Repetitively Negative Changing T Waves at 24-h Electrocardiographic Monitors in Patients With the Chronic Fatigue Syndrome*

Left Ventricular Dysfunction in a Cohort

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This study surveys the occurrence of repetitively negative to flat T waves, alternating with normal upright T waves in 24-h electrocardiographic recordings from a subspecialty infectious diseases outpatient practice during the years 1982 to 1990. Patients with normal resting electrocardiogram in the assayed leads, but with repetitively inverted to isoelectric abnormal T waves at Holter monitors, were considered to have abnormal readings. A total of 300 patients had undergone a 24-h Holter monitor. This group included 24 individuals with chronic fatigue syndrome (CFS). This population was restricted to individuals 50 years old or younger, and the patients with CFS are compared with the patients without CFS. One of the more striking differences between the two groups was the difference in abnormal Holter readings. The patients with CFS all had abnormal Holter readings, while 22.4 percent patients without CFS had abnormal readings ($p<0.01$). We further report the occurrence of mild left ventricular dysfunction in 8 of 60 patients in continuing studies of this population with CFS, younger than 50 years old, and with no risk factors for coronary artery disease. All 60 patients with CFS showed repetitively flat to inverted T waves alternating with normal T waves. Stress multiple gated acquisitions (MUGAs) (labeled erythrocytes with stannous pyrophosphate) were abnormal in eight patients with CFS. Although resting ejection fractions (EFs) were normal (mean, 60 percent), with increasing work loads (Kilopon meters [Kpms]), gross left ventricular dysfunction occurred. The fatigue of patients with CFS may be related to subtle cardiac dysfunction occurring at work loads common to ordinary living. *(Chest 1993; 104:1417-21)*

CFS = chronic fatigue syndrome; Kpm = Kilopon meters; MUGA = multiple grated acquisition

Inverted T waves at stationary electrocardiograms have been associated with subendocardial ischemia[1] and subsequent myocardial scarring, active myocarditis,[2] coronary artery disease, and several metabolic abnormalities of normal individuals. On standard electrocardiogram the upright posture and hyperventilation have been associated with inverted T waves in as many as 5 percent of normal individuals.[3-5] Transient, inverted T wave changes have been found in patients with known coronary artery disease and the significance of these changes has been noted.[6,7] We have found repetitively changing flat to negative T waves in a group of young adults with the chronic fatigue syndrome (CFS).[8]

Methods

Study A

Patient Population: All Holter monitor studies performed in this outpatient practice during the years 1982 to 1990 were reviewed, regardless of the initial complaint or final diagnosis. Indications for the Holter monitors were complaints of palpitations, chest pain, or ongoing (greater than 6 months) unexplained fatigue.

There were 304 24-h electrocardiographic monitor studies performed during the period. Four patients were HIV positive and were excluded from the analysis. Of the remaining 300 patients, there were 115 (38.3 percent) abnormal (positive) tests with changing flat/negative T waves.

Holter Monitors: Twenty-four-hour continuous electrocardiographic recordings were obtained using a modified standard lead I and precordial lead V_5. One of two systems was used: the (a) Delmar Monitor or (b) Epicardia 1250-1350.

A patient's 24-h Holter monitor was considered positive if T waves became intermittently inverted or flat, *ie*, the T waves were below the horizontal described by inceptions of p and Q waves in one of the two monitored leads with two or more episodes for at least 25.0 normally conducted QRS complexes. A uniformly flat T wave (isoelectric) was considered positive. T waves were evaluated independent of possible ST segment changes. Biphasic T waves were considered normal. U waves (a small, shallow, positive rounded deflection inscribed immediately after the T wave) did not interfere with this analysis. Other abnormal findings were not analyzed.

When Holter monitors showed changing T waves, Bruce protocol, thallium 201 scans, and stress multiple gated acquisition (MUGA) tests were performed at William Beaumont Hospital, Royal Oak, Mich.[9,10]

Chronic Fatigue Syndrome: The US Centers for Disease Control and Prevention (CDC) case definition of the CFS was used.[8] In this definition, CFS is considered to be a persisting or relapsing fatigue that reduces a person's activity level to below 50 percent of their normal activity level for a period of at least 6 months. The condition may include fever, chills, sore throat, painful lymph nodes, (*eg*, anterior or posterior cervical, axillary), muscle weakness, myalgia,

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prolonged generalized fatigue after levels of exercise that would have previously been easily tolerated, generalized headaches, migratory arthralgia, neuropsychologic complaints, and sleep disturbance.

Patients with conditions that might produce similar symptoms were not diagnosed as suffering from CFS.

Medical Records: Medical records were reviewed for demographic information, alcohol and tobacco use, exercise patterns, results of blood tests, and other illnesses and complaints.

Statistical Methods: χ^2 tests were used to analyze nominal and ordinal levels of measurement. Two sample *t* tests were used to analyze normally distributed interval levels of measurement. Wilcoxon rank sum tests were used for interval levels of measure not normally distributed.

A statistical package (SAS Version 5.16) was used for all statistical analyses.

Study B

Patients fitting the diagnosis of CFS were similarly studied to reach a continuing total of 60 patients. Demographics of the entire group of 60 patients did not differ from that of study group A. All 60 patients with CFS had abnormal Holter monitor results as defined above in study group A. Since stress thallium tests did not add to our knowledge, this test was not done regularly in patients 25 through 60. All 60 CFS study patients with CFS were from the same pool and were younger than 50 years old and had no risk factors for coronary artery disease.

Results

Demographics and Diseases

Patients with CFS were compared with patients without CFS during the study years. For comparisons, both groups were restricted to patients ≤50 years old to minimize age differences in the two populations as CFS was rare after 50 years old. There were 24 patients with and 116 patients without CFS. Patients with CFS were predominantly women (75 percent), while patients without CFS were split equally among men and women ($p = 0.03$) (Table 1). Both groups were similar in racial composition (both over 90 percent white), mean age (36 years old CFS vs 38 years old non-CFS), marital status (54.2 percent CFS vs 62.1 percent non-CFS married), educational attainment (58.3 percent vs 53.4 percent college graduate or greater), and income level (71 percent vs 61 percent income, ≥$25,000 per year). They were also similar in cigarette smoking (33.3 percent CFS vs 21.6 percent non-CFS smoked). Both groups drank <1 to 2 oz of alcohol per week. None of the patients with CFS had diabetes, hypertensive vascular disease, or coronary artery disease. In the non-CFS population, one patient had diabetes, 19 patients had hypertensive vascular disease, and 10 had coronary artery disease. These group differences were significant only for hypertensive vascular disease ($p = 0.03$).

Symptoms and Signs

The majority of patients with CFS (75 percent) reported a febrile illness at the time of onset of their fatigue state, while 51 percent of the patients without CFS had similar complaints. Ninety-two percent of the patients with CFS complained of overwhelming fatigue at their first visit, while 35 percent of the patients without CFS had no specific complaint. Similarly, myalgia at first visit (70.8 percent CFS vs 40.5 percent non-CFS, $p<0.01$), and a nonproductive cough (41.7 percent CFS vs 17.2 percent non-CFS, $p<0.01$) distinguished the two patient groups. There were also statistically different differences in blood pressure (systolic, 116 mm Hg CFS vs 126 mm Hg non-CFS, $p = 0.02$, and diastolic, 73 mm Hg CFS vs 80 mm Hg non-CFS, $p = 0.01$). Results of complete physical examinations in patients with CFS were uniformly normal.

Laboratory Studies

Results of laboratory tests for white blood cell counts, erythrocytes, cytomegalovirus, and Epstein-Barr virus antibody titers and cholesterol values were not different for patients with and without CFS.

Table 1—*Demographics and Chronic Diseases: Comparison of Patients With and Without CFS**

Demographics	24 Patients With CFS	116 Patients Without CFS	p Value
Sex, %			
Female	75	50	0.03
Male	24	50	
Race: white, %	95.8	89.7	NS
Age, yr, mean	36	38	NS
Marital status: married, %	54.2	62.1	NS
Education, %			
College graduate or higher	58.3	53.4	NS
Income, %			
≥$25,000-$50,000	45.8	32.5	NS
≥$50,000	25	28.1	NS
Chronic diseases, %			
Diabetes mellitus	0	0.7	NS
Hypertensive vascular disease	0	16.4	0.03
Coronary artery disease	0	8.6	NS

*NS = not significant.

Table 2—*Electrocardiographic Findings for Patients With and Without CFS**

	Patients With CFS	Patients Without CFS	p Value
Standard electrocardiogram, initial, abnormal, %	45.8	33.9	NS
Mitral valve prolapse, at echocardiogram, %	22.7	24.5	NS
Holter monitor, initial, changing T-wave inversions, or flat T waves, %	100	22.4	<0.01

NS = not significant.

Standard ECGs, Holter Monitors, and Stress Tests

Despite absence of diabetes mellitus, hypertensive vascular disease, or known coronary artery disease, 46 percent of the patients with CFS had abnormal initial standard electrocardiograms (Table 2). Most changes were minor isolated T wave inversions. Q waves, intraventricular blocks, and arrhythmias were rare in patients with CFS. A single patient, a 40-year-old woman, developed an intermittent left bundle branch block. Mitral valve prolapse was the only abnormality seen at echocardiogram, and occurred almost equally in patients with CFS (22.7 percent) and control subjects (24.5 percent).

Holter monitor results were abnormal at initial visits in all patients with CFS (Table 2). T waves in monitored leads were upright, but at varying times during the 24-h records became repetitively inverted or flat (Fig 1). Negative T waves were more frequent with increasing cardiac rate and in lead B (precordial lead V_5). Patients without CFS differed. Only 22.4 percent of the patients without CFS had similarly changing T waves. One non-CFS patient had paroxysmal hypertension due to a pheochromocytoma. After removal of the tumor, elevated blood pressures and T-wave inversions in the patient disappeared. Stress test results for both groups in study A were too small for analysis.

Study B

Stress MUGAs: Resting ejection fractions (EF) were unremarkable (mean, 60 percent), but at increasing work levels of 200 Kpms and 400 Kpms, left ventricular dysfunction appeared in 8 patients. In one patient (No. 004, Table 3) with increasing work load, EF was flat. The EFs decreased in three others (patients 005, 007, and 009). Left ventricular dilatation was seen in five patients, and ventricular wall motion abnormalities were seen in three.

Discussion

A disorder of immunoregulatory function following Epstein-Barr virus, human herpesvirus type 6, or enterovirus infections has been suspected in patients with the CFS.[11-15] IgG subclass deficiencies, increased or impaired natural killer cell cytotoxicity,[16,17] and increased antibody titers to Epstein-Barr virus early antigen with lower than expected antibody titers to nuclear antigen have been described.[11] Likewise, increased antibody titers to Epstein-Barr virus-specific DNase and DNA polymerase have been reported.[18] The cytokines, neopterin (a product of monocyte/macrophage activation) and interleukin 6 (a product of activated mononuclear phagocytes) have been increased in some patients.[19] Coxsackievirus B2 genomic RNA at muscle biopsy or viral polypeptide VP1C, an enterovirus-specific antigen, has been detected.[20,21] In all cases, prolonged generalized fatigue after levels of exercise that would have been easily tolerated before the onset of illness has been de-

Table 3—*Findings in Eight Patients With CFS With Left Ventricular Dysfunction**

Patient	Age, yr	Occupation	Date First Seen	Current Holter Monitor	No. of Months Follow-up	Stress MUGAs		Currently Fatigued
						Initial	Follow-up	
Men								
001	30	Chef	02/19/90	A	3, 5	LVD	A	Yes
002	30	Business executive	08/09/88	N	2	LVD	N	No
Women								
004	31	Housewife	10/08/90	N	5	Flat EF, stress	N	No
005	35	Office manager	11/23/90	L	L	LVD ↓ EF, stress	L	L
006	42	Housewife	06/26/91	A	9	Wall motion	A	Yes
007	44	Secretary	06/28/91	A	11	abnormality LVD, ↓ EF, stress, wall motion abnormality	A	Yes
008	46	Housewife	02/15/89	A	36	LVD	A	Yes
009	48	Dental hygienist	03/06/91	A	14	↓ EF, wall motion abnormality	A	Yes

*N = normal; A = abnormal; L = unavailable for follow-up; LVD = left ventricular dilatation; ↓ EF = decreased ejection fraction.

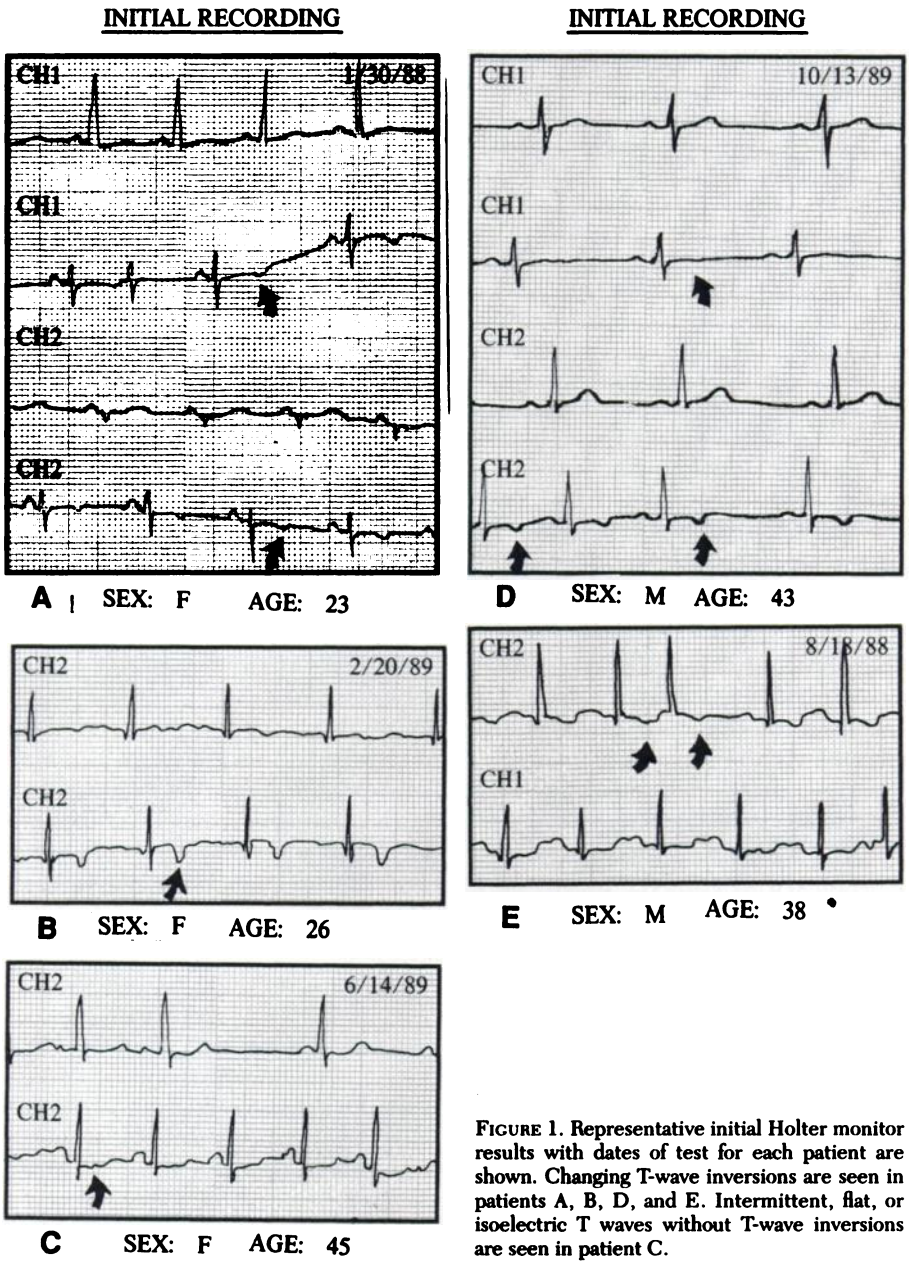

FIGURE 1. Representative initial Holter monitor results with dates of test for each patient are shown. Changing T-wave inversions are seen in patients A, B, D, and E. Intermittent, flat, or isoelectric T waves without T-wave inversions are seen in patient C.

scribed.[22] Surface sums of positive T wave integrals have been normal at 24-h ambulatory ECGs, and there have been no differences in sinus rates or ventricular dysrhythmias.

We have found an unusual occurrence of abnormal Holter monitor results in 60 consecutive patients all younger than 50 years old with CFS who had no evidence of coronary artery disease, hypertension, diabetes mellitus, or hypercholesterolemia. Standard ECGs and two-dimensional echocardiograms were uniformly unremarkable. We suggest that the abnormal T waves described herein may be an important feature of the CFS. In three patients with CFS, coronary angiograms were normal. Stress thallium tests in patients with CFS did not reveal coronary artery disease. Left ventricular dilatation and wall motion abnormalities, however, suggest a cardiomyopathy. Abnormal T waves in Holter monitor results were most frequent with increased work of the heart at sinus tachycardias. Lead B (precordial lead V_5), reflecting left ventricular repolarization potentials, was most often abnormal. Resting EFs were normal, but flat or decreasing EFs were often seen with increasing cardiac work loads. None of the remaining 52 patients with CFS had abnormal stress MUGAs. Further studies are required to assess the role of the cardiomyopathy we have found in patients with CFS.[23]

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