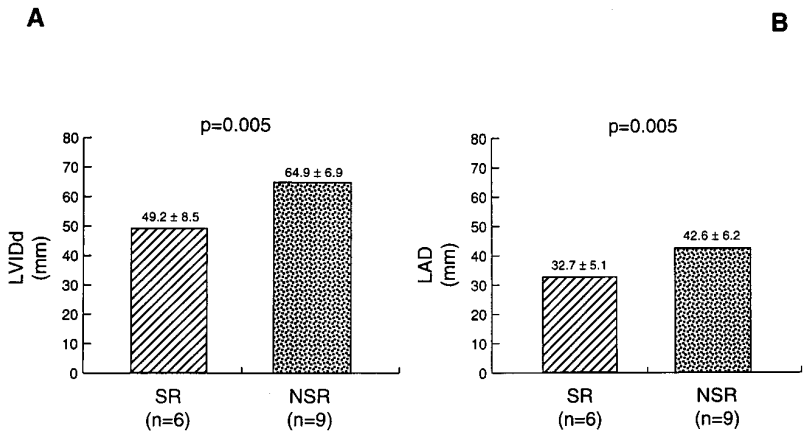

Figure 1. *Left ventricular internal diameter at end-diastole (LVIDd)* (A) *and left atrial dimension (LAD)* (B) *were statistically smaller in spontaneous recovery patients (SR) vs non-spontaneous recovery patients (NSR).*

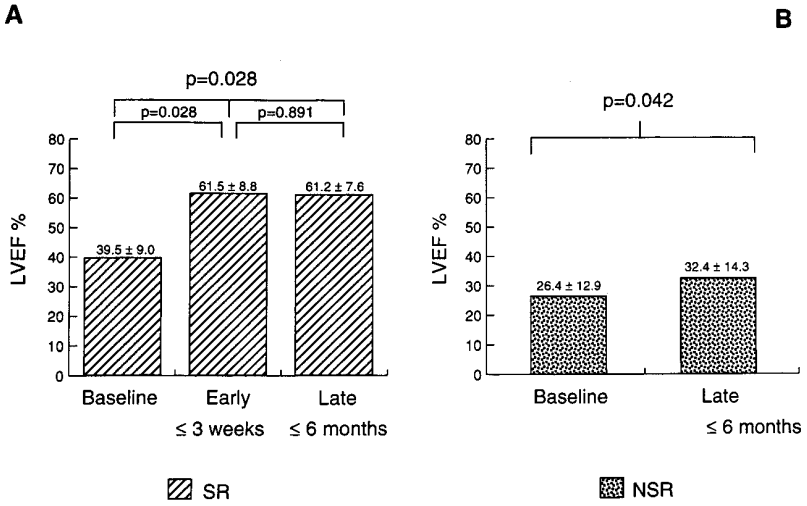

Figure 2. A: *restoration of left ventricular ejection fraction (LVEF) at early and late follow-up in spontaneous recovery patients (SR).* B: *moderate improvement in LVEF at late follow-up without restoration to normal in non-spontaneous recovery patients (NSR).*

showed stabilization of symptoms with modest improvement in congestive heart failure symptoms and signs at the time of discharge; 6 achieved class II and 3 achieved class III (NYHA). In this group there was only a moderate improvement in ejection fraction; by late follow-up the mean ejection fraction was 32.4 ± 14.3% (range 9 to 50%) (Fig. 2).

Discussion

The natural history of human myocarditis is indeed variable. Most patients with mild symptoms (asymptomatic myocarditis) usually recover completely or rarely develop dilated cardiomyopathy after a long latency period. Of the patients with symptomatic myocarditis a small number has a fulminant presentation while the majority a nonfulminant form. In this latter group few are characterized by a progressive downhill course over months or years ending in death from heart failure or intractable arrhythmias; some spontaneously recover and others have an asymptomatic period followed by the development of dilated cardiomyopathy[1,2].

In this report we describe 6 patients with symptomatic biopsy proven myocarditis who had remarkable early SR. Of note, those patients who recovered spontaneously had significantly smaller left-sided chambers compared to those who did not recover spontaneously, despite the fact that they had similar degree of severity of illness and similar duration of illness prior to admission ($p = 0.005$; Tables I and II). In fact only 1 SR patient had a definitely enlarged left ventricle and another had increased left atrial dimension with a borderline enlargement of the left ventricle. The left ventricular ejection fraction in the NSR group was less than that in the SR group at admission, but this difference was not significant (Table I). In a study of 27 patients with acute dilated cardiomyopathy, of which 18 (67%) had evidence of myocarditis on biopsy, Dec et al.[7] noted that neither histologic features of the biopsy specimen nor clinical features at presentation were clearly correlated with subsequent improvement, whether or not immunosuppressive drugs were given.

Despite the fact that the diagnosis of myocarditis was well established by histologic means, the precise etiology was not determined. Serologic studies to identify a viral etiology were not carried out systematically. Although cocaine-related myocarditis is possible[11], we do not think this is likely based on patients' history and denial of its use. An ischemic cause of myocarditis with left ventricular dysfunction is certainly possible as was suggested in one older patient with dyslipidemia in the NSR group (Table II). Coronary angiography in 3 of our oldest patients in the SR group failed to reveal obstructive coronary artery disease. In the 3 remaining SR patients with ages ranging from 19 to 27 years, coronary angiography was not carried out in light of their youth and the absence of ECG evidence of ischemia and significant risk factors for premature coronary artery disease. In the presence of histologic evidence of myocarditis in all our SR patients, it appears extremely unlikely that ischemic stunning produced global dysfunction in many of our SR patients. A repeat endomyocardial biopsy in 3 out of the 6 patients with SR showed resolution of their myocarditis, as they maintained their improved clinical status and cardiac function. Because of the recent published data indicating no convincing evidence of benefit of immunosuppressive therapy in patients with chronic myocarditis, we did not feel that repeat biopsies in all our NSR patients were justified[5]. Moreover, the 5 NSR patients who had repeat biopsy at follow-up showed no residual myocarditis, including in the 2 not treated with immunosuppressive therapy.

In summary, SR of myocarditis may occur. Our study identified two biological predictors of SR of myocarditis, namely left ventricular and left atrial diastolic dimensions. These predictors may ultimately provide insight into the underlying mechanisms determining the varied outcomes following myocarditis. Other independent predictors may also be important. Our study only identified some, not all predictors of recovery. A larger study could identify other predictors as well as to confirm the importance of left ventricular and left atrial dimension as predictors of outcome.

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