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High Prevalence of Myocardial Monoclonal Antimyosin Antibody Uptake in Patients With Chronic Idiopathic Dilated Cardiomyopathy

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Monoclonal antimyosin antibody studies were undertaken to assess the presence of myocardial uptake in patients with chronic idiopathic dilated cardiomyopathy. Three groups were studied: 17 patients with chronic (>12 months) idiopathic dilated cardiomyopathy, 12 patients with a large, poorly contracting left ventricle not due to dilated cardiomyopathy (control patients) and 8 normal individuals. The patients in the cardiomyopathy and control groups showed a similar degree of clinical and functional impairment.

Imaging was undertaken 48 h after antimyosin injection. The heart/lung ratio of antimyosin uptake was used to assess the results. The mean ratio in the cardiomyopathy group was 1.83 ± 0.36 (range 1.40 to 2.80), a value significantly higher than that obtained in the control patients without cardiomyopathy (mean 1.46 ± 0.04, range 1.38 to 1.50) or normal subjects (mean 1.46 ± 0.13, range 1.31 to 1.6) ($p < 0.01$). No difference in the ratio was noted between the normal subjects and control patients. Abnormal antimyosin uptake was seen in 12 (70%) of the 17 patients with cardiomyopathy and in only 1 (8%) of the 12 control patients. Positive monoclonal antimyosin antibody studies are highly prevalent in chronic idiopathic dilated cardiomyopathy.

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The clinical course of dilated cardiomyopathy is exceedingly variable. A few patients present an illness that resolves spontaneously or with immunosuppressive treatment; in others the illness evolves rapidly, within months, and the patient eventually dies or requires transplantation. Most patients follow a long-term clinical course. The natural history of dilated cardiomyopathy is that of a steady deterioration of functional class; the survival curves indicate a downhill course, especially during the first years after the diagnosis is made (1,2).

The progressive nature of dilated cardiomyopathy has been explained as being a result of the long-term exhaustion of compensatory mechanisms initiated by a decrease in myocardial cell mass (3). However, necropsy studies in patients with this condition seldom reveal myocardial necrosis (4); in fact, there is a striking lack of correlation between the microscopic findings and the degree of cardiac dysfunction in patients with end-stage dilated cardiomyopathy (3).

Monoclonal antimyosin antibodies labeled with indium-111 have been useful in detecting active myocyte damage. When disruption of myocardial cell membrane occurs, this antibody specifically binds to the exposed myosin, and myocardial uptake is detected (5–8). This technique has been useful to diagnose active myocyte damage in acute myocardial infarction, acute myocarditis and acute cardiac rejection (9–12). In the present investigation, antimyosin studies were undertaken to assess the presence of myocardial uptake in patients with chronic idiopathic dilated cardiomyopathy.

Methods

Study patients. Three groups were studied with antimyosin: 8 healthy individuals (normal group) 17 patients with chronic idiopathic dilated cardiomyopathy (study group) and 12 patients with a large, poorly contracting left ventricle not due to dilated cardiomyopathy (control group).

Normal healthy individuals. Eight men aged 28 to 38 years (mean 32 ± 3), were selected for the normal group. Clinical data showed absent cardiac signs or symptoms; and normal physical findings, electrocardiogram (ECG) and chest roentgenogram; a two dimensional echocardiographic study disclosed a normal heart in each subject.

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Table 1. Clinical Features and Detection of Myocyte Damage in Patients With Chronic Idiopathic Dilated Cardiomyopathy

Patient No.	Age (yr) & Gender	Onset of CHF (mo)	EF (%)	Biopsy	Antimyosin Uptake	
					Visual	Heart/Lung Ratio
1	52M	84	28	–	3	1.90
2	42M	38	25	–	3	2.80
3	46F	48	40	+	2	1.76
4	34F	36	20	–	1	1.50
5	40F	60	23	–	2	2.16
6	35M	52	28	–	2	2.22
7	49M	25	23	–	2	1.89
8	39M	13	32	–	2	2.00
9	38F	36	31	–	1	1.60
10	51M	40	45	–	0	1.40
11	42M	108	20	–	2	1.70
12	53M	40	52	–	1	1.50
13	41M	48	54	–	1	1.50
14	37M	48	*	–	1	1.55
15	48F	33	32	–	0	1.60
16	56M	84	28	–	3	2.20
17	51M	36	26	–	2	1.80

*Poor quality echocardiogram for measurements. CHF = duration of signs or symptoms of congestive heart failure; EF = echocardiographic left ventricular ejection fraction; – = negative for myocarditis; (+) = positive for myocarditis.

Patients with chronic idiopathic dilated cardiomyopathy. During a 14 month interval (January 1987 to March 1988) 30 patients with idiopathic dilated cardiomyopathy were studied with antimyosin. Thirteen patients were excluded: six patients who had had an acute or subacute (<1 year) clinical course, two with past myocarditis and spontaneous recovery, four with a history of alcoholism and one patient with isolated right ventricular cardiomyopathy. Only patients with a clinical history >12 months were included. Therefore, a total of 17 patients, 12 men and 5 women, aged 34 to 56 years (mean 44 ± 7), formed the study group (Tables 1 and 2). Signs or symptoms of heart failure had been detected 13 to 108 months (mean 48 ± 24) before inclusion, and patients had been followed up in the outpatient clinic for 1 to 108 months (mean 26 ± 30). At the time of antimyosin study all patients were in a stable state. Their functional classification, ventricular end diastolic diameter and ejection fraction assessed by two-dimensional echocardiography are shown in Tables 1 and 2. Cardiac catheterization showed normal coronary arteries in every patient. Right ventricular biopsy was undertaken with use of a Cordis bioptome (13); four to eight samples were taken. Biopsy interpretation for myocarditis followed the Dallas criteria (14).

Patients with a large left ventricle not due to cardiomyopathy (control group). Twelve patients, 10 men and 2 women aged 29 to 72 years (mean 49 ± 12) with left ventricular dilation and low ejection fraction due to causes other than dilated cardiomyopathy, were studied with antimyosin. Angiographically proved coronary heart disease was present in 10 and valvular heart disease in 2. To minimize the possibility of detecting myocardial uptake secondary to myocardial ischemia, patients with a history of chest pain <12 months before antimyosin study were excluded.

The clinical and echocardiographic features of patients in

Table 2. Clinical and Echocardiographic Features of Patients With Chronic Idiopathic Dilated Cardiomyopathy and Control Patients*

	Patients With Dilated Cardiomyopathy (n = 17)	Control Group (n = 12)	Significance
Age (yr)			
Mean	44 ± 7	49 ± 12	NS
Range	34 to 52	29 to 72	
NYHA class			
1	1 (6%)	0	
2	11 (65%)	4 (33%)	
3	4 (23%)	7 (58%)	
4	1 (6%)	1 (8%)	
LVDD (mm)			
Mean	76 ± 15	68 ± 5	NS
Range	52 to 113	60 to 76	
LVEF (%)			
Mean	31 ± 10	29 ± 5	NS
Range	20 to 54	22 to 37	

*Control patients are those with a dilated poorly contracting left ventricle not due to dilated cardiomyopathy. NYHA = New York Heart Association functional class; LVDD = left ventricular diastolic diameter; LVEF = left ventricular ejection fraction; NS = difference not significant.

the control and cardiomyopathy groups are compared in Table 2. The patients in these two groups were older than the normal individuals; no other clinical or functional differences between groups were noted.

Antimyosin Imaging Study

After giving informed consent, patients and subjects received an intradermal injection of 0.1 ml of labeled antibody; skin tests were negative in all patients studied; 30 min later patients received an intravenous injection of 0.5 mg of R11D10-Fab-DTPA labeled with 2 mCi of indium-111 (Centocor). Imaging and interpretation of the studies were performed according to our previously described protocol (15). Planar scintigraphic images were obtained 48 h after antimyosin injection. Imaging was undertaken in anterior and left anterior oblique projections with use of a conventional large field of view camera with a high resolution medium energy collimator and 20% window centered on 247 and 173 keV peaks. A minimum of 500,000 counts was collected in 5 to 10 min. Analog and digital images collected in a 128 × 128 matrix were stored for subsequent analysis.

Interpretation of the isotopic studies (Fig. 1). This was performed by two experienced observers who did not know the results of the biopsy or clinical data.

Visual interpretation. A visual score derived from analog images read from the unprocessed gray scale monitor display was used: 0 = no myocardial uptake; 1 = mild or faint uptake; 2 = clear but moderate uptake; 3 = intense uptake.

A heart/lung ratio. The digital unprocessed anterior projection was used to adjust a region of interest in the myocardium and a region of interest in each lung. Average counts per pixel in the myocardium were divided by average counts per pixel in the lungs to obtain the final ratio. Interobserver and intraobserver variability and reproducibility of this ratio have been previously assessed (15).

Statistical analysis. One-way analysis of variance and the Student's *t* test were used to analyze differences between pairs of groups. The Statistical Package for Social Sciences (SPSS/PC) program was used for analysis of the data.

Results

Tracer distribution of antimyosin in the normal group. At 48 h, no tracer distribution within the cardiac region was usually seen; occasionally, a faint signal in the lower left parasternal region could be detected (score 0 to 1) (Fig. 1A). The heart/lung ratio was 1.46 ± 0.04 (1.38 to 1.50) (Fig. 2).

Antimyosin in dilated cardiomyopathy and control groups. Mean heart/lung ratio in the cardiomyopathy group was 1.83 ± 0.36 (range 1.40 to 2.80); this ratio was higher than the ratio obtained in the control group (1.46 ± 0.15, range 1.26 to 1.80) or in the normal group (1.46 ± 0.04, range 1.38 to 1.50) ($p < 0.01$) (Fig. 2). No difference was noted between the normal and the control group. Visual score was 1.65 ± 1.0 in the cardiomyopathy group (Fig. 1B and C) and 0.50 ± 0.67 in the control group ($p < 0.001$); no difference in visual score was observed between the normal and the control groups. Positive antimyosin studies, taking a ratio >1.58 as a cutoff point (mean ratio in the normal group + 3 SD), was seen in 12 (70%) of the 17 patients with cardiomyopathy and in only 1 (8%) of the 12 control patients.

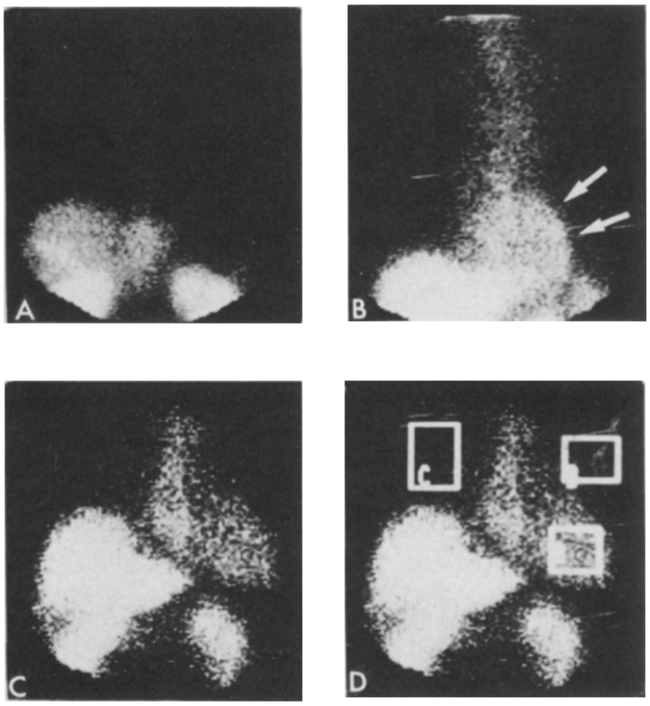

Figure 1. Interpretation of antimyosin studies. **A,** No uptake in the cardiac area in a normal subject; uptake by the liver and upper region of both kidneys is seen. **B,** Important antimyosin uptake (visual score 3) in a patient with chronic dilated cardiomyopathy; **arrows** indicate the cardiac uptake border. **C,** Moderate uptake (visual score 2) in a patient with chronic dilated cardiomyopathy. **D,** Calculation of the heart/lung ratio of the study shown in **C;** isotopic activity in the cardiac area is divided by the activity in different pulmonary areas of interest to obtain an averaged heart to lung ratio.

Endomyocardial biopsy in dilated cardiomyopathy. Only 1 of the 17 patients with dilated cardiomyopathy fulfilled the diagnostic pathologic criteria for myocarditis (Patient 3, Table 1). The antimyosin study showed an abnormal uptake (ratio 1.76, visual estimation 2).

Discussion

Antimyosin uptake in dilated cardiomyopathy. The present report is the first to describe antimyosin studies in a group of patients with stable chronic idiopathic dilated cardiomyopathy. Our results indicate that 1) there is a high prevalence of antimyosin uptake in such patients, and 2)

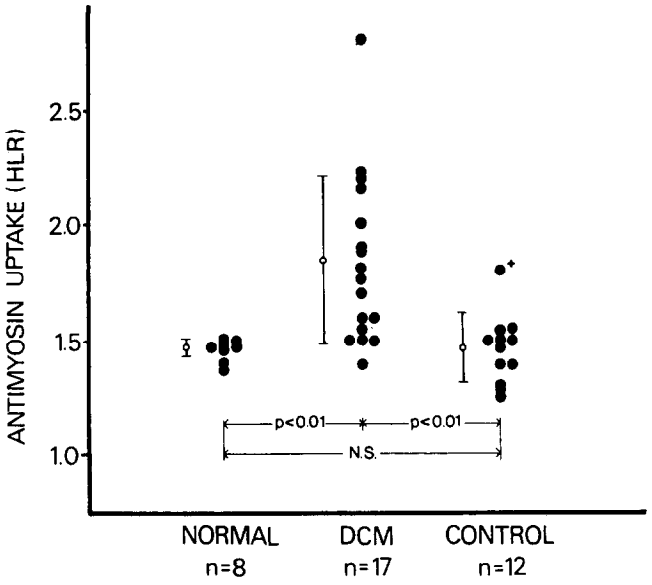

Figure 2. Antimyosin uptake in the three study groups. Normal = normal individuals; DCM = patients with chronic idiopathic dilated cardiomyopathy; Control = patients with end-stage heart disease not due to dilated cardiomyopathy.

positive studies are not due to left ventricular dilation or to the consequences of heart failure, as a similar cardiac impairment was present in the control group of patients with left ventricular dilation and dysfunction. Only one patient in the control group, with coronary heart disease, showed mild positive antimyosin uptake; he died suddenly 3 weeks after the antimyosin study, and it is possible that myocardial ischemia, despite our care in selecting control patients without chest pain, could be responsible for this finding (16).

Antimyosin uptake to detect active myocyte damage. Myocardial uptake of antimyosin in patients with chronic dilated cardiomyopathy probably reflects the presence of active myocyte damage, despite the fact that endomyocardial biopsies revealed myocyte damage in only 1 of 17 patients. A similar discrepancy has been described in myocarditis and cardiac transplantation (10–12,15). In the present group of patients, it is not clear whether myocardial uptake reflects a diffuse cellular damage undetected by microscopy or a false positive isotopic study. An excellent clinical model to shed light on this question can be provided by antimyosin studies performed after cardiac transplantation. In a recent study, we (12) demonstrated that soon after transplantation, patients invariably show antimyosin uptake that gradually decreases during the first few months. By 1 year after transplantation, some patients have a negative and others a positive scan; in subsequent biopsies, the former do not manifest rejection, whereas cell damage can be detected in the latter patients at some stage during biopsy follow-up (unpublished observations). Interestingly, the heart/lung ratios of patients after cardiac transplantation are similar to those seen in our current study group of patients with chronic stable dilated cardiomyopathy.

Clinical and prognostic implications. The implications of myocardial uptake of antimyosin are only speculative. It was recently suggested (3) that dilated cardiomyopathy is a common pathway of many diverse end-stage heart diseases, including valvular and coronary disease. However, the high prevalence of antimyosin uptake in patients with dilated cardiomyopathy compared with that in patients with other types of end-stage heart disease indicates that dilated cardiomyopathy may be a distinct clinical condition. This would reinforce the definition of dilated cardiomyopathy as an idiopathic muscle disease of unknown origin not secondary to coronary, valvular or congenital heart disease (17).

The prognostic significance of antimyosin uptake in patients with chronic dilated cardiomyopathy is uncertain. Several clinical series (1,2) of such patients have shown the progressive nature of the disease. Recently, Diaz et al. (2) provided a fine description of the natural history of a very large series of these patients: their study revealed that the probability of survival steadily decreases during the first 4 years after the diagnosis, and a certain plateau is attained thereafter. The present study identified patients who have antimyosin uptake and those who have a negative scan. It is tempting to correlate these patterns of myocardial antimyosin uptake with clinical outcome; possibly, continual myocardial uptake could explain the steady clinical deterioration in some patients with dilated cardiomyopathy and the stable course in others without such activity.

Interruption of this myocardial lesional activity could be considered. Although further studies are needed to address this problem, it is possible that patients with dilated cardiomyopathy and a positive antimyosin study might respond to some form of therapy (for example, immunosuppression) directed to halting such activity, whereas those with absent uptake would not.

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