

CARDIAC INVOLVEMENT IN PATIENTS WITH CHRONIC FATIGUE SYNDROME AS DOCUMENTED WITH HOLTER AND BIOPSY DATA IN BIRMINGHAM, MICHIGAN, 1991–1993

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We report the prevalence of abnormal oscillating T-waves at Holter monitoring in a consecutive case series of 67 chronic fatigue syndrome (CFS) patients from an infectious diseases center in Birmingham, Michigan, in the years 1991–1993, and compare these abnormal T-waves to similar tests in 78 non-CFS patients matched for age, place, time, and the absence of known other confounding medical diseases. Patients in both groups had normal resting 12-lead electrocardiograms (ECGs), rest/stress myocardial perfusion studies (thallium 201 or TC-99 sestamibi studies and two-dimensional echocardiograms (except for the incidental findings of mitral valve prolapse without significant regurgitation or, an incidental nonsignificant aortic stenosis). The prevalence of labile T-wave abnormalities by Holter monitoring was greater in CFS patients than in non-CFS patients ($P < .01$). Repetitive T-wave flattening was a sensitive indicator of the presence of CFS. The absence of these abnormal T-waves made the diagnosis of CFS unlikely (statistical sensitivity, 0.96). The combination (e.g., the presence of both oscillating T-wave flattenings plus T-wave inversions) was an accurate indicator of the possible presence of CFS. Right ventricular endomyocardial biopsies in CFS patients showed a single patient with a lymphocytic myocarditis. Light and electron microscopic cardiomyopathic changes were present in the others.

THE T-WAVE OF THE STANDARD scalar 12-lead electrocardiogram (ECG) describes ventricular repolarization of the left ventricle [1]. When a coronary artery of the canine heart is progressively clamped, producing increasing degrees of ischemia along with rising concentrations of lactic acid within the affected myocardium, T-waves first flatten, and then the T-waves invert and become increasingly negative, as viable cardiac tissue is threatened with necrosis [2]. Abnormal in-

verted T-waves at ECG may be seen in hypertensive vascular disease [3], hyperthyroidism with an increased serum ferritin [4], high theophylline [5] or calcium [6] levels, or a low serum potassium level [7]. Cardiotropic medicines, including digitalis [7], as well as the upright posture (in about 5% of normal individuals), may be associated with abnormal inverted T-waves [8]. Inverted T-waves have been associated with mitral valve prolapse, but a causal relationship has not been established [9]. If there is no significant mitral regurgitation, patients with mitral valve prolapse have normal ventricular function [10].

We have observed that abnormal oscillating T-waves (e.g., flattening and/or inversions) in one or both precordial leads (modified lead 1 or V_2) at Holter monitoring are integral to chronic fatigue syndrome (CFS) [11–13]. In CFS patients, oscillating abnormal T-waves were regularly seen with the onset of sinus tachycar-

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dias, and the abnormal T-waves typically then resolved with reappearance of normal sinus rhythms [13]. Despite an absence of any known associated diseases in CFS patients, every CFS patient, but only 22.4% of the non-CFS patients, showed abnormal oscillating T-wave flattenings or inversions at Holter monitoring. ($P < .01$) [13]. In this earlier study, both the CFS and non-CFS patients were consecutive case series seen in Birmingham, Michigan, during the years 1982–1990. Recently, Rowe and colleagues [14] reported abnormal tilt-table testing in a high proportion of CFS patients. They suspected an abnormal neural reflex or another unknown cause for their findings.

Twenty-four percent of 87 nonselected CFS patients from a recent consecutive case series exhibited left ventricular dysfunction, by stress radioisotopic multiple gated acquisition (blood pool image) (MUGA) method [15,16 Lerner AM, Sayyed T, Dworkin HJ, et al. Abnormal left ventricular myocardial dynamics in patients with the chronic fatigue syndrome in Birmingham, Michigan, 1987–1994 (submitted for publication)]. Abnormal cardiac wall motion at rest and stress, dilatation of the left ventricle, and segmental wall motion abnormalities were present. Although the normal left ventricular resting ejection fraction is $\geq 50\%$, left ventricular ejection fractions, at rest and with exercise, of as low as 30% were seen in CFS patients.

This study compares the prevalence of the abnormal T-wave oscillations at Holter monitoring in a new consecutive case series of CFS patients with a similar consecutive case series in non-CFS patients from a cardiology practice. We also report light and electron microscopic findings from right ventricular endomyocardial biopsies in nine CFS patients.

Methods

Holter monitoring. The 67 CFS patients were seen in the Birmingham, Michigan, infectious diseases referral center during the years 1991–1993. Patients were diagnosed with CFS using the CDC case definition [11,12]. Mitral valve prolapse was not an exclusion criterion in either the CFS or non-CFS groups. Patients selected for the Holter monitoring study were ≤ 50 years old and had no known coronary artery or primary myocardial diseases, diabetes mellitus, hypertension (blood pressure $\leq 140/90$ mmHg), or hypercholesterolemia (total cholesterol ≤ 250 mg). Both CFS patients and non-CFS patients were selected so that they received no cardiac medicines, diuretics, or antidepressants. The excluded diseases or medicines are known to be associated with abnormal T-waves [2,3,4–7]. The 78 non-CFS patients

were concurrently seen, and from a cardiology practice from the same community. Non-CFS patients were < 50 years old and did not have hypertension, diabetes mellitus, coronary artery or primary myocardial diseases, or hypercholesterolemia. The 78 non-CFS patients sought cardiologic consultations for complaints of palpitations chest pain, or syncope. CFS and non-CFS patients were $> 95\%$ Caucasian.

Values for sodium, potassium, calcium, and magnesium were normal in both CFS and non-CFS patients. Known cardiac diseases in CFS and non-CFS patients were excluded by standard resting 12-lead ECG, two-dimensional (2-D) echocardiographic study (other than mitral valve prolapse and insignificant aortic stenosis), and exercise stress thallium-20/perfusion scintigraphy. All of these tests/studies were normal in both groups. Ultimate diagnoses in the non-CFS patients were: no cardiac disease (59%), mitral valve prolapse (35%), and mild hemodynamically insignificant aortic stenosis at 2-D echocardiogram (6%).

Abnormal T-wave oscillations (T-wave flattenings or T-wave inversions) of at least 25 normally conducted beats were necessary to be considered abnormal. Abnormal T-wave oscillating flattenings and T-wave inversions varied in frequency and depth, and frequently appeared only with the advent of sinus tachycardias. T-wave flattenings and T-wave inversions occurred in dramatic series with sinus tachycardias, usually reverting to normal upright T-waves when the cardiac rate decreased to < 100 bpm: often with sinus tachycardias > 120 bpm T-wave inversions deepened further. All T-wave readings were made without regard to any ST segment abnormalities, which were very rarely seen. Biphasic T-waves were arbitrarily considered to be normal. U-waves did not interfere with these analyses. Two cardiologists unaware of the position of the patient in this study reviewed the Holter tracings.

Statistical methods. Differences in gender and in mitral valve prolapse between CFS and non-CFS patients were determined by χ^2 analysis. Analyses of the two Holter readers were compared. Only patients for whom both readers' findings were concordant for the presence and type, or absence of T-wave abnormalities, were included in the analysis. To determine if there were significant differences in the prevalence of T-wave inversions and T-wave flattenings in CFS and non-CFS patients, χ^2 analysis was used. The sensitivity and specificity of T-wave inversions and T-wave flattenings in the diagnosis of CFS were calculated. Sensitivity was defined as the percentage of patients with CFS who met criteria for abnormal Holter monitoring

findings, whereas specificity was measured by the percentage of non-CFS patients without these abnormalities. The predictive accuracy of T-wave inversions and T-wave flattenings for determining the presence or absence of CFS was calculated. Two-by-two tables were analyzed (patient type by presence/absence of T-wave inversions and patient type by presence/absence of T-wave flattenings).

Light and electron microscopy of cardiac biopsies.

After informed consent in a simultaneous study, nine CFS patients underwent right ventricular endomyocardial biopsies [17]. Specimens were taken from the right ventricular septum. Seven specimens were examined by light and electron microscopy. For two cases, only light microscopy was available. Two to six pieces of biopsy tissue (average, 4.5 pieces) measuring 1–2 mm were obtained from each patient. The specimens were immediately placed in 2.5% cacodylate buffered glutaraldehyde solution for electron microscopy and in 10% formalin for light microscopy. Light microscopic sections were cut and stained with hematoxylin-eosin, Masson trichome, Congo red, and iron stains. Specimens for electron microscopy were postfixed in 1% osmium tetroxide, dehydrated in graded alcohol and propylene oxide, and embedded in Epon 812. Ten serial 1- μ m-thick sections were obtained from each block, stained with toluidine blue, and examined by light microscopy. Areas suspicious for abnormalities were selected for thin sectioning and electron microscopy. Thin sections for electron microscopy were stained with uranyl acetate, followed by lead citrate. Each specimen was examined for myofiber hypertrophy, myofiber disarray, interstitial fibrosis, perimysial fat infiltration, cellular infiltration, myofiber necrosis, amount of mitochondria, fat droplets, and amount of lipofuscin granules. Each category was graded as (–), not present or no increase; (+), minimal focal or marginal; (++) mild, moderate, or (+++), severe.

Results

Holter monitoring. The average ages of CFS and non-CFS patients were 40 years and 36 years, respectively (Table 1). CFS patients were predominantly women (87%) compared with 61% in the non-CFS patients ($P < .05$) [13,16]. A female sex predominance is characteristic of CFS patients. Non-CFS patients had a significant increase in the occurrence of mitral valve prolapse when compared with CFS patients (35% vs. 12%, $P < .05$). This latter difference in study groups reflects the symptoms of palpitations that brought these non-CFS

TABLE 1. Demographic features of CFS and non-CFS patients

	CFS (n = 67)	non-CFS (n = 78)	P
Age (mean) (y)	40	36	NS
Sex (% wome)	87	61	<.05
Diagnosis	CFS	No cardiac disease (59%)	
	Mitral valve prolapse (12%)	Mitral valve prolapse (35%)	<.05
		Mild aortic stenosis (6%)	

Note. Abbreviations used: NS, not significant.

cardiologic consultations. Both CFS and non-CFS patients had no known coronary artery disease, diabetes mellitus, hypertension, or total cholesterol of >250 mg. CFS and non-CFS patients had normal values for serum sodium, potassium, calcium, and magnesium. They were taking no cardiac medicines or antidepressants.

Holter monitoring readings were concordant between the two cardiologists-readers for the absence/presence of T-wave inversions and T-wave flattenings in 128 of 145 patients (88% agreement). There was disagreement in the presence of T-wave inversions in 11 CFS patients. There were discordant readings for the presence of T-wave flattenings in six patients, five of whom were CFS patients. The prevalence of both T-wave inversions (CFS, 61% vs. 34%; non-CFS, $P < .01$); and T-wave flattenings (CFS, 96% vs. 71%; non-CFS, $P < .01$) were significantly different between the groups (Table 2). T-wave abnormalities, both T-wave inversions and T-wave flattenings, were significantly greater in CFS patients than in non-CFS control patients (Figure 1).

Forty-nine of 51 CFS patients exhibited oscillating abnormal T-wave flattenings. T-wave flattenings are a sensitive indicator of CFS (0.96), but this Holter monitoring abnormality is not specific (0.29) (Table 2). T-wave inversions (Table 2) are a less sensitive indicator of CFS (0.61), but they are a more specific finding (0.66). Analysis of the combination of T-wave inversions and T-wave flattenings did not enhance the predictive value of these tests.

TABLE 2. Incidence of T-wave inversions and t-wave flattenings in CFS and non-CFS patients at holter monitoring

T-wave findings	CFS (n = 51)	non-CFS (n = 77)	P
Inversion	61%	34%	<.01
Flattening	96%	71%	<.01
Sensitivity of flattening	0.96 (49/51)		
Sensitivity of inversion	0.61 (31/51)		
Specificity of flattening	0.29 (22/77)		
Specificity of inversion	0.66 (51/77)		

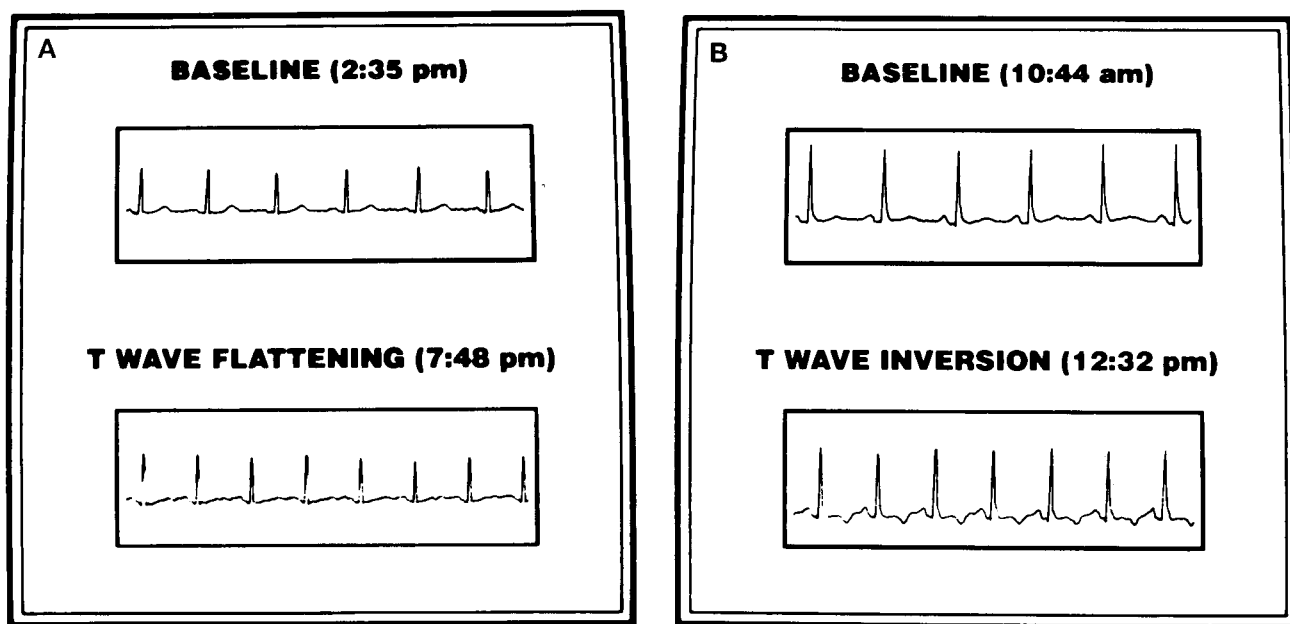


FIGURE 1. *Left*, this strip shows a normal sinus rhythm at 90/min (standard lead 1 at 2:35 P.M., October 4, 1993, from this 30-year-old woman with CFS). At 7:48 P.M., there is a sinus tachycardia of 122/min. At this time, repetitive flattening T-waves are apparent. Her right ventricular endomyocardial biopsy showed cardiomyopathic changes (Table 3, patient 4). *Right*, at 10:44 A.M., September 20, 1993, this 51-year-old man with CFS shows a normal sinus rhythm at 80/min with upright T-waves. At 12:32 P.M., there is a sinus tachycardia at 115/min. Seven inverted T-waves from a larger series are shown with the tachycardia. The right ventricular endomyocardial biopsy in this patient showed cardiomyopathic changes (Table 3, patient 8).

Light and electron microscopic findings in CFS patients undergoing cardiac biopsies (Table 3, Figures 2-7). A single endomyocardial biopsy showed lymphocytic myocarditis, but the eight other specimens showed no inflammatory infiltrates or degeneration of myocytes indicative of active myocarditis [17-20]. No amyloidosis, hemosiderosis, mitochondrial abnormalities, or storage diseases were detected by histochemical

stains or electron microscopy. Seven of the nine patients who had right ventricular endomyocardial biopsies also had electron microscopic studies. Six patients showed myocardial fiber hypertrophy, five patients showed myofiber disarray (Figures 3 and 6), three patients showed focal interstitial fibrosis, and five patients showed perimysial fat infiltration (Figure 7). Six patients showed increased mitochondria (Figure 7), and

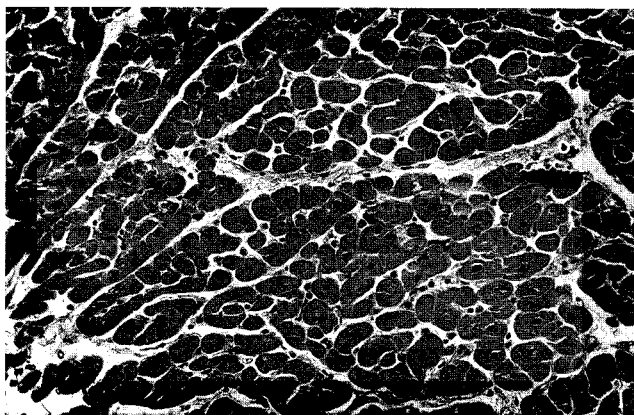


FIGURE 2. Light micrograph of histologically normal myocardium from a routine postcardiac transplant biopsy: note a regular arrangement of muscle fibers in cross-section (hematoxylin-eosin stain; original magnification, 1000 \times).

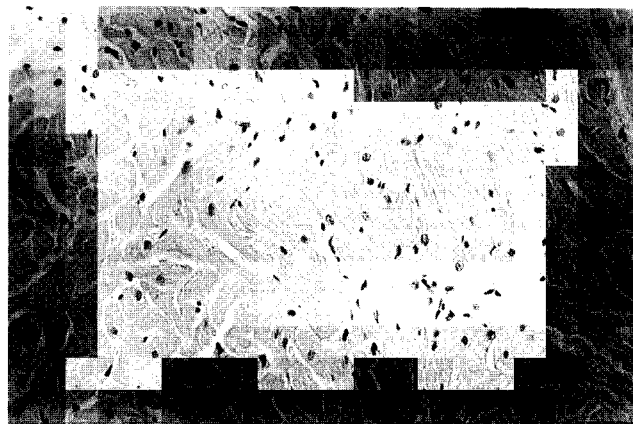


FIGURE 3. Light micrograph of myocardium from patient 2 (Table 3): note myofiber disarray characterized by disordered branching and orientation of myofibers seen in the center of the field (hematoxylin-eosin stain, original magnification, 1000 \times).

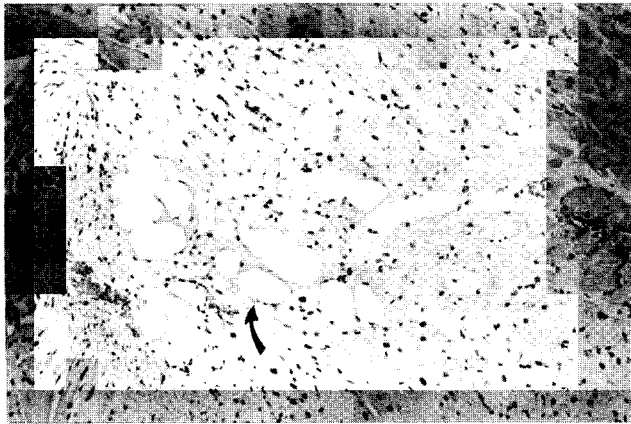


FIGURE 4. Light micrograph of myocardium from patient 4: note the myocardium is interspersed by groups of fat globules (arrow) (hematoxylin-eosin stain; original magnification, $\times 100$).

five patients showed increased fat droplets and increased lipofuscin granules in myofibers. No patient showed myofiber necrosis. However, one muscle fiber in patient 4 at electron microscopy (Table 3) showed focal myofiber necrosis. These changes describe an early cardiomyopathy [19].

Discussion

This study confirms our earlier report that CFS patients uniformly have abnormal oscillating T-wave flattenings and T-wave inversions by Holter monitoring. Moreover, the absence of these T-wave abnormalities is an excellent method (sensitivity, 0.96) to exclude the CFS in a patient with chronic fatigue of unknown cause. As

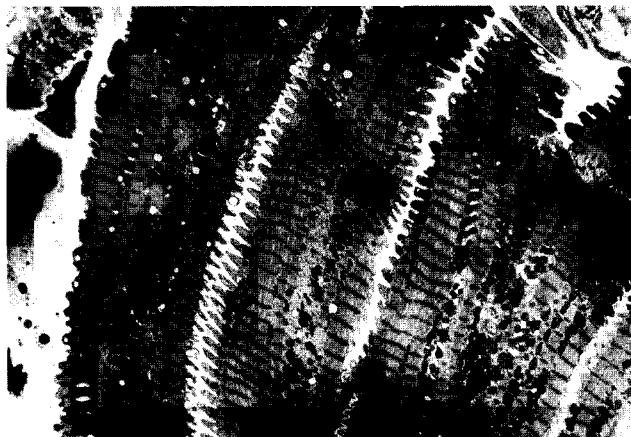


FIGURE 5. Electron micrograph of myofibers from normal appearing area: note a regular arrangement of sarcomeres in the muscle fibers. A muscle fiber in the center of the field shows a contraction band (lead citrate stain; magnification, $\times 3000$).

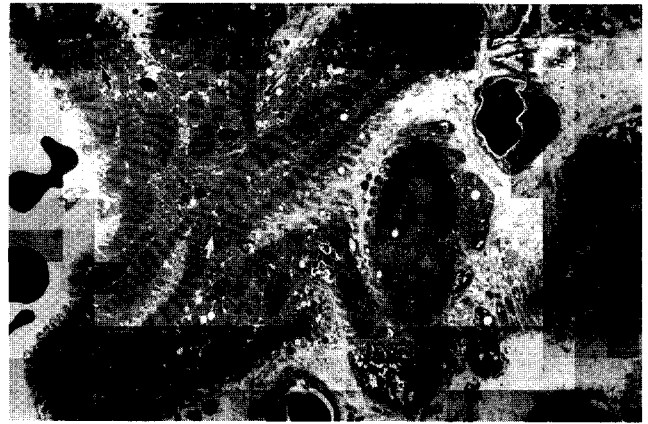


FIGURE 6. Electron micrograph of myofibers from patient 9: note myofibrillary disarray characterized by intersecting of myofibrils. Intercalated discs are indicated by arrows (lead citrate stain; magnification, $\times 2360$).

described here, abnormal Holter monitoring is important to the explicit diagnosis of patients with the CFS and should be, we suggest, added to the working case definition of the CFS established by CDC [11,12].

The CFS patients in this study were young and did not have chronic diseases, such as hypertensive vascular disease, diabetes mellitus, hyperlipidemia, coronary artery disease, or any other significant structural cardiac disease that might reasonably account for the abnormal oscillating T-waves at Holter monitoring. To be sure, an ideal control group for our study might have been age-, time-, and place-matched well patients not seeking any medical advice. However, the T-wave abnormalities we describe would likely be less frequent in such a healthier "control" population of well persons not seeking medical consultations. This study comparing CFS pa-

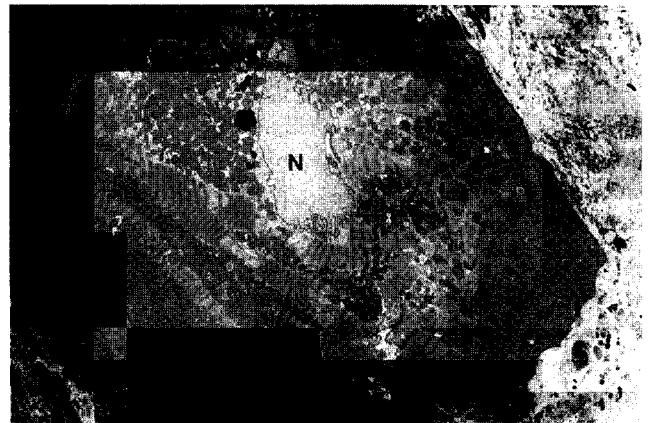


FIGURE 7. Electron micrograph of a myofiber from patient 8: note abundant mitochondria in perinuclear and intermyofibrillar spaces, displacing the myofibrils. A few lipofuscin granules around the nucleus (N) and scattered small fat droplets are also seen (lead citrate stain; magnification, $\times 3500$).

TABLE 3. Light and electron microscopic findings in myocardial biopsies from nine CFS patients

Patient no., age (y), sex	Date of endomyocardial biopsy (mo/d/y)	Myofiber hypertrophy	Myofiber disarray	Interstitial fibrosis	Perimysial fat infiltration	Cellular infiltration	Myofiber necrosis	Amount of mitochondria	Amount of fat droplets	Amount of lipofuscin granules
1 (58) M ^a	11/-/88	±	ND	+	-	+	-	ND	ND	ND
2 (44) F	1/2/93	+	-	-	++	-	-	ND	ND	ND
3 (49) F	3/4/93	±	+	-	++	-	-	+	+	+
4 (30) F	3/25/93	+	+	-	-	-	-	++	-	+
5 (45) F	5/20/93	±	-	+	++	-	-	-	+	-
6 (47) F	5/25/93	++	+	+	-	-	-	+	+	-
7 (53) F	7/8/93	+	-	±	+	-	-	+	-	+
8 (51) M	10/21/93	++	+	-	+	-	-	++	+	+
9 (44) F	11/15/93	++	+	-	-	-	-	++	+	+
Total (no. patients)		6	5	3	5	1	0	6	5	5

Note. Abbreviations and symbols used: ND, not done. Key to pathologic grading: -, not present or no increase; ±, minimal focal or marginal; +, mild; ++, moderate.

^a Patient 1 had endomyocardial biopsy at the Cleveland Clinic.

tients to non-CFS patients seeking a cardiologic evaluation is, therefore, biased "against" the hypothesis that the appearance of the repetitively oscillating abnormal T-wave inversions and/or T-wave flattenings at Holter monitoring occurs more frequently in CFS patients. The increased incidence of mitral valve prolapse in our study's non-CFS patients who had no known cardiac diseases and who sought cardiologic evaluation reflects, we believe, this non-CFS group. In unselected populations, the prevalence of mitral valve prolapse ranges from 4% to 17% in women and from 2% to 12% in men [10]. The occurrence of mitral valve prolapse in 12% of the CFS patients here but in 35% of the non-CFS patients is not surprising (Table 1). No patient, CFS or non-CFS, had significant mitral valve regurgitation.

If the abnormal T-wave oscillations in CFS patients were due to mitral valve prolapse, the increase in T-wave abnormalities in CFS patients compared with non-CFS controls would not have been found. Oscillating abnormal T-wave inversions would have been more frequent in the non-CFS group with the markedly greater proportion of patients with mitral valve prolapse. Our results indicate that the abnormal T-wave oscillations are a characteristic of CFS.

At light and electron microscopic review, eight of the nine patients with right ventricular endomyocardial biopsies had cardiomyopathic changes. One patient had an inflammatory myocarditis. Myocardial fiber hypertrophy, myofiber disarray, interstitial fibrosis, perimysial fat infiltration, and increases in mitochondria—findings indicative of a cardiomyopathy—were seen. A single muscle fiber showed localized necrosis of myofibrils accompanied by an accumulation of glycogen granules suggestive of recent myofiber injury. Although

artifact of the endometrial biopsy, the other morphologic changes (myofiber hypertrophy, interstitial fibrosis, perimysial fat infiltration, and increased numbers of fat droplets and lipofuscin granules) are not such procedure-induced changes. Moreover, 24% of 87 CFS patients have demonstrated abnormal left ventricular dynamics [15,20,21; Lerner AM, Sayyed T, Dworkin HJ, et al. Abnormal left ventricular myocardial dynamics in patients with the chronic fatigue syndrome in Birmingham, Michigan, 1987–1994 (submitted for publication)], including decreased left ventricular ejection fractions at rest and stress; decreased mean ejection fractions at stress; abnormal wall motion at rest; abnormal wall motion at stress; and ventricular dilatation at stress. Of 20 CFS patients with abnormal responses to the MUGA rest/stress study, four had abnormal 2-D echocardiograms including global left ventricular dilatation and inferobasilar hypokinesis. Rest/stress myocardial perfusion studies (thallium 201 or TC-99 sestamibi) excluded in each case a diagnosis of coronary artery disease. In two of our sickest (most fatigued) patients who had normal coronary arteries at cardiac catheterization, abnormal stress myocardial perfusion studies were seen [20,21]. These abnormal ejection fractions demonstrate abnormal left ventricular function and are not seen with normal persons living a sedentary lifestyle [22]. The abnormal oscillating T-wave flattenings and T-wave inversions at Holter monitoring, which we describe more fully and confirm here, appear to be an essential element to the pathologic physiology of the cardiomyopathy of the CFS [21].

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