Objective: Electrocardiographic repolarization intervals were evaluated to determine the extent of cardiac autonomic dysfunction in patients with familial dysautonomia (FD) and to determine if any of these intervals could serve as a possible predictor of clinical symptoms.

Methods: Thirty-seven electrocardiograms of patients with FD were retrospectively evaluated. QT, JT, rate-corrected QT and JT intervals were calculated as well as QT and QTC dispersion. Results were compared to normative data and electrocardiograms of 20 age-matched control subjects.

Observations: In the FD group, prolongation of QTc (>450 msec) was noted in 5/37 (13.5%) patients, as compared to 0/20 normal controls (p = NS), and prolongation of JTc (>340 msec) in 16/37 (43.3%) patients, as compared to 0/20 normal controls (p < 0.001). QT and QTC dispersion were abnormal in 3/37 (8.1%) and 5/37 (13.5%), respectively. In the 16 FD patients with prolonged JTc, six had a positive history of syncope, whereas none of the 21 with normal JTc had syncope or symptoms suggesting arrhythmia (p < 0.003). The positive predictive value of having syncope or symptoms suggestive of arrhythmia with an abnormal JTc is 37.5% (95% CI [15%, 65%]). The negative predictive value is 100% (95% CI [87%, 100%]).

Conclusion: In the FD population, the electrocardiographic measure of repolarization that was most frequently abnormal was the JTc interval. Prolongation of the JTc interval was significantly more frequent than prolongation of the QTc interval (p < 0.001) QT and QTC dispersions were less significantly affected in the FD population, indicating uniform ventricular recovery time. These results suggest that a prolonged JTc interval may be a more sensitive indicator of abnormal ventricular repolarization and cardiac autonomic dysfunction. Due to the known sympathetic denervation inherent in patients with FD, they are at risk for unopposed parasympathetic predominance. FD patients, therefore, are more likely to have bradyarrhythmias and asystole rather than polymorphic ventricular tachycardia. The increased incidence of syncope in patients with prolonged JTc suggests that this measure may serve as a helpful marker to predict which FD patients are at increased risk of serious clinical sequelae including bradyarrhythmias with asystole or sudden death.

Keywords: familial dysautonomia, cardiac autonomic dysfunction, ECG repolarization abnormalities.

Familial dysautonomia is an autosomal recessive disorder affecting the development and survival of sensory, sympathetic, and some parasympathetic neurons [1]. Cardiovascular instability is a prominent and well-recognized manifestation of the autonomic dysfunction seen in these patients. Blood pressures are labile and both hypertensive crises and orthostatic hypotension without compensatory tachycardia can occur [2].

What is less well understood in the FD population are the mechanisms of intrinsic cardiac regulation. The autonomic nervous system, in particular the sympathetic nervous system, is an important modulator of cardiac ventricular repolarization and influences the QT interval [3]. Sympathetic dysfunction can be an important cofactor in the development of malignant arrhythmia. The QT interval, along with the rate-corrected QT interval (QTc), is a reproducible, easily measured electrocardiographic parameter of ventricular depolarization and repolarization. When abnormal, the QT interval may identify patients at risk of developing ventricular fibrillation and sudden cardiac death. It has been reported that patients with an autonomic neuropathy have prolonged QTc intervals [4,5]. Similarly, FD patients have an increased frequency of prolongation of QTc intervals with a lack of appropriate shortening with exercise. We have suggested that these measures might serve as a noninvasive means of demonstrating an aberration in the autonomic regulation of cardiac repolarization [6]. However, because QT and QTc intervals include both repolarization and depolarization, they may not be sensitive indicators of isolated repolarization abnormalities. The JT and JTc intervals
(the time from the end of the QRS to the end of the T wave electrophysiologically) provide another means of evaluating ventricular repolarization by eliminating the QRS duration variability. JTc has been shown to be an independent measure of repolarization not related to depolarization [7]. Prolongation of the JTc can reflect cardiac repolarization abnormalities and also cardiac autonomic dysfunction [8].

QT interval dispersion, measured as the interlead variability of the QT interval on a 12 lead electrocardiogram (ECG), has been proposed as a marker of regional variation in ventricular repolarization and hence of electrical instability [9]. There is increasingly convincing evidence that dispersion of ventricular refractoriness is associated with ventricular instability and ventricular arrhythmias [4].

In this study we hypothesized that in FD patients, JTc would be more sensitive than QTc as an indicator of ventricular repolarization abnormalities by eliminating QRS variability in the calculations. By measuring QT and QTc dispersions we sought to evaluate whether these patients with autonomic dysfunction had a proclivity for regional variation in ventricular repolarization. Using multiple electrocardiographic measures, our goal was to determine the extent of cardiac autonomic nervous system dysfunction in patients with FD and to determine if any of these intervals could serve as a possible predictor of clinical symptoms.

Methods and subjects

The ECGs of 50 adolescent and adult patients with familial dysautonomia (FD) were reviewed. These 50 patients, who were examined annually at the Dysautonomia Treatment and Evaluation Center at New York University Medical Center, had their ECGs performed as part of a previous study. Thirteen ECGs could not be evaluated as muscle tremors caused confounding artifacts. Thus 37/50 ECGs could be used for calculation of electrocardiographic intervals. None of the FD subjects was receiving medications known to modify the QT interval duration and all had normal ionized serum calcium and potassium determinations on the day the ECG was obtained. In the FD group, there were 20 males and 17 females; mean age 18.3 ± 9.3 years. The control group was comprised of 20 patients, 8 males and 12 females; mean age 15 ± 6.9 years. These patients were seen in the pediatric cardiology clinic and all were found to have normal physical exams and normal ECGs. They were not known to have any heart disease or any other diseases which could affect their cardiac autonomic function. The person who evaluated all the ECGs (J.G.) was blinded to the clinical status of the FD patients.

Electrocardiographic measurements

QT intervals were measured from routine 12 lead electrocardiograms recorded at 25 mm/s at rest. The JT, QT, and RR intervals of at least two sinus beats (range 2–3) were measured from each of the 12 leads, and the mean QT and RR intervals calculated. None of the sinus beats were post premature beats. The JT, QT, and RR intervals were measured manually with hand-held calipers. The QT intervals were measured from the onset of the QRS interval to the end of the T wave. The end of the T wave was defined as the point of return to the isoelectric line regardless of the polarity of the T wave. U waves were not present in any of the ECGs. Electrocardiographic indices (QTC and JTc intervals)

Statistical analysis

The Mann Whitney Test was used to compare the variables age, QTc dispersion, QTc dispersion, QTc and JTc between the FD and control groups. The QTc and JTc values in the FD group were compared to the established normative values for QTc and JTc. The McNemar test was used to compare the sensitivities of QT dispersion versus QTc dispersion and QTc versus JTc to classify abnormal FD patients. A p value < 0.05 was considered to be statistically significant. Normal ranges for QT and QTc dispersion were obtained by calculating the usual 95% confidence interval for their respective means in the age-matched control group (ie, mean QTc dispersion ± 1.96 × SD of QTc dispersion and mean QTc dispersion ± 1.96 × SD of QTc dispersion). The Fisher's Exact Test was used to test for significant differences in the number of abnormal QTc and JTc values between the FD patients and the control group. A p value < 0.05 was considered statistically significant. The Fisher's Exact Test was also used to test for significant differences among FD patients with JTc abnormalities with clinical symptoms versus without clinical symptoms. Using the exact Binomial Confidence Interval Procedure, the positive predictive value and the negative predictive value for clinical symptoms associated with JTc abnormalities in the FD population were calculated.

Results

Electrocardiographic indices (QTC and JTc intervals)

The QTc was abnormally prolonged (>450 msec) in 5/37 (13.5%) of the FD patients as compared to none